SUPPLEMENTARY APPENDIX

Clinical management of adult patients with COVID-19 outside intensive care units: guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

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References

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Francesco Blasi
Role: presidents of SITA and SIP, project concept, voting panel members, revision of final manuscript and appendix

Project coordinator

Daniele Roberto Giacobbe
Role: participation in methodology and systematic reviews, assessment of evidence with the GRADE system, drafting of recommendations, drafting of final manuscript and appendix, supervision of voting process, non-voting panel member

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Role: voting panel members, revision of final manuscript and appendix

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QUESTION 1

When should a patient with COVID-19 be hospitalized?

Question 1. Search strings and databases

Pubmed

(hospitalization[Text Word] OR admission [Text Word]) AND (outpatient[Text Word] OR "home care" [Text Word] OR community[Text Word] OR mild[Text Word] OR "hospital discharge"[Text Word] OR score[Text Word] OR "Pneumonia severity index" [Text Word] OR "CURB-65" [Text Word] OR "SMART-COP" [Text Word] or "risk factor*"[Text Word) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])*

Embase

(hospitalization:ti,ab,kw OR admission:ti,ab,kw) AND (outpatient:ti,ab,kw OR 'home care':ti,ab,kw OR community:ti,ab,kw OR mild:ti,ab,kw OR score:ti,ab,kw OR 'risk factor*':ti,ab,kw OR 'hospital discharge':ti,ab,kw OR index:ti,ab,kw OR 'curb-65':ti,ab,kw OR 'smart-cop':ti,ab,kw) AND (coronavirus:ti,ab,kw OR 'covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)*

Cochrane COVID-19 Study Register

Admission OR Hospitalization AND score OR prognos OR outpatient OR "risk factor*" OR predict**

– filter: report results

Question 1. Literature review details

Search strings development:

Antonio Vena

Nadia Castaldo

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

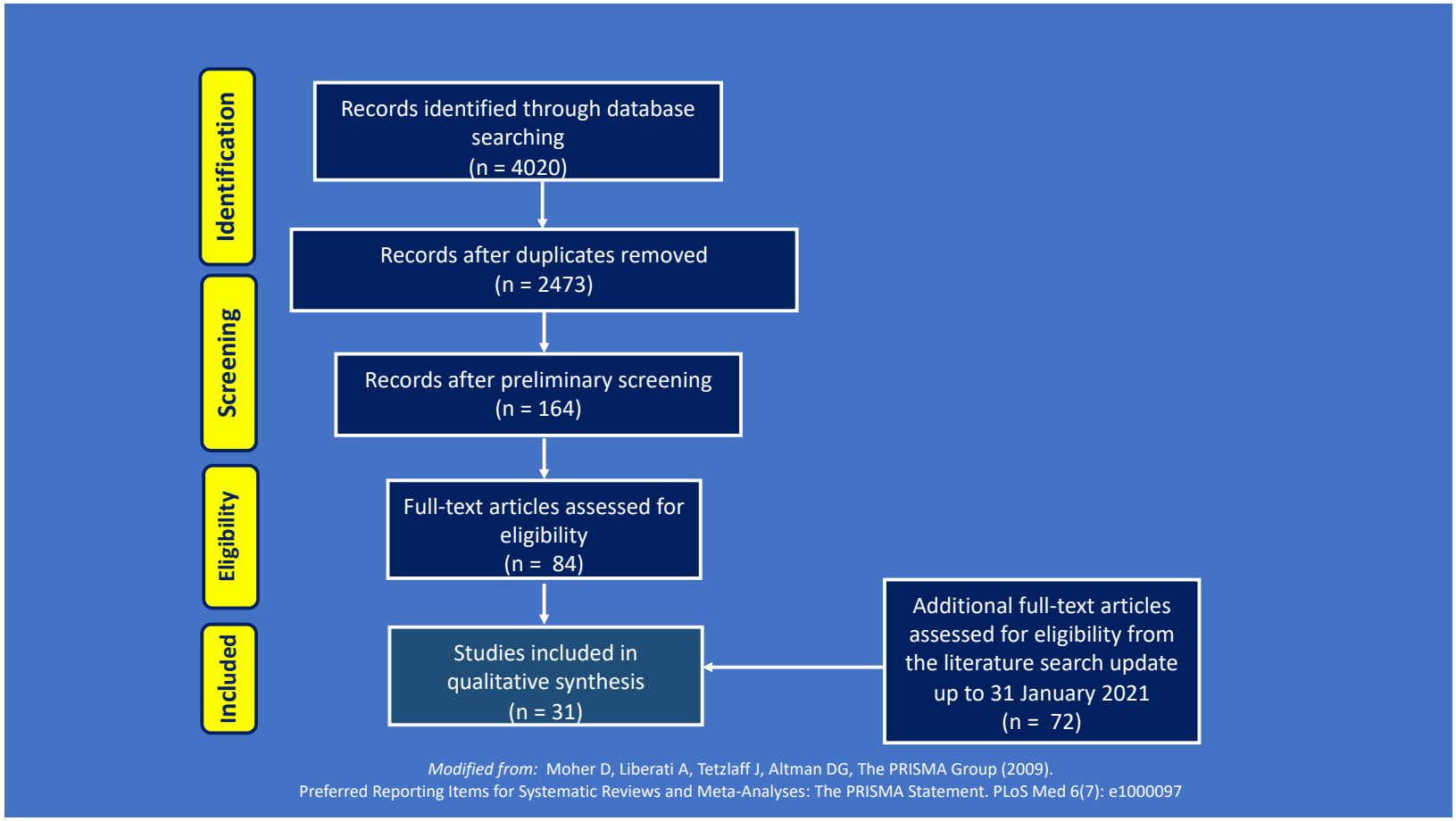
Antonio Vena

Nadia Castaldo

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 1. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 1838 de-duplicated records, with the ultimate evaluation of 72 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, no randomized controlled trials (RCTs) were retrieved during the final literature search update up to 30 April 2021. Overall, 22 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 1. GRADE tables

Recommendation:

Pending further evidence, it might be prudent not to base the decision to hospitalize or not patients with COVID-19 only on prognostic models or scores

Number of studies	Studies design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
22 studies [1-22]	Retrospective and prospective cohort studies plus 2 systematic reviews	Very serious risk of bias due to confounding and possible information bias	Serious inconsistency	Serious indirectness as most studies evaluated the prognostic effect of scores in inpatients	Serious imprecision due to the small sample sizes of many studies	Serious risk of publication bias for prognostic models developed for COVID-19	Very low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.

Recommendation:

Hospitalization should be considered in patients with at least one of the following: low oxygen saturation on room air ≤ 92% at rest or partial pressure of oxygen < 60 mmHg at arterial blood gas analysis; respiratory rate > 30 breaths per minute; new onset of dyspnea at rest or during speaking; reduction of oxygen saturation on room air below 90% during walking test; high value of prognostic scores; presence of anuria, confusion, hypotension, cyanosis, and/or other medical conditions requiring hospitalization per se*

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

* This does not strictly apply to patients with chronic obstructive pulmonary disease or other chronic respiratory disease, in whom similar values may be well tolerated, but who nonetheless need a careful personalized evaluation for hospitalization considering the presence of a baseline respiratory disease besides COVID-19

QUESTION 2

Which drugs should be administered to outpatients with COVID-19?

Question 2. Search strings and databases

Pubmed

(outpatient[Text Word] OR home[Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])

Embase

(outpatient:ti,ab,kw OR home:ti,ab,kw) AND ('covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)

Cochrane COVID-19 Study Register

outpatient OR home

– filter: report results

Question 2. Literature review details

Search strings development:

Guido Granata

Emanuela Sozio

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

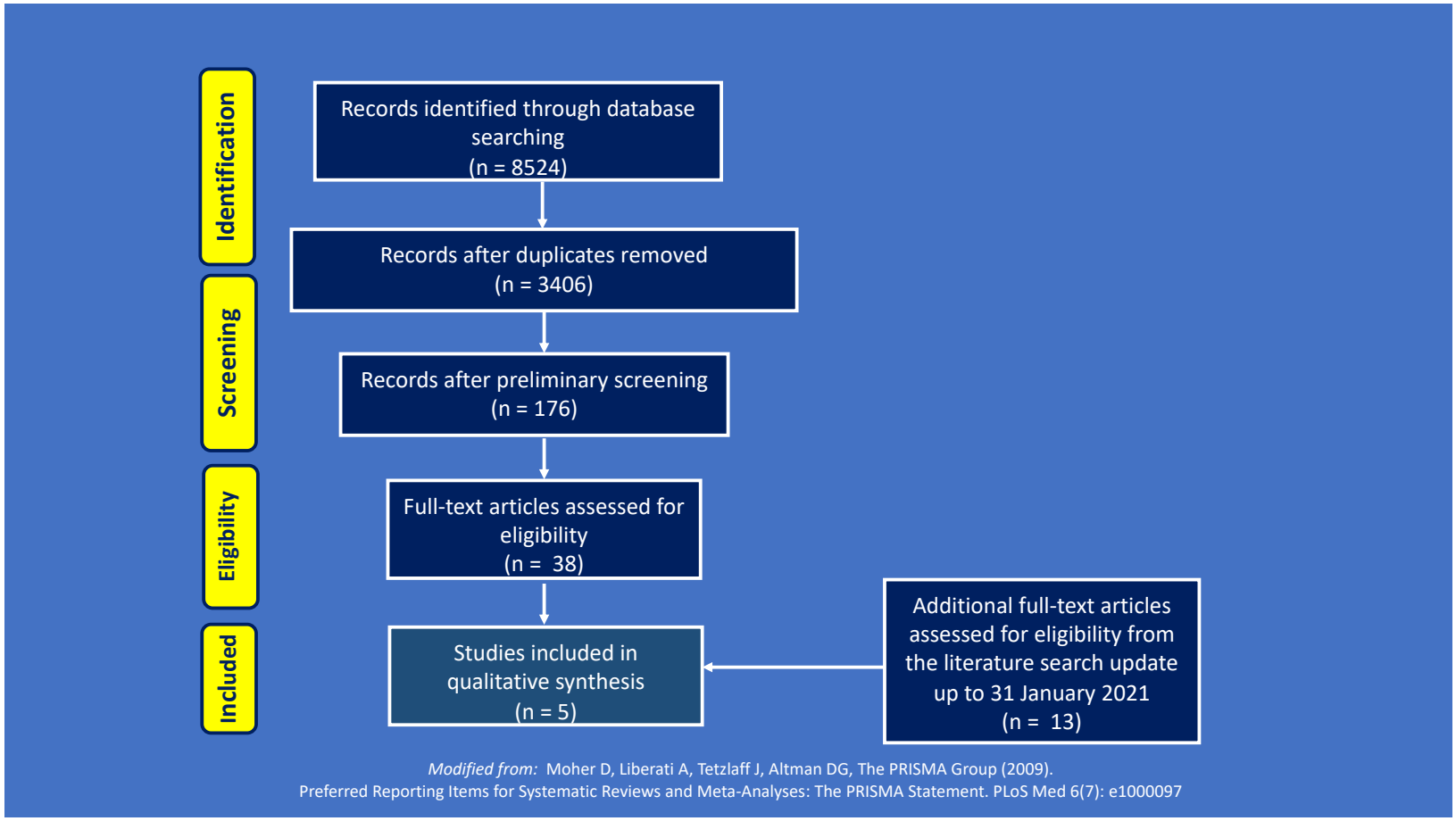
Guido Granata

Emanuela Sozio

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 2. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 2944 de-duplicated records, with the ultimate evaluation of 13 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 10 randomized controlled trials (RCTs) were evaluated during the final literature search update up to 30 April 2021. Overall, 8 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 2. Extended evidence summary

The efficacy of hydroxychloroquine in outpatients with COVID-19 was assessed in a multicenter, open label, randomized, controlled trial conducted in Spain [25]. Enrolled patients were non-hospitalized adults with COVID-19 and less than five days of symptoms. Patients were randomized to receive hydroxychloroquine (800 mg on day 1, followed by 400 mg once daily for 6 days) or usual care alone. The primary outcome was the reduction of viral load in nasopharyngeal swabs at days 3 and 7 days after treatment start. Overall, 293 patients were included in the intention-to-treat population: 136 in the intervention arm and 157 in the control arm, respectively. No differences were found in the mean reduction of viral load at day 3 or at day 7. With regard to secondary outcomes, hydroxychloroquine did not reduce the risk of hospitalization (5.9% vs. 7.1% in treatment and control groups, respectively; risk ratio 0.75, with 95% confidence interval [CI] 0.32-1.77) nor shortened the median time to complete resolution of symptoms (10 days vs. 12 days in hydroxychloroquine and control group, respectively; p = 0.38).

In a randomized, double-blind, controlled trial conducted across the US and Canada hydroxychloroquine was compared to placebo in terms of change in overall symptom severity over 14 days using a 10-point visual analogue scale (primary endpoint) [26]. The study population consisted of 423 symptomatic, non-hospitalized adults with COVID-19. Patients in the treatment arm received hydroxychloroquine at the dosage of 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 more days. No differences between groups were observed with respect to the ordinal primary endpoint. Adverse effects (AEs) were observed in 92/212 (43%) participants receiving hydroxychloroquine vs. 46/211 (22%) receiving placebo, with the difference being mainly driven by a higher frequency of gastrointestinal AEs in the hydroxychloroquine arm.

In a double-blind RCT conducted in 129 high-risk outpatients with confirmed COVID-19, patients were randomized in three groups (hydroxychloroquine [HCQ], HCQ plus

azithromycin, and placebo) [27]. The primary clinical endpoint was a composite of 14-day progression to lower respiratory tract infection (LRTI), hospitalization, or death. LRTI developed in 4.7% of patients (2 and 4 in control and HCQ plus azithromycin arms, respectively) and hospitalization in 5.4% of patients (4,1, and 2 patients in placebo, HCQ, and HCQ plus azithromycin arms, respectively). There were no deaths.

In a double-blind RCT conducted in 685 high-risk outpatients with confirmed COVID-19, patients were randomized in three groups (HCQ, lopinavir/ritonavir, and placebo) [28]. The primary endpoints were hospitalization and death at 90 days after randomization. Overall, 3.7%, 5.7%, and 4.8% in HCQ, lopinavir/ritonavir, and placebo arms were hospitalized (hazard ratio [HR] vs. placebo 0.76 with 95% from 0.30 to 1.88 for HCQ and 1.16 with 95% CI from 0.53 to 2.56 for lopinavir/ritonavir). The trial was prematurely halted for futility.

The efficacy and safety of colchicine for the treatment of outpatients aged 40 years or older, with suspected/proven COVID-19, and with a least one risk factor for disease progression (70 years or older, obesity, diabetes, uncontrolled hypertension, known respiratory disease, known heart failure, known coronary disease, fever ≥38.4°C within the previous 48 hours, dyspnea at the time of presentation, bicytopenia, pancytopenia, or high neutrophil count plus low lymphocyte count) was assessed in a double-blind, 1:1 RCT, the results of which have been recently published [29]. Colchicine was administered at the dosage of 0.5 mg twice daily for 3 days and then once daily for the subsequent 27 days. The primary endpoint was a composite of death or hospitalization. Overall, 4488 patients were enrolled (of whom 4159 patients with confirmed COVID-19 by molecular tests). In the entire population (proven plus suspected COVID-19), the primary endpoint was registered in 4.7% and 5.8% of patients in the colchicine and placebo arms, respectively (odds ratio [OR] 0.79, with 95% CI from 0.61 to 1.03). The effect was more marked, which achievement of superiority, in outpatients with proven COVID-19 and in the subgroup of patients with

proven COVID-19 (4.6% and 6.0% in colchicine and placebo arms, respectively; OR 0.75, with 95% CI from 0.57 to 0.99). When the different components of the composite endpoint were addressed separately in outpatients with proven COVID-19, ORs were 0.75 for hospitalization (95% CI from 0.57 to 0.99) and 0.56 for death (95% CI from 0.19 to 1.66). With regard to AEs, pneumonia was more frequently observed in the placebo arm than in the colchicine arm (4.1% vs. 2.9%), whereas diarrhea was more frequent in the colchicine arm (13.7% vs. 7.3%). The trial was early terminated by the investigators once 75% of the planned patients were recruited, for logistic reasons and for anticipating dissemination of results during the pandemic.

In a controlled, open-label trial, hospitalized patients with COVID-19 were randomly assigned to receive oral or intravenous dexamethasone at the dosage of 6 mg once daily for up to 10 days or to receive usual care alone. The primary outcome measure was death within 28 days after randomization. Overall, 6425 patients were enrolled in the trial, of whom 2104 and 4312 were assigned to dexamethasone and to usual care arms, respectively. As many as 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio 0.83, with 95% CI 0.75-0.93). However, the proportional and absolute between-group differences in the primary outcome varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization: mortality was indeed lower in the dexamethasone group than in the usual care group among patients receiving oxygen, but not among patients not receiving respiratory support at randomization (17.8% vs. 14.0%; rate ratio 1.19, with 95% CI 0.91-1.55) [30]. Of note, the rate ratio and 95% CI estimates were derived from an age-adjusted model involving an interaction term between level of respiratory support and treatment assignment [30].

In an open-label RCT conducted in 146 outpatients with mild COVID-19, inhaled budesonide was compared to standard care alone [31]. The primary endpoint was

emergency department assessment or hospitalization for COVID-19. In the intention-to-treat population, the primary endpoint was registered in 15% and 3% of patients in the usual care alone and budesonide arms, respectively (difference 0.12, with 95% CI from 0.03 to 0.21). In the per-protocol population, the primary endpoint was registered in 14% and 1% of patients in the usual care alone and budesonide arms, respectively (difference 0.13, with 95% CI from 0.04 to 0.22). The trial was halted prematurely due to unlikeliness of variation of results with further enrollment.

A multicenter, randomized, open-label, three-group, controlled trial was conducted to assess the efficacy and safety of azithromycin plus hydroxychloroquine administration in 504 hospitalized patients with confirmed COVID-19 [32]. Patients were randomly assigned in a 1:1:1 ratio to receive: (*i*) standard care; (*ii*) standard care plus hydroxychloroquine at the dosage of 400 mg twice daily for 7 days; (*iii*) standard care plus hydroxychloroquine at the dosage of 400 mg twice daily plus azithromycin at the dosage of 500 mg once daily for 7 days. Patients enrolled in this trial were receiving either no supplemental oxygen or a maximum of 4 liters per minute of supplemental oxygen. The primary outcome was clinical status at 15 days assessed with the use of a seven-level ordinal scale. No beneficial effect with respect to the primary outcome was found for azithromycin plus hydroxychloroquine administration in comparison to standard care (OR 0.99, with 95% CI from 0.57 to 1.73).

In an open-label, multi-arm, adaptive RCT, outpatients with suspected COVID-19 aged ≥ 65 years, or ≥ 50 years with at least one comorbidity, who had been unwell for ≤ 14 days were randomized to azithromycin 500 mg daily for 3 days plus usual care, usual care plus other interventions (results for other interventions will be provided subsequently in other manuscripts), or usual care alone [33]. The two coprimary endpoints were time to first self-reported recovery, and COVID-19-related hospital admission or death. Overall, 500 patients receiving azithromycin and 823 patients receiving usual care alone were included in the primary analysis. Azithromycin was not associated with better time to first reported recovery

compared with usual care alone (HR 1.08, with 95% Bayesian credibility interval from 0.95 to 1·23). Sixteen out of 500 outpatients (3%) in the azithromycin arm and 28 out of 823 outpatients (3%) in the usual care alone arm were hospitalized (absolute benefit in percentage 0.3%, with 95% Bayesian credible interval from –1.7 to 2.2). No death was observed, and safety was similar across arms. Of note, 1148/1388 subjects (83%) had a SARS-CoV-2 molecular result available, and only 434 subjects (31% of the entire population) had a positive result (no superiority of azithromycin was also observed in subgroup analysis in confirmed COVID-19 cases, which is consistent with the primary study results, although a larger imprecision of estimates should be taken into account).

In a pre-planned interim analysis of a double-blind RCT evaluating the efficacy of bamlanivimab in outpatients with mild to moderate COVID-19, a total of 495 subjects were randomized to receive a single dose (at three possible different dosages) of bamlanivimab or placebo [34]. Patients who receive a dosage of 2800 mg of bamlanivimab showed a better mean decrease in viral load from baseline (primary endpoint), assessed at day 11 (difference in log viral load −0.53, with 95% CI from −0.98 to −0.08). Of note, no acceleration in the natural decrease of viral load (observed also in the placebo group) was registered for the other bamlanivimab dosages (700 mg and 7000 mg). Overall, 1.6% and 6.3% COVID-19-related hospitalizations/emergency department visits were registered in bamlanivimab and placebo arms, respectively. AEs were similar between arms and no serious AEs were registered in patients receiving bamlanivimab. Subsequently, full results of the trial, including among a total of 531 patients also those receiving the combination of bamlanivimab plus etesevimab, were released [35]. The previous positive results with respect to the primary endpoint were not confirmed for the 2800 mg dose of bamlanivimab (difference in log viral load 0.31, with 95% CI from –0.13 to 0.76), whereas a positive effect was detected for the combination of 2800 mg of bamlanivimab and 2800 mg of etesevimab (difference in log viral load –0.57, with 95% CI from –1.00 to –0.14) [35]. Overall, 0.9% and 5.8% COVID-19-

related hospitalizations/emergency department visits were registered in bamlanivimab plus etesevimab and placebo arms, respectively. In post-hoc subgroup analyses, these results were maximized in patients aged ≥ 65 years or with a body mass index ≥ 35 or greater (0% hospitalization vs. 13.5% in the placebo group). Only one serious AE was detected in the combination arm (a urinary tract infection that was deemed as unrelated to treatment).

In a preplanned interim analysis of a double-blind RCT evaluating the efficacy of the casirivimab/imdevimab combination in outpatients with non-severe COVID-19 and recent onset of symptoms (<7 days), a total of 275 subjects were randomized to receive a single dose (at two possible different dosages) of casirivimab/imdevimab or placebo [36]. The primary endpoints were: (*i*) the time-weighted average viral load change from day 1 through day 7; and (*ii*) the percentage of patients with at least one Covid-19–related medical visit through day 29. The least-squares mean difference in the time-weighted viral load average change was −0.41 $\log_{10}$ cp per mL, with 95% CI from −0.71 to −0.10. This effect was maximized in the subgroup of patients who were serum-antibody negative at the baseline (least-squares mean difference in the time-weighted viral load average change −0.56 $\log_{10}$ cp per mL, with 95% CI from −1.02 to −0.11). Overall, 6% and 3% medical visits were registered in casirivimab plus imdevimab and placebo arms, respectively. The safety outcomes were similar between arms.

In a double-blind RCT conducted in 243 high-risk outpatients with COVID-19, sulodexide was compared with placebo (within 3 days form symptoms onset) with respect to a primary endpoint of need of hospital care [37]. Overall, 17.7% and 29.4% of patients in sulodexide and placebo arms required hospitalization, respectively.

With regard to RCTs assessing the efficacy of ivermectin administration in outpatients with mild COVID-19, in a small open-label RCT of 50 patients, ivermectin was compared to usual care alone, with 36% and 40% of patients in ivermectin and usual care group becoming symptomatic by day 7 [38]. In a double-blind RCT of 24 outpatients with COVID-

19, no difference was observed between ivermectin and placebo in terms of the primary outcome of PCR positive patients (relative risk 0.92, with 95% CI from 0.77 to 1.09) [39]. In another double-blind RCT of 400 outpatients and inpatients with mild to moderate COVID-19, ivermectin plus doxycycline were compared to placebo with respect to a primary endpoint of duration from treatment to clinical recovery, with the median recovery time being 7 and 9 days in ivermectin/doxycycline and placebo arms, respectively (HR 0.73, with 95% CI from 0.60 to 0.90) [40]. In an open-label study of 62 outpatients with mild to moderate COVID-19, ivermectin was compared to usual care with respect to a primary endpoint of time to symptoms resolution, with resolution being observed after a median time of 10.1 e 11.5 days in the intervention and usual care arms, respectively (95% CI for difference from -0.9 to 3.6) [41]. Finally, in a large, double-blind RCT of 400 outpatients and inpatients with mild COVID-19, ivermectin was compared to placebo with respect to a primary endpoint of time to resolution of symptoms, with the median time to resolution being 10 and 12 days in the ivermectin and placebo arms, respectively (HR 1.07, with 95% CI from 0.87 to 1.32) [42].

Results of a trial of peginterferon Lambda 1a vs. placebo in 120 outpatients with mild to moderate COVID-19 show no advantages of peginterferon administration in terms of duration of viral shedding or symptoms improvement [43].

Question 2. GRADE tables

Recommendation:

Based on available results from RCTs, we do not recommend the administration of hydroxychloroquine in outpatients with COVID-19

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
4 studies [25-28]	RCTs	No serious risk of bias, although it should be noted that in one study the primary population also included patients with suspected COVID-19	No serious inconsistency	No serious indirectness	Serious imprecision	No serious risk of publication bias	Moderate

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.

Recommendation:

We do not recommend the use of corticosteroids in outpatients with COVID-19, unless needed for other medical reasons

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:

In the absence of proven bacterial infections, the administration of antibiotics in outpatients with COVID-19 should be considered only as empirical treatment of highly suspected bacterial coinfection or superinfections

Number of studies	Studies design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
1 study [33]**	RCT	No serious risk of bias	Unable to assess (only one study included)	Serious indirectness (only 31% of the study population had confirmed COVID-19 by molecular test)	Serious imprecision (only a part of the entire cohort had confirmed COVID-19)	No serious risk of publication bias	Very low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.
** GRADE system used only for azithromycin.

Recommendation:

At the present time, antivirals should not be administered in outpatients with COVID-19 outside RCTs

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:

The use of neutralizing monoclonal antibodies may be considered in COVID-19 outpatients with mild/moderate diseases at risk of progression and within ≤ 10 days after symptoms onset

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
3 studies [34-36]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	No serious risk of publication bias	Low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.

QUESTION 3

Should anticoagulant agents be administered to inpatients with COVID-19?

Question 3. Search strings and databases

Pubmed

(heparin[Text Word] OR thrombosis[Text Word] OR anticoagulation[Text Word] OR anticoagulant[Text Word] OR "venous thromboembolism"[Text Word] OR emboli[Text Word] OR thromboprophylaxis[Text Word] OR DOAC[Text Word] OR "novel oral anticoagulant"[Text Word] OR "direct oral anticoagulant*"[Text Word] OR rivaroxaban[Text Word] OR betrixaban[Text Word] OR Edoxaban[Text Word] OR dabigatran[Text Word] OR apixaban[Text Word] OR "Vitamin K antagonist"[Text Word] OR hypercoagulability[Text Word] OR Coagulopathy[Text Word] OR Thromboembolic[Text Word] OR thrombotic[Text Word] OR Dalteparin[Text Word] OR Enoxaparin[Text Word] OR LMWH[Text Word] OR fondaparinux[Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])*

Embase

(heparin:ti,ab,kw OR thrombosis:ti,ab,kw OR anticoagulation:ti,ab,kw OR anticoagulant:ti,ab,kw OR 'venous thromboembolism':ti,ab,kw OR emboli:ti,ab,kw OR thromboprophylaxis:ti,ab,kw OR doac:ti,ab,kw OR 'novel oral anticoagulant':ti,ab,kw OR 'direct oral anticoagulant*':ti,ab,kw OR rivaroxaban:ti,ab,kw OR betrixaban:ti,ab,kw OR edoxaban:ti,ab,kw OR dabigatran:ti,ab,kw OR 'apixaban vitamin k antagonist':ti,ab,kw OR hypercoagulability:ti,ab,kw OR 'coagulopathy thromboembolic':ti,ab,kw OR thrombotic:ti,ab,kw OR dalteparin:ti,ab,kw OR enoxaparin:ti,ab,kw OR lmwh:ti,ab,kw OR*

fondaparinux:ti,ab,kw) AND ('covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)

Cochrane COVID-19 Study Register

anticoagulant OR heparin OR anticoagulation OR antithrombotic OR thrombosis OR coagulopathy OR emboli

– filter: report results

Question 3. Literature review details

Search strings development:

Dejan Radovanovic

Andrea Gramegna

Elena Tagliabue

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

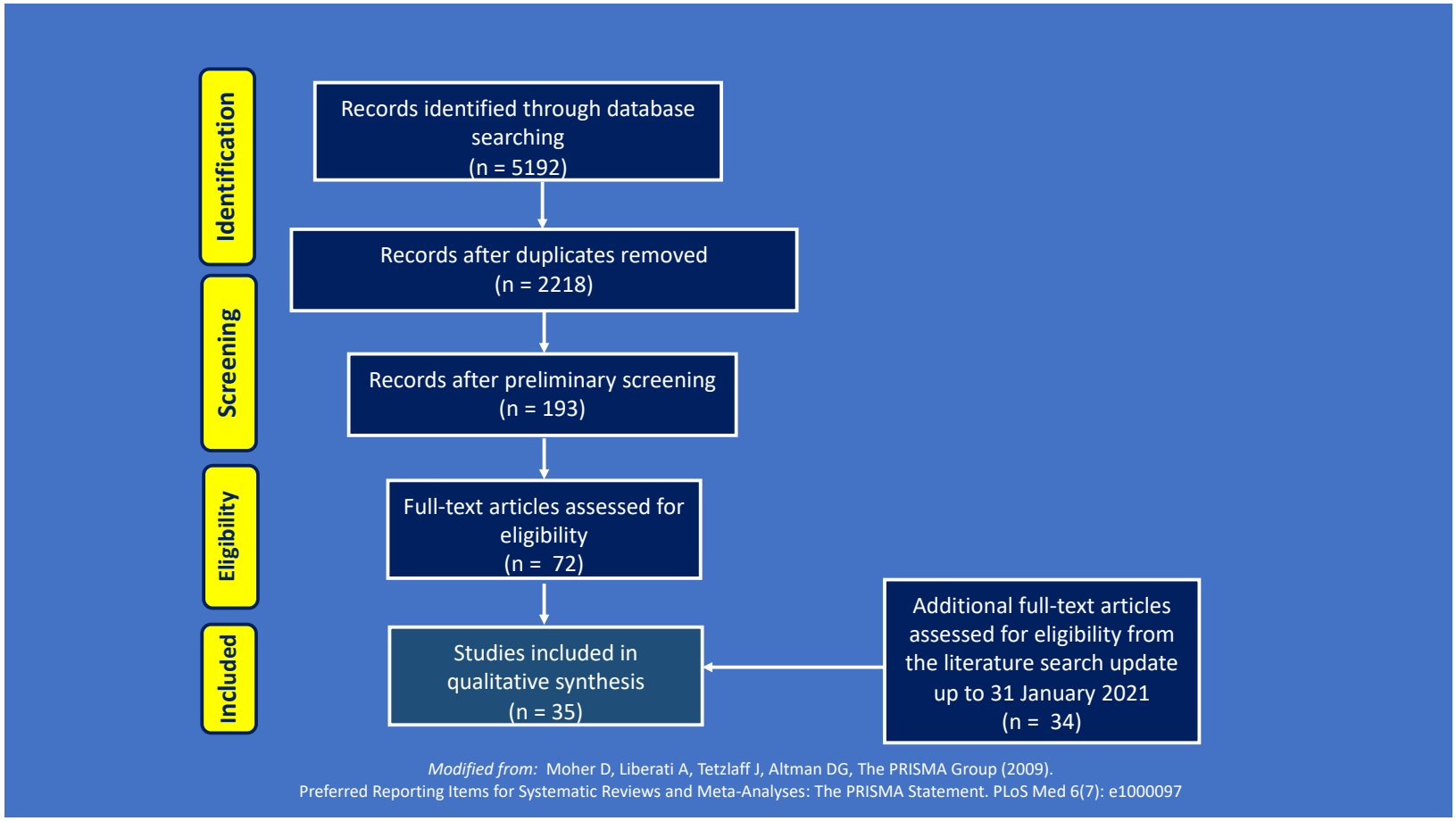
Dejan Radovanovic

Andrea Gramegna

Third reviewer for resolving possible disagreements:

Elena Tagliabue

Question 3. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 1641 de-duplicated records, with the ultimate evaluation of 34 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 3 randomized controlled trials (RCTs) were evaluated during the final literature search update up to 30 April 2021. Overall, 35 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 3. Extended evidence summary

Retrieved studies are divided in different sections according to the relevant comparison for the study primary endpoint/s.

Comparison of anticoagulant agents vs. no anticoagulant agents

In a retrospective, single-center study including 1376 hospitalized patients with COVID-19, 780 (56.7%) received at least a prophylactic dosage of enoxaparin (defined as receiving at least one dose of enoxaparin) during the hospitalization and 596 (43.3%) patients did not receive enoxaparin [44]. The primary outcome measure was in-hospital mortality. Intensive care unit (ICU) admission was a secondary outcome measure. In-hospital mortality was 25.7% (354/1376). Overall, prophylactic and therapeutic dosages were administered to 61.0% and 39.0% of patients receiving enoxaparin. Receipt of enoxaparin was associated with reduced in-hospital mortality in a propensity score-adjusted multivariable logistic regression model (OR 0.53, with 95% C] 0.40-0.70). ICU admission occurred in 10.4% and 11.0% of patients receiving and not receiving enoxaparin, respectively. Nonetheless, despite these similar unadjusted frequencies, receipt of enoxaparin was associated with reduced ICU admission in a propensity score-adjusted multivariable logistic regression model (OR 0.48, with 95% CI from 0.32 to 0.69). Thrombotic complications were observed in 2.2% and 2.5% of patients not receiving enoxaparin and receiving enoxaparin at prophylactic dosage, respectively. Hemorrhagic complications were observed in 2.5%, 1.2%, and 3.2% of patients not receiving enoxaparin, receiving enoxaparin at prophylactic dosage, and receiving enoxaparin at therapeutic dosage, respectively.

In a retrospective, single-center study including 413 hospitalized patients with COVID-19, 187 (45.3%) received low molecular weight heparin (LMWH) during the hospitalization and 226 (54.7%) patients did not receive LMWH [45]. In this study, patients receiving LMWH, those with a serum d-dimer levels lower than 1 μg/mL were given LMWH

at prophylactic dosage, whereas those with a serum d-dimer levels higher than 1 μg/mL and/or with severe COVID-19 were given LMWH at therapeutic dosage. In this study, admission to ICU occurred in 0.0% (0/187) and 2.7% (6/226) of patients receiving and not receiving LMWH (Fisher exact test, p = 0.031). No deaths were observed. Two patients among those not receiving LMWH developed pulmonary embolism. No information regarding possible hemorrhagic complications was reported.

In a retrospective, multicenter study including 2075 hospitalized patients with COVID-19, data regarding administration of heparin (formulations not further specified) was available for 2019 patients (97.3%) [46]. Overall, 1734 patients (85.9%) received LMWH during the hospitalization and 285 (14.1%) patients did not receive heparin [36]. No information regarding the distribution of patients in non-ICU and ICU words was reported. Death was registered in 14.0% (242/1734) and 15.4% (44/285) of patients receiving and not receiving heparin, respectively. In a logistic regression model adjusted for age and gender, receipt of heparin was associated with lower mortality (OR 0.55, with 95% CI from 0.37 to 0.82, p = 0.003). The association was retained also when other covariates such as oxygen saturation <90% or antiviral and immunomodulatory treatments were included in the multivariable model. No information regarding occurrence of thrombotic or hemorrhagic events was reported.

In a retrospective, multicenter study including 3625 hospitalized patients with COVID-19, 58.8% received standard thromboprophylaxis, 4.0% received high-dose prophylaxis, and 19.6% received therapeutic anticoagulant agents [47]. Overall, the preferred agents for prophylaxis were subcutaneous unfractionated heparin (42.7%) and enoxaparin (32.9%), whereas apixaban was the preferred agent for anticoagulant therapy (66.8%). Only 7% of patients were admitted to ICU at baseline. Overall, apixaban prophylaxis (OR 0.46, with 95% CI from 0.30 to 0.71, p = 0.001), apixaban therapy (OR 0.57, with 95% CI from 0.38 to 0.85, p = 0.006), and enoxaparin prophylaxis (OR 0.49, with 95% CI from 0.32 to 0.73, p = 0.001)

were independently associated (as dummy variable with no anticoagulant agents as the reference group) with reduced mortality in the entire study population by employing a multivariable logistic regression model. Data regarding baseline d-dimer levels were available for 2450/3625 patients (67.6%). In the subgroup of patients with d-dimer levels < 1 μg/mL (n = 779), apixaban prophylaxis (OR 0.87, with 95% CI from 0.26 to 2.88, p = 0.82), enoxaparin prophylaxis (OR 0.93, with 95% CI from 0.31 to 2.81, p = 0.89), and unfractionated heparin prophylaxis (OR 2.20, with 95% CI from 0.76 to 6.38, p = 0.15) were not associated with reduced mortality (as were also not associated their therapeutic regimens). In the subgroup of patients with d-dimer levels 1-2 μg/mL (n = 991), apixaban prophylaxis (OR 0.49, with 95% CI from 0.25 to 0.94, p = 0.033), apixaban therapy (OR 0.48, with 95% CI from 0.23 to 0.97, p = 0.041), enoxaparin prophylaxis (OR 0.50, with 95% CI from 0.26 to 0.96, p = 0.036), and unfractionated heparin therapy (OR 0.22, with 95% CI 0.05–0.90, p = 0.035) were associated with reduced mortality. In the subgroup of patients with d-dimer levels 3-9 μg/mL (n = 439), despite a general trend towards protection (OR for mortality < 1 for all agents, with the exclusion of high-dose unfractionated heparin prophylaxis), no anticoagulant prophylactic/therapeutic regimens showed a statistically significant association with mortality. In the subgroup of patients with d-dimer levels ≥ 10 μg/mL (n = 269), apixaban therapy (OR 0.26, with 95% CI from 0.09 to 0.70, p = 0.008) and enoxaparin prophylaxis (OR 0.15, with 95% CI from 0.04 to 0.62, p = 0.008) were associated with reduced mortality. The study did not report information on possible thrombotic complications. With regard to possible hemorrhagic complications, all the different prophylactic and therapeutic regimens reported above were not independently associated (as a unique dummy variable with no antithrombotic agents as the reference group) with bleeding (defined as transfusion requirement) in a multivariable logistic regression model.

A retrospective, single-center study included 258 hospitalized patients with COVID-19 not requiring invasive mechanical ventilation, but with radiological evidence of bilateral

pneumonia and at least one of the following: (*i*) respiratory rate ≥ 30 breaths per minute; (*ii*) peripheral oxygen saturation ≤ 93%; (*iii*) ratio of the partial pressure of oxygen in arterial blood to the fractional concentration of oxygen (PaO2/FiO2) at room air ≤ 300 mmHg [48]. In unadjusted Kaplan-Meier curves of cumulative survival comparing different schemes vs. no anticoagulant agents, standard prophylactic enoxaparin dosages were not associated with improved survival, whereas a favorable association was observed for higher enoxaparin dosages. A favorable association was also observed for the combination of enoxaparin plus direct oral anticoagulant agents. No information regarding possible thrombotic or hemorrhagic complications was reported.

In a prospective, single-center study including 108 hospitalized patients with COVID-19 aged 65 years or older, 61/108 (56.5%) received anticoagulant agents at prophylactic dosage (type of agents not further specified), 32/108 (29.6%) received anticoagulant agents at therapeutic dosages (type of agents not further specified), and 15/108 (13.9%) received no antithrombotic agents [49]. In a multivariable Cox regression model, anticoagulant agents were included as a dummy variable. With therapeutic dosages as the reference category, no receipt of anticoagulant agents was associated with increased mortality (HR 4.20, with 95% CI from 1.36 to 12.9), whereas prophylactic dosages were not (HR 1.20, with 95% CI from 0.43 to 3.31). The overall p for the dummy variable was 0.02. No information regarding ICU admission or thrombotic/hemorrhagic complications was reported.

In a retrospective, single-center study including 575 patients with COVID-19 admitted to the hospital emergency department (of whom 7.1% were rapidly discharged because of mild symptoms, 82% were hospitalized in non-ICU wards, and 10.9% required ICU admission at baseline) [50]. Overall, 240/575 patients received LMWH at prophylactic dosage in the emergency department (41.7%). In-hospital mortality was 20.9% (120/575). In a multivariable logistic regression model, administration of LMWH in the emergency

department was associated with reduced mortality (OR 0.4, with 95% CI from 0.2 to 0.6, p < 0.001). No information regarding thrombotic/hemorrhagic complications was reported.

In a retrospective, multicenter study including 1240 hospitalized patients with COVID-19, the primary outcome measure was development of a thrombotic complication (pulmonary embolism) [51]. Transfer to ICU (although information on whether it occurred before or after start of anticoagulant agents) was necessary in 14.9% of patients (185/1240). Anticoagulation agents at prophylactic dosage during hospitalization (daily LMWH or twice daily subcutaneous unfractionated heparin) were administered to 63.0% of patients for whom the information was available (738/1172). Already existing pre-admission therapy with anticoagulant agents was present in 11% of patients (136/1240). In a multivariable logistic regression model, both prophylactic anticoagulation introduced during hospitalization (OR 0.83, with 95% CI from 0.79 to 0.85, p < 0.001) and pre-existing therapeutic anticoagulation (OR 0.87, with 95% CI from 0.82 to 0.92, p < 0.001) were associated with a reduced risk of pulmonary embolism.

A retrospective, single-center study included 127 hospitalized patients with COVID-19 who died during hospitalization because of COVID-19-related reasons. The primary time-to-event endpoint was time to in-hospital death [52]. Overall, 47/127 patients (37.0%) received anticoagulant agents (subcutaneous unfractionated heparin, subcutaneous enoxaparin) at prophylactic dosage, 67/127 patients (52.8%) received anticoagulation agents (intravenous unfractionated heparin, subcutaneous enoxaparin, or pre-existing oral anticoagulation with warfarin or direct anticoagulation agents) at therapeutic dosage, and 13/127 patients (10%) received no anticoagulation agents. ICU admission, although not specified if occurred before or after initiation of anticoagulation agents, was necessary in 59% of patients (75/127). In a multivariable Cox regression model, both prophylactic anticoagulation (HR 0.29, with 95% CI from 0.15 to 0.58, p < 0.001) and therapeutic anticoagulation (HR 0.15, with 95% CI from 0.07 to 0.32, p < 0.001), compared with no

anticoagulation as reference, were associated with delayed time to death. In a subgroup analysis in patients not admitted to ICU (40.9%, 52/127), both prophylactic anticoagulation (HR 0.36, with 95% CI from 0.16 to 0.80, p = 0.014) and therapeutic anticoagulation (HR 0.27, with 95% CI from 0.08 to 0.55, p = 0.001) retained an association with time to death.

In a retrospective, single-center study including 388 hospitalized patients with COVID-19, the primary endpoint was development of thromboembolic complications [53]. Overall, 16% of patients (61/388) required ICU admission. Among patients not requiring ICU admission, anticoagulant agents (LMWH) at prophylactic dosage were administered in 41% of cases, anticoagulant agents at intermediate dosage were administered in 21% of cases, anticoagulant agents at therapeutic dosage were administered in 23% of cases, and no anticoagulant agents were administered in 15% of cases. Thromboembolic complications occurred in 20/246 non-ICU patients (8.1%), with 11/20 events (55%) occurring in the small fraction of patients not receiving anticoagulation agents. No formal comparison of risk for thromboembolic complications between patients receiving and not receiving anticoagulation agents was performed.

In a retrospective, single-center study including 761 hospitalized patients with COVID-19, 186 received LMWH (25%) [54]. Of them, 109 (58.6%) and 77 (41.4%) received prophylactic and therapeutic dosages, respectively. Invasive mechanical ventilation was required only in 4% of patients, although it was not specified in how many cases ventilation was started before or after initiation of anticoagulant agents. In a multivariable Cox regression analysis, LMWH use (including both prophylactic and therapeutic dosages) was associated with reduced mortality (HR 0.22, with 95% CI from 0.09 to 0.55). Clinically relevant bleeding events in patients not subjected to invasive mechanical ventilation occurred in 1.1% and 0.18% of patients receiving LMWH and patients not receiving LMWH, respectively.

In a retrospective, multicenter study including 844 hospitalized patients with COVID-19, 65 were already taking oral anticoagulant agents prior to hospitalization for other medical reasons (7.7%) [55]. Of them, 22 were taking vitamin-K antagonists (33.8%), whereas 43 were taking direct oral anticoagulants (66.2%). Overall, 394/844 patients (46.7%) received heparin (not further specified in terms of agents and prophylactic/therapeutic dosage), including 56.7% of patients shifted to heparin from those previously taking anticoagulant agents. Only 5.4% of patients required ICU admission, although it was not specified in how many cases ICU admission occurred before or after initiation of heparin. In a multivariable logistic regression model, receipt of heparin was associated with improved survival to discharge (OR for mortality 0.60, with 95% CI from 0.38 to 0.94, $p < 0.001$), while no association with mortality was observed for use of oral anticoagulant agents. Mortality was 44.6% and 19.8% in patients receiving oral anticoagulant agents and in patients not receiving oral anticoagulant agents, respectively. No information was reported regarding possible hemorrhagic complications.

A retrospective, single-center study included 449 hospitalized patients with severe COVID-19 [56]. Severe disease was defined in presence of at least one of the following: (*i*) respiratory rate ≥ 30 breaths/min; (*ii*) arterial oxygen saturation ≤93% at room air; (*iii*) PaO2/FiO2 ≤ 300 mmHg. Information about the distribution of patients in ICU and non-ICU wards was not reported. Overall, 99 patients (22.0%) received anticoagulant agents at either prophylactic or therapeutic dosage (enoxaparin or unfractionated heparin) for at least 7 days. In the entire cohort, mortality was 30.3% and 29.7% in patients receiving at least 7 days of anticoagulant agents and in patients receiving less than 7 days or not receiving anticoagulant agents, respectively. In subgroup analyses, an imbalance in mortality was observed in the subgroup of patients with serum d-dimer levels > 3.0 μg/mL, with mortality being 32.8% and 52.4% in patients receiving at least 7 days of anticoagulant agents and in patients receiving less than 7 days or not receiving anticoagulant agents, respectively.

Bleeding complications were described as unusual and commonly mild, but no further details were provided. No information regarding thrombotic complications was reported.

In a retrospective, multicenter study, 450 hospitalized patients with COVID-19 in non-ICU wards were divided in two groups: (i) those receiving anticoagulant therapy (n = 140, mainly LMWH, either at prophylactic or therapeutic dosage); (ii) those not receiving anticoagulant agents (n = 310) [57]. The development of thrombotic complications was registered in 4/140 (3%) and 15/310 (5%) patients receiving and not receiving anticoagulant agents, respectively. Mortality was 22% (31/140) and 14% (42/310) in patients receiving and not receiving anticoagulant agents, respectively.

In a retrospective, multicenter study including 2574 hospitalized patients with COVID-19, treatment with heparin (mainly LMWH, either at prophylactic or therapeutic dosages) was registered in 70% of patients. Overall, heparin treatment was associated with reduced mortality in a multivariable, propensity score-adjusted Cox regression model (HR 0.60, with 95% CI from 0.49 to 0.74) [58].

In a multicenter, prospective study among 315 hospitalized patients with COVID-19 pneumonia, treatment with LMWH (either at prophylactic or therapeutic dosages) as a time-dependent covariate was independently associated with reduced mortality in a multivariable Cox regression model (adjusted HR 0.36, with 95% CI from 0.21 to 0.6, $p < 0.001$) [59]. Overall, major bleeding events were observed in 11 patients (4.5%).

In a retrospective, multicenter study including 3480 hospitalized patients with COVID-19, both receipt of prophylactic anticoagulant agents vs. no anticoagulant agents (adjusted HR 0.35, with 95% CI from 0.22 to 0.54) and receipt of therapeutic anticoagulant agents vs. no anticoagulant agents (adjusted HR 0.14, with 95% CI from 0.08 to 0.23) were associated with improved survival in a propensity-score adjusted, multivariable Cox regression model [60]. Overall, major bleeding events were observed in 20 (5.5%), 46 (2.2%), and 81(8.1%)

patients receiving no anticoagulants, prophylactic anticoagulants, and therapeutic anticoagulants, respectively.

In a retrospective, single center study including 162 hospitalized patients who underwent computed tomography pulmonary angiography for severe disease, the primary endpoint was presence of pulmonary embolism [61]. In multivariable analysis, any anticoagulant regimen (either prophylactic or therapeutic) was independently associated with reduced mortality in multivariable analysis (OR 4.5, with 95% CI from 1.1 to 7.4).

In a retrospective single center study including 355 hospitalized patients with COVID-19, the primary endpoint was development of major bleeding, that was observed in 4% (7/178), 5% (1/20), and 11% (11/102) of patients receiving prophylactic, subtherapeutic, and therapeutic dosages of anticoagulant agents, respectively [62]. Major bleeding was observed also in 2% (1/55) of patients not receiving anticoagulant agents.

In a retrospective, single center study of 34 hospitalized patients with COVID-19 aged 90 years or older, Kaplan-Meier survival curves showed a difference in survival between patients receiving or not receiving LMWH either at prophylactic or therapeutic dosages ($p < 0.0001$) [63].

In a retrospective, single center study including 525 hospitalized patients with COVID-19, administration of LMWH (either at prophylactic or therapeutic dosages) was associated with increased mortality in univariable analysis (OR 2.21, with 95% CI from 1.30 to 3.77) [64]. However, when adjusting for severity of disease, the effect was favorable (OR 0.20, with 95% CI from 0.09 to 0.46). This latter effect was also confirmed in a propensity score-weighted model (OR 0.18, with 95% CI from 0.10 to 0.30).

In a retrospective, multicenter study including COVID-19 patients admitted to cardiology units, receipt of heparin (either at prophylactic or therapeutic dosage) during hospitalization (information available for 364 patients), was associated with reduced

mortality both in unadjusted (HR 0.57, 95% CI from 0.41 to 0.81) and adjusted (HR 0.41, with 95% CI from 0.25 to 0.67) Cox regression models [65].

In a retrospective, single center study including 289 hospitalized patients with COVID-19, lack of prophylaxis with anticoagulants (either LMWH or unfractionated heparin) was associated with an increased risk of thromboembolic complications both in unadjusted (OR 12.03, with 95% CI from 5.31 to 27.23) and adjusted (OR 27.85, with 95% CI from 9.35 to 82.95) logistic regression models [66].

Comparison of anticoagulant agents at prophylactic dosage vs. anticoagulant agents at therapeutic dosage

A retrospective, single-center study included 81 patients with COVID-19 hospitalized in a geriatric ward (median age 88 years), all receiving anticoagulant agents (unfractionated heparin, fondaparinux, or enoxaparin) at either prophylactic dosage (57/81, 70.4%) or therapeutic dosage (24/81, 29.6%) at the discretion of the treating physicians (based on clinical, radiological, and/or laboratory data in a non-standardized fashion) [67]. Overall crude mortality was 50% both in patients receiving prophylactic dosages and in patients receiving therapeutic dosages. In a multivariable Cox regression model, therapeutic dosages were not associated with improved survival in comparison with prophylactic dosages (HR 0.89, with 95% CI from 0.30 to 2.71, p = 0.84). No information regarding ICU admission or thrombotic/hemorrhagic complications was reported.

In a retrospective, single-center study including 59 hospitalized patients with severe COVID-19 pneumonia, 20 (33.9%) received enoxaparin at prophylaxis dosage and 39 (66.1%) received enoxaparin at therapeutic dosage for suspected thromboembolic complications [68]. ICU admission was more frequent in patients receiving therapeutic dosages than in those receiving prophylactic dosages (64.1% vs. 25.0%, respectively, chi square test p = 0.004), although it is unclear in how many cases ICU admission was an

outcome or a baseline condition. Overall, mortality was 0.0% (0/20) and 7.7% (3/39) in patients receiving prophylactic and therapeutic dosages, respectively (Fisher exact test p = 0.54). Bleeding occurred in 0.0% (0/20) and 7.7% (3/39) of patients receiving prophylactic and therapeutic dosages, respectively (Fisher exact test p = 0.54).

In a retrospective, single-center study including 402 hospitalized patients with COVID-19, 250/402 received anticoagulant agents at prophylactic dosage (62.2%) and 152/402 received anticoagulant agents at therapeutic dosage (37.8%) [69]. Anticoagulant agents employed in this study were unfractionated heparin, enoxaparin, and direct oral anticoagulants. Overall, 108/402 patients required ICU admission (26.9%), although it was not specified in how many cases this occurred before or after initiation of anticoagulant agents. The primary endpoint was in-hospital mortality. Although in-hospital mortality was higher in patients receiving therapeutic dosages than in those receiving prophylaxis dosages (34.8% vs. 15.2%, respectively), in a multivariable logistic regression model adjusted for other covariates including disease severity, therapeutic dosages were not associated with increased mortality in comparison with prophylaxis dosages (effect size for the multivariable model not reported in detail). Nearly 9% of patients receiving therapeutic dosages experienced a clinically significant bleeding or thrombocytopenia vs. 3% of those receiving prophylactic dosages.

In a retrospective, single-center study including 2773 hospitalized patients with COVID-19, 786 received anticoagulant agents (not further specified) at therapeutic dosage (28.3%) [70]. No differentiation between patients receiving prophylactic dosages and patients receiving no anticoagulant agents was provided (among patients not receiving therapeutic dosages). Invasive mechanical ventilation was necessary in 29.8% and 8.2% of patients receiving therapeutic dosages and patients not receiving therapeutic dosages, respectively, although it was not specified in how many cases intubation occurred before or after initiation of anticoagulation agents. The primary endpoint was in-hospital mortality,

which was 22.5% and 22.8% in patients receiving therapeutic dosages and in patients not receiving therapeutic dosages, respectively. In a multivariate Cox regression model, therapeutic dosages were associated with delayed mortality (HR 0.86, with 95% CI from 0.82 to 0.89, $p < 0.001$). Bleeding events were observed in 3% and 1.9% of patients receiving therapeutic dosages and patients not receiving therapeutic dosages, respectively.

In a retrospective, single-center study including 324 hospitalized patients with COVID-19, 240 received anticoagulant agents at prophylactic dosage (74.1%) and 84 received anticoagulant agents at higher, subtherapeutic dosage (25.9%) [71]. Anticoagulant agents employed in this study were unfractionated heparin, enoxaparin, and direct oral anticoagulants. The primary endpoint was a composite of major bleedings and clinically relevant non-major bleeding. In this study, higher, subtherapeutic dosages were associated with an increased risk of the primary composite endpoint in comparison to standard prophylactic dosages (HR 3.89, with 95% from 1.90 to 7.97, $p < 0.001$). Subsequent ICU admission was necessary in 27.4% and 2.9% of patients receiving prophylactic dosages and patients receiving higher, subtherapeutic dosages, respectively. Mortality was 6.3% and 16.7% in patients receiving prophylactic dosages and in patients receiving higher, subtherapeutic dosages, respectively. Venous thromboembolism developed in 2.5% and 3.6% of patients receiving prophylactic dosages and patients receiving higher, subtherapeutic dosages, respectively.

In a retrospective, single-center study including 115 hospitalized patients with COVID-19, 64 patients (55.6%) and 45 patients (39.1%) received anticoagulant agents at prophylactic (fondaparinux or enoxaparin) or therapeutic (enoxaparin, warfarin, or direct oral anticoagulant agents) dosages, respectively [72]. No information was reported for the remaining 6 patients (5.2%). ICU admission was necessary in 26.1% of patients, although it was not specified in how many cases it occurred before or after initiation of anticoagulant agents. In-hospital mortality was 16.5% (19/115). In a multivariable logistic regression

model, anticoagulant agents at therapeutic dosage were associated with reduced mortality (OR 0.06, with 95% CI from 0.01 to 0.39, p = 0.03). No information regarding thrombotic or hemorrhagic complications was reported.

In a retrospective, single-center study including 171 hospitalized patients with COVID-19, 61/171 (36%) and 110/171 (64%) received anticoagulant agents (mostly enoxaparin) at prophylactic or intensified dosage (i.e., increased with the increase in d-dimer values, according to a local protocol), respectively [73]. In univariable analysis, the intensified regimen was associated with less thrombotic events (8.2% vs. 24.6%, Fisher exact test p = 0.007) and less ICU admissions (11.8% vs. 28.1%, chi square p = 0.016).

In a retrospective, single-center study including 154 hospitalized patients with severe COVID-19, 98/154 (64%) and 56/154 (36%) received LMWH at prophylactic or therapeutic dosage, respectively [74]. In univariable analysis, the prophylaxis regimen was associated with increased mortality compared with the therapeutic regimen (44.8% vs. 17.9%, p = 0.001). The frequency of ICU admission was similar in patients receiving LMWH at prophylactic or therapeutic dosage (46.9% vs. 50.0%, Fisher exact test p = 0.843). In an adjusted logistic regression model, an independent unfavorable effect on mortality was confirmed for prophylactic vs. therapeutic dosages (OR 6.50, with 95% CI from 2.39 to 17.62, Fisher exact test p = 0.001).

In the previously cited multicenter, retrospective study by Di Castelnuovo and colleagues, an increased instantaneous risk of mortality was observed in hospitalized patients receiving therapeutic vs. prophylactic heparin (adjusted HR 1.54, with 95% CI from 1.06 to 2.25) [58]. Important limitations were the lack of timing of heparin initiation and the reason for administering therapeutic dosages (i.e., possibly for already present thrombotic complications).

In a retrospective, multicenter study including 468 hospitalized patients with COVID-19, 30-day mortality was found to be lower in multivariable analysis (model not shown in the

study) in patients who received high-intensity, subtherapeutic anticoagulants vs. patients receiving standard prophylactic dosages (adjusted relative risk 0.26, with 95% CI from 0.07 to 0.97, p = 0.045) [75].

In a retrospective, single center study including 374 hospitalized patients with COVID-19, therapeutic heparin/enoxaparin (administered preemptively at admission) was found to be associated with increased mortality vs. prophylactic heparin/enoxaparin in multivariable analysis (absolute risk reduction 2.3, with 95% CI from 1.0 to 4.9, p = 0.04) [76]. Similar results were registered in a propensity score-weighted model (absolute risk reduction 2.4, 95% CI from 0.9 to 6.6, p = 0.09).

In an already cited retrospective single center study including 355 hospitalized patients with COVID-19, the primary endpoint was development of major bleeding, that was observed in 4% (7/178), 5% (1/20), and 11% (11/102) of patients receiving prophylactic, subtherapeutic, and therapeutic dosages of anticoagulant agents, respectively [62].

Recently, combined results of the open-label ATTACC, ACTIV-4a, and REMAP-CAP RCTs have been released in pre-print form [77], showing a higher probability (Bayesian statistical models) of organ support-free days and survival compared to thromboprophylaxis in non-critically ill COVID-19 patients, independent of D-dimer values. The same was not observed for critically ill COVID-19 patients, with enrollment having been discontinued for futility [78].

Comparison of different anticoagulant agents

In a retrospective, multicenter study including 120 patients with COVID-19 hospitalized in internal medicine wards, 74 received prophylactic enoxaparin (61.7%) and 46 received prophylactic fondaparinux (38.3%) [79]. The primary outcome measures were: (*i*) a composite of major bleeding and clinically relevant non-major bleeding; (*ii*) a composite of pulmonary embolism and deep venous thrombosis. Bleeding events occurred in 4.1% and.

6.5% of patients receiving enoxaparin and fondaparinux, respectively, whereas thromboembolic events occurred in 13.5% and. 6.5% of patients receiving enoxaparin and fondaparinux, respectively. Mortality was 9.5% and 10.9% in patients receiving enoxaparin and fondaparinux, respectively. No information regarding ICU admission or need for invasive mechanical ventilation was reported. Acute respiratory distress syndrome developed in 18.9% and. 15.2% of patients receiving enoxaparin and fondaparinux, respectively.

In a retrospective, single center study of 308 hospitalized patients with COVID-19, anticoagulant prophylaxis with enoxaparin was compared with anticoagulant prophylaxis with fondaparinux in terms of admission to ICU (5% vs. 5%), thrombotic complications (3% vs. 3%), and major bleeding (5% vs. 1%) [80].

Supplementary table S1. Summary of the impact of anticoagulants on major endpoints

Study, year [ref]	Design	No. patients	Endpoint/s of interest for the present review	Anticoagulant agents (dosages)	Effect (95% CI)
Anticoagulant agents vs. no anticoagulant agents					
Albani et al., 2020 [44]	Retrospective	1376	Mortality	Enoxaparin (either prophylactic or therapeutic)	uOR 0.98 (0.77-1.24)* aOR 0.48 (0.32-0.69)
				No enoxaparin	(ref)
Arslan et al., 2020 [45]	Retrospective	413	ICU admission	LMWH (either prophylactic or therapeutic)	uOR 0.09 (0.01-1.62)*
				No LMWH	(ref)
Ayerbe et al., 2020 [46]	Retrospective	2019	Mortality	Heparin	uOR 0.89 (0.63-1.26)* aOR 0.55 (0.37-0.82)
				No heparin	(ref)
Billett et al., 2020 [47]	Retrospective	3625	Mortality	Apixaban (prophylactic)	uOR unavailable aOR 0.46 (0.30-0.71)
				No anticoagulants	(ref)
				Apixaban (therapeutic)	uOR unavailable aOR 0.57 (0.38-0.85)
				No anticoagulants	(ref)
				Enoxaparin (prophylactic)	uOR unavailable

					aOR 0.49 (0.32-0.73)
				No anticoagulants	(ref)
				Enoxaparin (therapeutic)	uOR unavailable aOR 0.83 (0.44-1.56)
				No anticoagulants	(ref)
				UFH (prophylaxis twice daily)	uOR unavailable aOR 0.79 (0.54-1.17)
				No anticoagulants	(ref)
				UFH (prophylaxis thrice daily)	uOR unavailable aOR 1.04 (0.54-1.17)
				No anticoagulants	(ref)
				UFH (therapeutic)	uOR unavailable aOR 0.97 (0.51-1.84)
				No anticoagulants	(ref)
Boari et al., 2020 [48]	Retrospective	258	Mortality	LMWH (prophylactic) LMWH (prophylactic higher dose) LMWH (therapeutic)	Improved survival vs. no anticoagulant agents in Kaplan-Meier curves not observed for standard prophylactic enoxaparin, whereas a favorable association was observed for higher enoxaparin dosages
				No anticoagulants	(ref)

Bousquet et al., 2020 [49]	Prospective	108	Mortality	Anticoagulants (therapeutic)	(ref)
				Anticoagulants (prophylactic)	uHR 1.45 (0.55-3.78) aHR 1.20 (0.43-3.31)
				No anticoagulants	uHR 2.91 (1.00-8.47) aHR 4.20 (1.36-12.9)
Dalager-Pedersen et al., 2020 [57]	Retrospective	450	Mortality	Anticoagulants (either prophylactic or therapeutic)	uOR 1.81 (1.08-3.04)*
				No anticoagulants	(ref)
			Thrombotic complications	Anticoagulants (either prophylactic or therapeutic)	uOR 0.58 (1.19-1.78)*
				No anticoagulants	(ref)
Desai et al., 2020 [50]	Retrospective	575	Mortality	LMWH (prophylactic)	uOR 0.5 (0.3–0.8) aOR 0.4 (0.2-0.6)
				No LMWH	(ref.)
Di Castelnuovo et al., 2020 [58]	Retrospective	2574	Mortality	Heparin (mainly LMWH, either prophylactic or therapeutic)	uHR 0.54 (0.44-0.67) aHR 0.60 (0.49-0.74)**
				No heparin	(ref)
				Heparin (prophylactic)	uHR unavailable aHR 0.40 (0.30-0.52)
				No heparin	(ref)

				Heparin (therapeutic)	uHR unavailable aHR 0.65 (0.46-0.93)
				No heparin	(ref)
Falcone et al., 2020 [59]	Prospective	315	Mortality	LMWH (either prophylactic or therapeutic)	uHR 0.53 (0.35–0.79) aHR 0.61 (0.39–0.95)
				No LMWH	(ref)
Fauvel et al., 2020 [51]	Retrospective	1240	Pulmonary embolism	Anticoagulants (prophylactic)	uOR 0.11 (0.06–0.18) aOR 0.83 (0.79-0.85)
				No anticoagulants	(ref)
Ionescu et al., 2020 [52]	Retrospective	127	Mortality	Anticoagulants (prophylactic)	uHR unavailable aHR 0.29 (0.15-0.58)
				Anticoagulants (therapeutic)	uHR unavailable aHR 0.15 (0.07-0.32)
				No anticoagulants	(ref)
Ionescu et al., 2020 [60]	Retrospective	3480	Mortality	Anticoagulants (prophylactic)	uHR unavailable aHR 0.35 (0.22-0.54)
				Anticoagulants (therapeutic)	uHR unavailable aHR 0.14 (0.08-0.23)
				No anticoagulants	(ref)

Lodigiani et al., 2020 [53]	Retrospective	388	Thromboembolic complications	LMWH (either prophylactic or therapeutic)	No full denominators available for comparison; thromboembolic events occurred in 8.1% of the entire population, but 55% of thromboembolic events occurred in the small fraction of patients not receiving anticoagulation agents.
				No LMWH	(ref)
Mouhat et al., 2020 [61]	Retrospective	162	Pulmonary embolism	Anticoagulants (either prophylactic or therapeutic)	uOR 2.3 (0.9-5.9) aOR 4.5 (1.1-7.4)
				No anticoagulants	(ref)
Musoke et al., 2020 [62]	Retrospective	355	Major bleeding	Anticoagulants (prophylactic)	uOR 2.21 (0.27-18.87)*
				Anticoagulants (higher dose than prophylactic, subtherapeutic)	uOR 2.84 (0.17-47.71)*
				Anticoagulants (therapeutic)	uOR 6.53 (0.82-51.96)*
				No anticoagulants	(ref)
Qin et al., 2020 [54]	Retrospective	761	Mortality	LMWH (either prophylactic or therapeutic)	uHR unavailable aHR 0.22 (0.09-0.55)
				No LMWH	(ref)
Saifi et al., 2021 [63]	Retrospective	34	Mortality	LMWH (either prophylactic or therapeutic)	Improved survival vs. no anticoagulant agents

				No LMWH	observed in Kaplan-Meier curves
Schiavone et al., 2020 [55]	Retrospective	844	Mortality	Heparin (either prophylactic or therapeutic)	uOR unavailable aOR 0.60 (0.38-0.94)
				No heparin	(ref)
Shen et al., 2021 [64]	Retrospective	525	Mortality	LMWH (either prophylactic or therapeutic)	uOR 2.21 (1.30-3.77)*** aOR 0.20 (0.09-0.46)
				No LMWH	(ref)
Tang et al., 2020 [56]	Retrospective	449	Mortality	Anticoagulants (either prophylactic or therapeutic) for at least 7 days	uOR 1.03 (0.63-1.67)*
				No anticoagulants or anticoagulants for less than 7 days	(ref)
Tomasoni et al., 2020 [65]	Retrospective	364	Mortality	Heparin (either prophylactic or therapeutic)	uHR 0.57 (0.41–0.81) aHR 0.41 (0.25–0.67)
				No heparin	(ref)
Prophylactic dosage vs. therapeutic dosage					
Arachchillage et al. 2021 [73]	Retrospective	171	Thrombotic complications	Anticoagulants (intensified regimen according to local protocol)	uOR 0.27 (0.11-0.67)*
				Anticoagulants (prophylactic)	(ref)
			Major bleeding		uOR 1.47 (0.38-5.84)*

				Anticoagulants (intensified regimen according to local protocol)	(ref)
				Anticoagulants (prophylactic)	
			ICU admission		uOR 0.34 (0.15-0.78)*
				Anticoagulants (intensified regimen according to local protocol)	(ref)
				Anticoagulants (prophylactic)	
Bolzetta et al., 2020 [67]	Retrospective	81	Mortality	Anticoagulants (therapeutic)	uHR 1.06 (0.47-2.60) aHR 0.89 (0.30-2.71)
				Anticoagulants (prophylactic)	(ref)
Canoglu et al., 2020 [74]	Retrospective	154	Mortality	LMWH (therapeutic)	uOR* 0.27 (0.12-0.59)
				LMWH (prophylactic)	(ref)
			ICU admission	LMWH (therapeutic)	uOR* 1.13 (0.59-2.18)
				LMWH (prophylactic)	(ref)
Di Castelnuovo et al., 2020 [58]	Retrospective	2574	Mortality	Heparin (therapeutic)	uHR unavailable aHR 1.54 (1.06-2.25)
				Heparin (prophylactic)	(ref)
Elmelhat et al., 2020 [68]	Retrospective	59	Mortality	Enoxaparin (therapeutic)	uOR 3.93 (0.19-79.94)*
				Enoxaparin (prophylactic)	(ref)

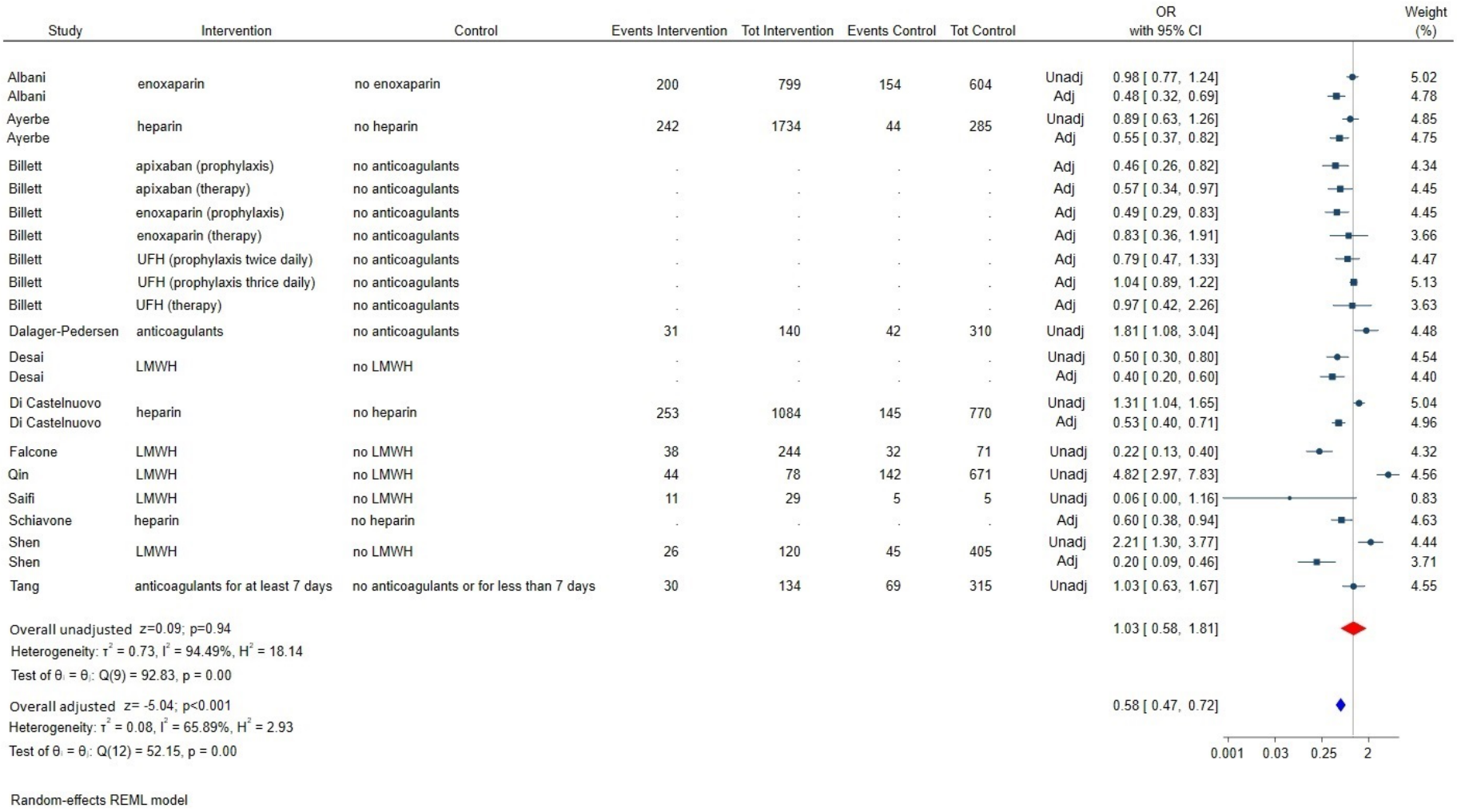
Hsu et al., 2020 [75]	Retrospective	468	Mortality	Anticoagulants (higher dose than prophylactic, subtherapeutic)	uRR unavailable (not clear denominator for calculation)
				Anticoagulants (prophylactic)	aRR 0.26 (0.07-0.97)
					(ref)
Lynn et al., 2020 [69]	Retrospective	402	Mortality	Anticoagulants (therapeutic)	Reported no difference vs. prophylaxis in multivariable logistic regression, but effect size not reported
				Anticoagulants (prophylactic)	(ref)
Motta et al., 2020 [76]	Retrospective	374	Mortality	Heparin (therapeutic)	uRR 2.7 (1.8-4.0) aRR 2.3 (1.0-4.9)
				Heparin (prophylactic)	(ref)
Musoke et al., 2020 [62]	Retrospective	355	Major bleeding	Anticoagulants (therapeutic)	uOR 2.95 (1.11-7.88)*
				Anticoagulants (higher dose than prophylactic, subtherapeutic)	uOR 1.29 (0.15-11.02)*
				Anticoagulant (prophylactic)	(ref)
Paranjpe et al., 2020 [70]	Retrospective	2773	Mortality	Anticoagulants (therapeutic)	uHR unavailable aHR 0.86 (0.82-0.89)
				Anticoagulants (prophylactic) or no anticoagulants	(ref)
Pesavento et al., 2020 [71]	Retrospective	324	Hemorrhagic complications	Anticoagulants (higher dose than prophylactic, subtherapeutic)	uHR unavailable aHR 3.89 (1.90-7.97)

				Anticoagulants (prophylactic)	(ref)
Secco et al., 2020 [72]	Retrospective	115	Mortality	Anticoagulants (therapeutic)	uOR 0.21 (0.06-0.78)* aOR 0.06 (0.01-0.39)
				Anticoagulants (prophylactic)	(ref)
Trimaille et al., 2020 [66]	Retrospective	289	Thrombotic complications	LMWH/UFH (prophylactic) No LMWH/UFH	(ref) uOR 12.03 (5.31-27.23) aOR 27.85 (9.35-82.95)
Comparison of different anticoagulant agents					
Prandoni et al., 2020 [80]	Retrospective	308	Mortality	Enoxaparin (prophylactic)	uOR 1.06 (0.27-2.99)*
				Fondaparinux (prophylactic)	(ref)
			ICU admission	Enoxaparin (prophylactic)	uOR 1.40 (0.39-5.07)*
				Fondaparinux (prophylactic)	(ref)
			Thrombotic complications	Enoxaparin (prophylactic)	uOR 1.16 (0.31-4.41)*
				Fondaparinux (prophylactic)	(ref)
			Hemorrhagic complications	Enoxaparin (prophylactic)	uOR 0.13 (0.02-1.04)*
				Fondaparinux (prophylactic)	(ref)
Russo et al., 2020 [79]	Retrospective	120	Mortality	Enoxaparin (prophylactic)	uOR 0.86 (0.25– 2.88)
				Fondaparinux (prophylactic)	(ref)

Thrombotic complications	Enoxaparin (prophylactic)	uOR 2.25 (0.58-8.61)
	Fondaparinux (prophylactic)	(ref)
Hemorrhagic complications	Enoxaparin (prophylactic)	uOR 0.56 (0.11–2.91)
	Fondaparinux (prophylactic)	(ref)

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; LMWH, low molecular weight heparin; UFH, unfractionated heparin; uHR, unadjusted hazard ratio; uOR, unadjusted odds ratio; uRR, unadjusted relative risk.
* uOR and 95% not available in the original publication, calculated for the present review.
**aHR from a propensity score-weighted multivariable model, and with hospital as random effect
*** The population included many patients with mild disease not receiving anticoagulants. When adjusted for severity of disease, a favorable impact on survival of LMWH was detected

Supplementary figure S1. Summary of the impact of anticoagulants on mortality



Supplementary figure S1 legend. Studies reporting the impact on mortality of anticoagulant agents with prophylaxis intention (either at prophylaxis or therapy dosages, as detailed in parentheses in the intervention column) vs. no receipt of anticoagulant agents, although in some cases the denominators also included

patients with thrombotic complications (i.e., in some patients, anticoagulants were administered as treatment and not as prophylaxis). Controls were reported as defined in the study (no administration of the given intervention). Since no alternative anticoagulant agents were reported in control groups, all were eventually interpreted as no administration of anticoagulants. Random effects model was used to obtain the overall estimate for the unadjusted and adjusted reported results. For the study Billett et al., where multiple analyses with a common control group were included, at each comparison was given a lower weight splitting the control group for the number of comparisons. Studies with no information on n. of events/total or odds ratio were not included, CI, confidence interval; LMWH, low molecular weight heparin; OR, odds ratio; UFH, unfractionated heparin.

Question 3. GRADE tables

Recommendation:
Unless contraindicated, we recommend prophylactic anticoagulation in hospitalized patients with COVID-19

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
35 studies [44-80]	Prospective and retrospective cohort studies	Serious risk of bias due to confounding and possible information bias	No serious inconsistency (consistent direction of effect for adjusted estimates)	No serious indirectness	Serious imprecision due to small sample sizes in many studies	No serious risk of publication bias	Low (consistent direction of effect in adjusted analyses vs. no anticoagulant agents was particularly taken into account)

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.

Recommendation:
Hospitalized patients with COVID-19 who were already under chronic anticoagulant therapy for well-defined indications, unless contraindicated, should continue anticoagulant treatment
Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:
Therapeutic anticoagulation may be considered in patients possibly at higher risk of thrombotic events (serum d-dimer levels > 2.0 μg/mL) or with high suspicion for thrombotic complications
Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

QUESTION 4

Should systemic steroids be administered to inpatients with COVID-19?

Question 4. Search strings and databases

Pubmed

(steroid[Text Word] OR glucorticoid*[Text Word] OR corticosteroid*[Text Word] OR dexamethasone[Text Word] OR cortisol hydrocortisone[Text Word] OR cortisone[Text Word] OR prednisone[Text Word] OR prednisolone[Text Word] OR methylprednisolone[Text Word] OR betamethasone[Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])*

Embase

(steroid:ti,ab,kw OR glucorticoid*:ti,ab,kw OR corticosteroid*:ti,ab,kw OR dexamethasone:ti,ab,kw OR 'cortisol hydrocortisone':ti,ab,kw OR cortisone:ti,ab,kw OR prednisone:ti,ab,kw OR prednisolone:ti,ab,kw OR methylprednisolone:ti,ab,kw OR betamethasone:ti,ab,kw) AND ('covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)*

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steroid OR glucorticoid* OR corticosteroid* OR dexamethasone OR cortisol OR hydrocortisone OR cortisone OR prednisone OR prednisolone OR methylprednisolone OR betamethasone*

– filter: report results

Question 4. Literature review details

Search strings development:

Guido Granata

Elena Tagliabue

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

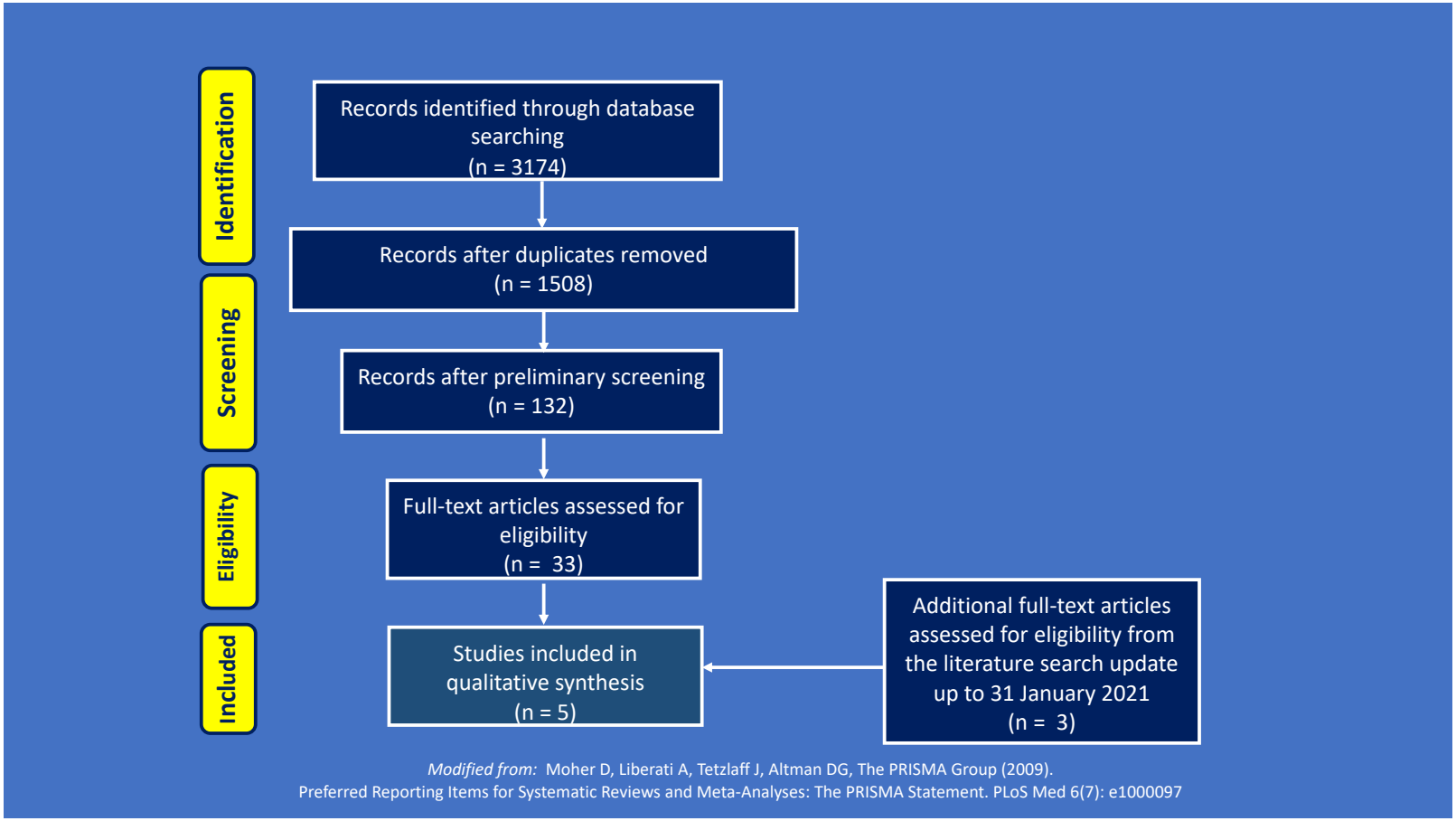
Guido Granata

Elena Tagliabue

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 4. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 1004 de-duplicated records, with the ultimate evaluation of 3 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 2 randomized controlled trials (RCTs) were evaluated during the final literature search update up to 30 April 2021. Overall, 5 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 4. Extended evidence summary

The RECOVERY study is an open-label, adaptive platform RCT comparing a range of possible treatments in hospitalized patients with COVID-19. A preliminary report, detailing the comparison of dexamethasone (at the dosage of 6 mg every 24 hours for up to 10 days) vs. usual care, has been published [30]. Among 6425 hospitalized patients with COVID-19, 2104 were assigned to receive dexamethasone and 4321 to receive usual care alone. Overall, 28-day mortality after randomization was lower in the dexamethasone arm than in the usual care arm (22.9% vs. 25.7%; age-adjusted rate ratio 0.83, with 95% CI 0.75-0.93). In a prespecified subgroup analysis, a significant trend ($p < 0.001$) of increasing efficacy of dexamethasone with increasing level of respiratory support, was observed. The reduction in 28-day mortality in the dexamethasone arm was maximal in in patients under invasive mechanical ventilation (29.3% vs. 41.4%, rate ratio 0.64, with 95% CI from 0.51 to 0.81), and intermediate in patients not receiving invasive mechanical ventilation, but needing oxygen therapy (23.3% vs. 26.2%; rate ratio 0.82, with 95% CI 0.72-0.94). Apparently, no reduction was present in the subgroup of hospitalized patients not receiving respiratory support at randomization (17.8% vs. 14.0% in dexamethasone and usual care arms, respectively; RR 1.19, with 95% CI from 0.91 to 1.55).

In a single-blind RCT conducted in 68 hospitalized, nonintubated patients with severe COVID-19 (defined as COVID-19 with blood oxygen saturation <90%, serum C-reactive protein levels >10 mg/L, and serum interleukin 6 values >6 pg/mL at the start of the pulmonary involvement [in turn defined as oxygen saturation <93%, respiratory rate >18 breaths per minute and little dyspnea]), methylprednisolone (250 mg/day for 3 days) was compared to standard care alone [81]. A favorable effect on survival was observed in patients randomized to receive methylprednisolone (HR for death 0.29, with 95% CI 0.154-0.556).

In a double-blind RCT aimed at assessing the efficacy of methylprednisolone administration in hospitalized patients with suspected/proven COVID-19, 194 and 199 received methylprednisolone (0.5 mg/kg twice daily for 5 days) and placebo, respectively, in addition to usual care [82]. Patients were included if either had SpO2 ≤ 94% in room air, required supplementary oxygen, or required invasive mechanical ventilation. The primary outcome measure was 28-day mortality. COVID-19 was confirmed by molecular tests in 81.3% of patients. The 28-day mortality was similar in the two arms (37% [72/194] vs. 38% [76/199] in methylprednisolone and placebo arms, respectively; HR 0.92, with 95% CI from 0.67 to 1.28). No difference in 28-day mortality (post-hoc analysis) was also observed both in the subgroup of patients receiving non-invasive oxygen therapy (18% [18/98] vs. 21% [19/90] in methylprednisolone and placebo arms, respectively; HR 0.82, with 95% CI from 0.43 to 1.56) and in the subgroup of patients receiving invasive mechanical ventilation (80% [53/66] vs. 85% [57/67] in methylprednisolone and placebo arms, respectively; HR 0.81, with 95% CI from 0.56 to 1.18). Of note, a reduced mortality after administration of methylprednisolone in post-hoc subgroup analyses were observed in patients aged 60 years or older (47% [34/73] vs. 62% [52/84] in methylprednisolone and placebo arms, respectively; HR 0.63, with 95% CI from 0.41 to 0.98).

In an open-label RCT conducted in 64 patients with COVID-19 requiring oxygen supplementation but not under mechanical ventilation, methylprednisolone was compared to standard care alone with respect to a primary composite endpoint of death, admission to the ICU, or requirement for noninvasive ventilation [83]. Among 64 patients included in the intention-to-treat population, the composite endpoint was registered in 40% and 48% of patients in the methylprednisolone and standard care arms, respectively.

In another small, double-blind RCT of 86 hospitalized patients with COVID-19, methylprednisolone was compared with dexamethasone with respect to a primary endpoint of clinical status (on a 9-point scale), with a better clinical status being registered in the

methylprednisolone arm than in the dexamethasone arm at day 5 (mean 4.02 vs. 5.21, respectively) and at day 10 (2.90 vs. 4.71, respectively) [84].

A double-blind RCT conducted in 149 COVID-19 patients with acute respiratory distress syndrome showed no difference with respect to the primary outcome measure (composite of death or persistent respiratory support at day 21) in patients receiving systemic hydrocortisone (200 mg once daily until day 7, then 100 mg once daily for 4 days and 50 mg once daily for 3 days, for a total of 14 days; a short course of 8 days was used in patients improved at day 4) vs. placebo (42% [32/76] vs. 51% [37/73] in hydrocortisone and placebo arms, respectively; difference –8.6%, with 95% CI from –24.9% to 7.7%), although early termination did not allow sufficient power and possible clinically meaningful differences could not be completely ruled out [85]. The number of patients not requiring invasive mechanical ventilation at baseline was limited to 16 patients in each group. In those patients, subsequent intubation was required in 8 patients (50%) in the hydrocortisone arm and in 12 patients (75%) in the placebo arm. No substantial differences in AEs were observed between arms.

The REMAP-CAP is an embedded, multifactorial, adaptive, platform RCT for community-acquired pneumonia (CAP) which also assessed the efficacy of hydrocortisone vs. placebo in patients with severe COVID-19 in intensive care unit (enrollment was halted after the positive results of dexamethasone administration in patients with severe COVID-19 were released) [86]. The primary endpoint was a composite of days alive and free of respiratory or cardiovascular support in the ICU at day 21). Patients were randomized to a 7-day course of fixed-dose hydrocortisone at 50-100 mg every 6 hours (n = 143), a shock-dependent course of hydrocortisone at 50 mg every 6 hours when shock was evident (n = 152), or no hydrocortisone (108). With no hydrocortisone as reference, the median adjusted OR and bayesian probability of superiority were 1.43 (with 95% credible interval from 0.91 to 2.27) and 93% for fixed-dose hydrocortisone, and 1.22 (with 95% credible interval from

0.76 to 1.94) and 80% for shock-dependent hydrocortisone. Progression to non-invasive mechanical ventilation, extracorporeal membrane oxygenation, or death was assessed as a secondary endpoint in patients not subjected to invasive mechanical ventilation at baseline (n = 168). With no hydrocortisone as reference, the median adjusted OR and bayesian probability of superiority for this endpoint were 2.74 (with 95% credible interval from 1.18 to 6.56) and 99% for fixed-dose hydrocortisone, and 1.24 (with 95% credible interval from 0.56 to 2.82) and 70% for shock-dependent hydrocortisone. Two serious AEs (severe neuromyopathy and fungemia) in the fixed-dose hydrocortisone arm were considered as possibly treatment-related.

Question 4. GRADE tables

Recommendation:

*Unless contraindicated, we recommend the use of dexamethasone at the dosage of 6 mg/day for 10 days in inpatients with COVID-19 requiring oxygen supplementation***

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
1 study [30]	RCT	No serious risk of bias	Unable to assess (recommendation based on one study only)	No serious indirectness	No serious imprecision	No serious risk of publication bias	Low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.
** Equivalent dosages of other steroids may be considered if dexamethasone is not available (although this should be considered as best practice recommendation, taking also into account the indirectness of evidence for steroids other than dexamethasone)

Recommendation:

Methylprednisolone at the dosage of 0.5 mg/kg twice daily for at least 5 days could be considered in inpatients with COVID-19 requiring oxygen supplementation and aged ≥ 60 years

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
4 studies [81-84]	RCTs	Serious risk of bias (subgroup analysis by age was not pre-planned in the RCT by Jeronimo and colleagues)	Serious inconsistency	No serious indirectness	Serious imprecision	No serious risk of publication bias	Very low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.

QUESTION 5

Should antiviral agents be administered to inpatients with COVID-19?

Question 5. Search strings and databases

Pubmed

(antiviral agents[MeSH Terms]) AND (coronavirus[MeSH Terms] OR COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word]) AND (trial[Text Word] OR "meta-analysis"[Text Word] OR "systematic review"[Text Word]" OR guideline [Text Word])

Embase

(favipiravir:ti,ab,kw OR remdesivir:ti,ab,kw OR ribavirin:ti,ab,kw OR arbidol:ti,ab,kw OR 'camostat mesylate':ti,ab,kw OR lopinavir:ti,ab,kw OR darunavir:ti,ab,kw OR hydroxychloroquine:ti,ab,kw OR chloroquine:ti,ab,kw OR interferon:ti,ab,kw) AND (coronavirus:ti,ab,kw OR 'covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw) AND (trial:ti,ab,kw OR 'meta-analysis':ti,ab,kw OR 'systematic review':ti,ab,kw OR guideline:ti,ab,kw)

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favipiravir OR remdesivir OR ribavirin OR arbidol OR camostat OR lopinavir OR darunavir OR hydroxychloroquine OR chloroquine OR interferon

– filter: report results

Question 5. Literature review details

Search strings development:

Andrea Lombardi

Silvia Corcione

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

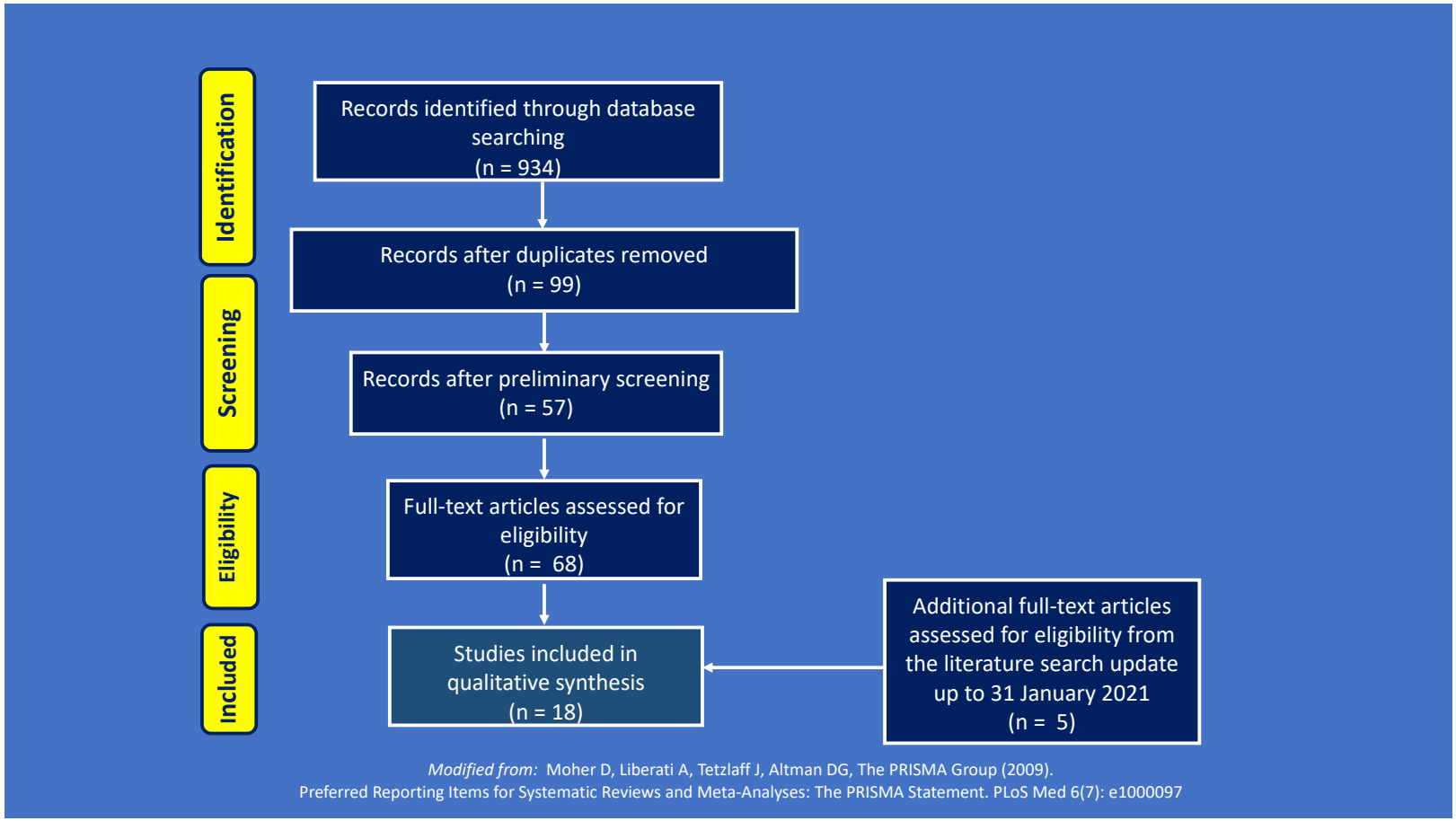
Andrea Lombardi

Silvia Corcione

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 5. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 368 de-duplicated records, with the ultimate evaluation of 5 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 14 randomized controlled trials (RCTs) were evaluated during the final literature search update up to 30 April 2021. Overall, 15 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 5. Extended evidence summary

Lopinavir/ritonavir

In an open-label RCT conducted in China and including 199 hospitalized patients with COVID-19, treatment with lopinavir/ritonavir (LPV/r) was compared with standard care alone [87]. The primary endpoint was time to clinical improvement, defined as the time elapsed from randomization to at least one of the following: (*i*) improvement of two points on a seven-category ordinal scale; (*ii*) discharge from the hospital. In the primary study population (intention-to-treat), LPV/r was not associated with a shorter time to clinical improvement (median 16 days in both study arms, with HR 1.31 and 95% CI from 0.95 to 1.80). Excluding three early deaths, the median time to clinical improvement was one day shorter in the LPV/r arm than in the standard care arm (median 15 days vs. 16 days in LPV/r and standard care arms, respectively; HR 1.39, with 95% CI from 1.00 to 1.91). With respect to 28-day mortality (which was a secondary endpoint), in the intention-to-treat population it was 19.2% and 25.0% in LPV/r and standard care arms, respectively (difference −5.8%, with 95% CI from −17.3 to 5.7), whereas in the modified intention-to-treat population it was 16.7% and 25.0% in LPV/r and standard care arms, respectively (difference −8.3%, with 95% CI from −19.6 to 3.0). Patients under invasive mechanical ventilation at enrollment were only 1% (1/99) and 0% (0/100) in LPV/r and standard care arms, respectively. More gastrointestinal adverse events (AE) were observed in the LPV/r arm, although serious AEs overall were more frequent in the standard care arm.

The RECOVERY study is a randomized, controlled, open-label, adaptive platform trial comparing a range of possible treatments in hospitalized patients with COVID-19. Results regarding the comparison of LPV/r vs. standard care alone have been published [88]. The primary endpoint was 28-day mortality, assessed in the intention-to-treat population. Only 4% of patients in both arms were under invasive mechanical ventilation at enrollment. Overall, 28-day mortality was 23% (374/1616) and 22% (767/3424) in patients randomized

to LPV/r and standard care arms, respectively (rate ratio 1.03, with 95% CI from 0.91 to 1.17). Consistent results were observed across different subgroups. In patients not under invasive mechanical ventilation at baseline, LPV/r was not associated with a reduced risk of progression to invasive mechanical ventilation or death as a composite secondary endpoint (rate ratio 1.09, with 95% CI from 0.99 to 1.20). LPV/r has been previously associated with possible cardiac arrhythmias, but there was not an increased frequency of novel cardiac events compared with standard care in the RECOVERY trial. With regard to the possible hepatic toxicity of LPV/r, there was a serious AE of increased alanine aminotransferase serum values, that was attributed to LPV/r and from which the patient recovered after interruption of treatment.

In the WHO-sponsored, open-label SOLIDARITY RCT, the interim results of which have been recently published [89], hospitalized patients with COVID-19 were randomly allocated to four different treatment arms (LPV/r, remdesivir, hydroxychloroquine, and interferon beta-1a) or to standard care alone. Each treatment arm was compared with a dedicated standard care alone arm, including patients receiving standard care in centers where the specific treatment arm was active (i.e., the treatment drug was available). Consequently, there were 4 partially overlapped standard care arms. The primary endpoint was in-hospital mortality in the intention-to-treat population. With regard to LPV/r, in-hospital death occurred in 9.7% (148/1399) and 10.3% (146/1372) of patients in the LPV/r and standard care arms, respectively (rate ratio 1.00, with 95% CI from 0.79 to 1.25). Overall, 8.0% and 8.3% of patients receiving LPV/r and standard care, respectively, were under mechanical ventilation at randomization. In the subgroup of patients not receiving mechanical ventilation at baseline, in-hospital death occurred in 8.1% (113/1287) and 8.7% (111/1258) of patients in the LPV/r and standard care arms, respectively (rate ratio 0.97, with 95% CI from 0.69 to 1.37). In the same subgroup of patients not under mechanical ventilation at baseline, LPV/r was not associated with a reduced risk of progression to

mechanical ventilation or death as a composite secondary endpoint (rate ratio 0.96, with 95% CI from 0.73 to1.26). Of note, the mechanical ventilation subgroup in the SOLIDARITY trial included both non-invasive and invasive mechanical ventilation. Death with a cardiac cause reported during the trial were 0.5% in 0.2% in LPV/r and standard care arms, respectively. No death due hepatic diseases were attributed to LPV/r. Randomization to LPV/r was discontinued for futility on 4 July 2020.

Remdesivir

The Adaptive Covid-19 Treatment Trial (ACTT-1) was a double-blind, randomized, placebo-controlled trial assessing efficacy and safety of remdesivir in hospitalized patients with COVID-19 and evidence of lower pulmonary tract infection [90]. The primary endpoint, assessed in the intention-to-treat population, was time to recovery. Recovery was defined as the first day in which the patient met one of the following categories (categories 1, 2, or 3) on an ordinary 8-category scale: (category 1) not hospitalized and no limitations of activities; (category 2) not hospitalized, with home oxygen requirement and/or limitation of activities (category 3) not requiring supplemental oxygen and no longer requiring ongoing medical care, but still hospitalized for infection-control purposes or for other nonmedical reasons. Overall, 541 and 521 patients were randomized to remdesivir and placebo arms, respectively. The employed dosage of remdesivir, administered intravenously, was of a 200 mg dose the first day followed by 100 mg/day for other nine days (total treatment duration of 10 days). At enrollment, 24.2% (131/541) and 29.6% (154/531) of patients in remdesivir and placebo arms, respectively, were under invasive mechanical ventilation. With respect to the primary endpoint, patients receiving remdesivir had a median recovery time of 10 days compared to 15 days in those receiving placebo (rate ratio 1.29, with 95% CI from 1.12 to 1.49). In pre-specified subgroup analyses of patients not undergoing invasive mechanical ventilation at baseline, the rate ratio for recovery was as follows: (*i*) 1.29, with 95% from 0.91

to 1.83, in hospitalized patients not requiring supplemental oxygen but requiring any other medical care (category 4 at baseline); (*ii*) 1.45, with 95% CI from 1.18 to 1.79, in hospitalized patients requiring any supplemental oxygen (category 5 at baseline); (*iii*) 1.09, with 95% CI 0.76 from 1.57, in hospitalized patients requiring noninvasive ventilation or use of high-flow oxygen devices. The effect in patients requiring any supplemental oxygen was consistent in post-hoc analyses including an interaction term between treatment and baseline ordinal score as a continuous variable. With regard to secondary endpoints, in the intention-to-treat population the HR for 14-day and 28-day mortality in patients receiving remdesivir vs. placebo (reference) were 0.55 (with 95% CI from 0.36 to 0.83) and 0.73 (with 95% CI from 0.52 to 1.03), respectively. In subgroups of patients not receiving invasive mechanical ventilation at baseline, the use of remdesivir was associated with reduced 14-day mortality (HR 0.28, with 95% CI from 0.12 to 0.66) and 28-day mortality (HR 0.30, with 95% CI from 0.14 to 0.64) in patients requiring any supplemental oxygen (category 5 at baseline). The most common nonserious AE was decreased glomerular filtration rate, occurring with similar frequencies in remdesivir and placebo groups. Overall, the distributions of the different AE did not differ between study arms. Frequency of serious AE was overall lower in the remdesivir arm than in the placebo arm (24.6% and 31.6%, respectively, mostly in the form of respiratory failure), and no death was attributed to remdesivir administration.

Another double-blind, placebo-controlled, randomized trial investigated the efficacy of a 10-day treatment course of remdesivir (at the same dosage of the ACTT-1 trial) in hospitalized patients with COVID-19 and oxygen saturation of 94% or less on room air or a PaO2/FiO2 of 300 mmHg or less, and radiological evidence of pneumonia [91]. The primary endpoint was time to clinical improvement up to day 28 on a 6 points ordinal scale, assessed in the intention-to-treat population. Overall, 158 and 79 patients were randomized to remdesivir and placebo groups, respectively. In this trial, remdesivir was not associated with improved time to clinical improvement (HR 1.23, with 95% CI from 0.87 to 1.75). Overall,

the 28-day mortality was 14% (22/158) and 13% (10/79) in remdesivir and placebo arms respectively (difference 1.1%, with 95% CI from –8.1 to 10.3). Constipation and hypoalbuminemia were the most frequent AE, that were similarly distributed between groups. Interruption of treatment because of AEs occurred in 12% and 5% of patients in remdesivir and placebo groups, respectively.

With regard to possible different dosages of remdesivir, in an open-label RCT involving 397 hospitalized patients with COVID-19 not requiring invasive mechanical ventilation at enrollment, a 5-day course and a 10-day course of remdesivir (both with a dose of 200 mg the first day and then 100 mg/day) were compared with respect to a primary outcome measure of clinical status at day 14, assessed on a 7 points ordinal scale [92]. Inclusion criteria were radiographic evidence of pulmonary infiltrates and one of the following: (*i*) oxygen saturation of 94% or less on room air; (*ii*) supplemental oxygen. At day 14, improvement of 2 points on the ordinal scale was registered in 64% (129/200) and 54% (107/197) of patients in the 5-day and 10-day groups, respectively (difference −6.5%, with 95% CI from −15.7 to 2.8). Overall, AE were similarly distributed between the two groups, but serious AE were more frequent in the 10-day arm than in the 5-day arm, mostly acute respiratory failure (9% vs. 5%, respectively).

In an open-label RCT conducted in hospitalized patients with moderate COVID-19 pneumonia (defined as any radiological evidence of pulmonary infiltrates plus oxygen saturation >94% on room air), patients were randomized to receive one of the following: (*i*) a 10-day course of remdesivir (at the dosage of 200 mg the first day and then 100mg/day for 9 days); a 5-day course of remdesivir (at the dosage of 200 mg the first day and then 100 mg/day for 4 days), or standard care alone [93]. The primary endpoint was clinical status at day 11, assessed on a 7 points ordinal scale. Clinical improvement at day 11 of at least 2 points on the scale was observed in 70% (134/191), 65% (126/193), and 61% (121/200) of patients in the 5-day remdesivir, 10-day remdesivir, and standard care arms, respectively

(difference vs. standard care was 9.7%, with 95% CI from 0.1 to 19.1, for 5-day remdesivir, and 4.8%, with 95% CI from −5.0 to 14.4 for 10-day remdesivir). Mortality at day 11 was 0%, (0/191), 1% (2/193), and 2% (4/200) in patients in the 5-day remdesivir, 10-day remdesivir, and standard care arms, respectively. The proportions of patients requiring invasive mechanical ventilation after enrollment were 0%, (0/191), 1% (1/193), and 2% (4/200) in the 5-day remdesivir, 10-day remdesivir, and standard care arms, respectively. Regarding AEs, nausea, hypokalemia, and headache were more frequent in patients receiving remdesivir than in patients receiving standard of care alone (10% vs. 3%, 6% vs. 2%, and 5% vs. 3%, respectively). None of the deaths registered in the trial were attributed to remdesivir.

As reported above for LPV/r, SOLIDARITY is an open-label RCT in which hospitalized patients with COVID-19 were randomly allocated to four different treatment arms (LPV/r, hydroxychloroquine, remdesivir, and interferon beta-1a) or to standard care alone [89]. The primary endpoint was in-hospital mortality in the intention-to-treat population and the results of an interim analysis have been recently published. With regard to remdesivir (administered as a 10-day course with the same dosage as above), in-hospital death occurred in 12.5% (301/2743) and 12.7% (303/2708) of patients in the remdesivir and standard care arms, respectively (rate ratio 0.95, with 95% CI from 0.81 to 1.11). Overall, 9.3% and 8.6% of patients receiving remdesivir and standard care, respectively, were under mechanical ventilation at randomization. In the subgroup of patients not receiving mechanical ventilation at baseline, in-hospital death occurred in 9.4% (203/2489) and 10.6% (232/2475) of patients in the remdesivir and standard care arms, respectively (rate ratio 0.86, with 95% CI from 0.67 to 1.11). In the same subgroup of patient not under mechanical ventilation at baseline, remdesivir was not associated with a reduced risk of progression to mechanical ventilation or death as a composite secondary endpoint (rate ratio 0.92, with 95% CI from 0.76 to 1.11). Death with a cardiac cause reported during the trial were 0.3% in 0.4% in remdesivir and standard care arms, respectively. With regard to the possible renal

and hepatic toxicity of remdesivir, no death due to renal or hepatic diseases were attributed to remdesivir.

Published results of the interim analysis of the SOLIDARITY trial also included a meta-analysis of all the RCTs including remdesivir reported above (with the exception of the one comparing two different dosages, without standard care arm), with respect to the mortality endpoint, with a summary rate ratio of 0.91 (95% CI from 0.79 to 1.05) using standard care as reference. Of note, although with the inherent limitations of subgroup analyses, a trend towards reduced mortality in remdesivir arms was observed across trials in the subgroups of non-ventilated patients, while an opposite trend towards increased mortality was observed in the subgroups of ventilated patients. Complete results of the SOLIDARITY trial will help to further (and possibly ultimately) clarify this point.

Hydroxychloroquine

An open-label RCT was conducted in Egypt among 194 hospitalized patients with COVID-19 and not undergoing invasive mechanical ventilation at enrollment [94]. The patients were randomized to HCQ (at the dosage of 400 mg twice daily on day 1, then 200 mg twice daily for a total of 15 days) or to standard care alone. The primary endpoints were: (*i*) recovery within 28 days; (*ii*) need for invasive mechanical ventilation within 28 days; (*iii*) death within 28 days. Distributions of primary outcome measures between groups were compared by means of chi-square test or Fisher exact test. Recovery within 28 days (not further defined) was achieved in 53.6% (52/97) and 34.0% (33/97) of patients in HCQ and standard care arms, respectively (p =0.06). Invasive mechanical ventilation within 28 days was required in 4.1% (4/97) and 5.2% (5/97) patients in HCQ and standard care arms, respectively (p = 0.75). Death within 28 days occurred in 6.2% (6/97) and 5.2% (5/97) patients in HCQ and standard care arms, respectively (p = 0.76). No safety information was reported.

In another open-label RCT, hospitalized patients with mild to moderate COVID-19 (i.e., they were receiving either no supplemental oxygen or a maximum of 4 liters per minute of supplemental oxygen) were randomly assigned in a 1:1:1 ratio to receive: (*i*) standard care; (*ii*) standard care plus hydroxychloroquine at the dosage of 400 mg twice daily for 7 days; (*iii*) standard care plus hydroxychloroquine at the dosage of 400 mg twice daily plus azithromycin at the dosage of 500 mg once daily for 7 days [32]. The primary outcome was clinical status at 15 days assessed with the use of a 7 points ordinal scale and evaluated in the modified intention-to-treat population (i.e., patients with a confirmed diagnosis of COVID-19). No beneficial effect in terms of proportional odds of having a higher score on the ordinal scale at day 15 was found for hydroxychloroquine compared to standard care (OR 1.21, with 95% CI from 0.69 to 2.11, p = 1.00) and for azithromycin plus hydroxychloroquine compared to standard care (OR 0.99, with 95% CI from 0.57 to 1.73, p = 1.00). With regard to secondary outcomes, use of invasive mechanical ventilation was necessary in 7.5% (12/159) vs. 6.9% (12/173) of patients in HCQ vs. standard care arms, respectively (OR 1.15, with 95% CI from 0.49 to 2.70), and in 11.0% (19/172) vs. 6.9% (12/173) of patients in HCQ plus azithromycin vs. standard care arms, respectively (OR 1.77, with 95% CI from 0.81 to 3.87). In-hospital death occurred in 4.4% (7/159) vs. 3.5% (6/173) of patients in HCQ vs. standard care arms, respectively (HR 1.47, with 95% CI from 0.48 to 4.53), and in 2.9% (5/172) vs. 3.5% (6/173) of patients in HCQ plus azithromycin vs. standard care arms, respectively (HR 0.64, with 95% CI from 0.18 to 2.21). Prolongation of the QTc interval was more frequent in patients treated with HCQ than in patients receiving standard care alone (14.6% and 14.7% in HCQ and HCQ plus azithromycin arms, respectively, compared to 1.7% in the standard care arm).

As reported above for LPV/r, the RECOVERY study is a randomized, controlled, open-label, adaptive platform trial comparing a range of possible treatments in hospitalized patients with COVID-19. Results regarding the comparison of HCQ vs. standard care alone

have been published [95]. The primary endpoint was 28-day mortality, assessed in the intention-to-treat population. Overall, 16.7% and 16.9% of patients in HCQ and standard care arms, respectively, were under invasive mechanical ventilation at enrollment. The 28-day mortality was 27% (421/1561) and 25% (790/3155) in patients randomized to HCQ and standard care arms, respectively (rate ratio 1.09, with 95% CI from 0.97 to 1.23). Consistent results were observed across different subgroups, including patients not receiving mechanical ventilation at baseline. In this latter subgroup, HCQ was associated with an increased risk of progression to invasive mechanical ventilation or death as a composite secondary endpoint (rate ratio 1.14, with 95% CI from 1.03 to 1.27). There was a small excess of 0.4% in death of cardiac causes in the HCQ arm than in the standard care arm, whereas the number of novel major cardiac arrhythmias was similar between groups. A case of torsade de pointes, from which the patient recovered without undergoing intervention, was attributed to HCQ.

As reported above for LPV/r and remdesivir, SOLIDARITY is an open-label RCT in which hospitalized patients with COVID-19 were randomly allocated to four different treatment arms (LPV/r, hydroxychloroquine, remdesivir, and interferon beta-1a) or to standard care alone [89]. The primary endpoint was in-hospital mortality in the intention-to-treat population and the results of an interim analysis have been recently published. With regard to HCQ (administered at the dosage of four tablets of 200 mg of HCQ sulfate at hour 0, followed by four tablets at hour 6, and, starting from hour 12, two tablets twice daily for 10 days), in-hospital death occurred in 10.2% (104/947) and 8.9% (84/906) of patients in the HCQ and standard care arms, respectively (rate ratio 1.19, with 95% CI from 0.89 to 1.59). Overall, 9.0% and 9.1% of patients receiving HCQ and standard care, respectively, were under mechanical ventilation at randomization. In the subgroup of patients not receiving mechanical ventilation at baseline, in-hospital death occurred in 7.4% (69/862) and 6.6% (57/824) of patients in the HCQ and standard care arms, respectively (rate ratio

1.16, with 95% CI from 0.73 to 1.84). In the same subgroup of patients not receiving mechanical ventilation at baseline, HCQ was not associated with a reduced risk of progression to mechanical ventilation or death as a composite secondary endpoint (rate ratio 1.07, with 95% CI from 0.75 to 1.54). Deaths with a cardiac cause reported during the trial were 0.6% in 0.2% in HCQ and standard care arms, respectively. No deaths due to multiorgan failure were attributed to HCQ. Randomization to hydroxychloroquine was discontinued for futility on 19 June 2020.

In a double-blind RCT in 247 hospitalized patients with COVID-19, HCQ was similar to placebo with respect to a primary composite endpoint of invasive mechanical ventilation or death (relative risk 1.12, with 95% CI from 0.45 to 2.80) [96]. In an open-label RCT of 500 hospitalized patients with mild COVID-19 [97], the primary endpoint was progression of disease, which was observed in 3% of patients in both arms (HCQ vs. standard care alone). In a double-blind RCT conducted in 479 hospitalized patients with COVID-19 (of whom 20% in ICU) [98], the primary endpoint of 14-day clinical status was similar in the HCQ and placebo arms (adjusted odds ratio 1.02, with 95% CI from 0.73 to 1.42). In another double-blind RCT of 128 hospitalized patients with COVID-19, the primary endpoint of disease progression was registered in 16.4% and 9.1% of patients in HCQ and placebo arms, respectively [99]. Of note, three RCTs compared HCQ with other treatments (azithromycin, favipiravir, ivermectin), showed no advantages of HCQ [100-102].

The results of at least two meta-analyses supported the lack of effect of HCQ in reducing short-term mortality in patients hospitalized with COVID-19, although mostly based on observational studies [103, 104]. Finally, three RCTs did not investigate clinical outcomes (mortality, need for mechanical ventilation, disease progression/improvement), but qualitative or quantitative changes in viral load (negative conversion of SARS-CoV-2 molecular tests on respiratory specimen by day 28, reduction of viral load in nasopharyngeal swabs by day 7, or decline in viral load by day 4) as the primary endpoints [25, 105, 106].

No substantial advantages of HCQ administration vs. standard care alone with respect to these virological primary endpoints were found in these trials [25, 105, 106].

Other antivirals

Umifenovir is an oral antiviral drug (membrane fusion inhibitor) that was licensed for the treatment and prophylaxis of influenza A and B virus infections in Russia in 1993 and in China in 2006 [107]. *In vitro* evidence showed activity of umifenovir against coronaviruses [108, 109]. Consequently, its use in COVID-19 has been proposed. Overall, there is currently either contrasting or insufficient observational evidence about the ability of umifenovir to accelerate reduction of viral load and impacting prognosis [107, 110-113]. In a small, open-label RCT of 101 hospitalized patients with COVID-19, in which the primary endpoints were length of hospital stay and clinical improvement at day 7, umifenovir was compared with HCQ followed by LPV/r. In this preliminary RCT, length of hospitalization was slightly shorter in the umifenovir arm, whereas the frequency of clinical improvement was similar between arms [114]. Preliminary favorable results in terms of duration of fever, oxygen saturation and respiratory rate on day 5 in patients with mild to moderate symptoms were also observed in another small RCT, possibly deserving further investigation [115].

Favipiravir is an antiviral agent that selectively inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses and is approved in Japan and China as a second- line treatment during influenza outbreaks [116]. Available RCTs exploring the use of favipiravir in hospitalized patients with COVID-19 assessed changes in viral load or in radiological lesions as primary endpoints. In this regard, the interim results of an open label, pilot RCT conducted in Russia and evaluating the use of favipiravir vs. standard care alone for the treatment of hospitalized patients with COVID-19 who were able to take the drug orally have been recently published [117]. The primary endpoint was negative conversion of SARS-CoV-2 molecular tests by day 10. Negative conversion was achieved in 37/40 (92.5%

(37/40) and in 86% (16/20) of patients in favipiravir and standard care arms, respectively. AEs were observed in 17.5% (7/40) of patients receiving favipiravir, they were mostly mild- to moderate (diarrhea, nausea, vomiting, increase in liver transaminase levels, and chest pain), and led to drug discontinuation in 5% (2/40) of cases. In an open-label RCT conducted in India, oral favipiravir was compared to standard care alone for the treatment of 150 hospitalized patients with mild to moderate COVID-19 not requiring invasive mechanical ventilation. Of note, in this trial subjects may have been hospitalized to allow daily molecular testing for SARS-CoV-2 and not exclusively because of the need for medical care. Moderate disease was defined as pneumonia documented by chest imaging, pyrexia, and a respiratory rate of 21 to 29 breaths per minute. The primary endpoint was time to negative conversion of SARS-CoV-2 molecular tests up to day 28. The median time to negative conversion was 5 days (95% CI from 4 to 7 days) and 7 days (95% CI from 5 to 8) in favipiravir and standard care arms. AEs were observed in 36% and 8% of patients receiving favipiravir and standard care alone, respectively. The most frequent AEs, all mild to moderate, that occurred more frequently in the favipiravir arm than in the standard care arm were increased serum uric acid and abnormal liver function tests. In a small, exploratory RCT (26 patients), a higher remission rate of lung lesions was observed in patients receiving a combination of tocilizumab and favipiravir than in those receiving only favipiravir [118]. An RCT comparing early vs. late favipiravir administration was not considered for evidence synthesis owing to the lack of non-favipiravir arms [119]. In a small open-label RCT of 96 patients with mild to moderate COVID-19 and comparing favipiravir vs. chloroquine, mortality was 2.3% and 4.2% in favipiravir and chloroquine arms, respectively [120]. In an open-label RCT of hospitalized patients with moderate to severe COVID-19 pneumonia, favipiravir was compared to LPV/r, with no substantial differences in terms of mortality, intubation, and ICU admission [121].

With regard to interferons (which have both antiviral and immunomodulatory effects), in the SOLIDARITY RCT (see above) hospitalized patients with COVID-19 were randomly allocated to four different treatment arms (LPV/r, hydroxychloroquine, remdesivir, and interferon beta-1a) or to standard care alone [89]. The primary endpoint was in-hospital mortality in the intention-to-treat population. With regard to interferon beta-1a (mostly administered subcutaneously as three doses of 44 μg over 6 days), in-hospital death occurred in 12.9% (243/205) and 11.0% (216/2050) of patients in the interferon beta-1a and standard care arms, respectively (rate ratio 1.16, with 95% CI from 0.96 to 1.39). Overall, 6.8% and 6.3% of patients who received interferon beta-1a and standard care, respectively, were under mechanical ventilation at randomization. In the subgroup of patients not receiving mechanical ventilation at baseline, in-hospital death occurred in 10.9% (188/1911) and 9.5% (176/1920) of patients in the interferon beta-1a and standard care arms, respectively (rate ratio 1.11, with 95% CI from 0.84 to 1.45). In the same subgroup of patients not under mechanical ventilation at baseline, interferon beta-1a was not associated with a reduced risk of progression to mechanical ventilation or death as a composite secondary endpoint (rate ratio 0.99, with 95% CI from 0.80 to 1.24). Deaths with a cardiac cause reported during the trial were 0.6% in 0.4% in interferon beta-1a and standard care arms, respectively. No deaths due to multiorgan failure were attributed to interferon beta-1a. Randomization to interferon beta-1a was discontinued for futility on 16 October 2020. In an open-label RCT conducted in 89 hospitalized patients with moderate to severe COVID-19 pneumonia, a combination of favipiravir plus inhaled interferon beta-1b was compared to HCQ [122]. No differences between groups were observed in terms of time to recovery, admission to ICU, and overall mortality. A couple of other small RCTs provided conflicting preliminary results regarding the use of interferons in hospitalized patients with COVID-19 [123, 124]. In an exploratory phase-2, double-blind RCT, inhaled nebulised interferon beta-1a (SNG001) was compared to placebo, showing greater odds for clinical improvement (OR

2.32, with 95% CI from 1.07 to 5.04), and thereby providing hypothesis-generating findings to support assessment in larger trials [125].

Novaferon is a recombinant interferon-like protein with wide antiviral properties [126]. In a small open-label, pilot RCT conducted in 89 hospitalized patients with moderate to severe COVID-19, a 3-day reduction in the time to negative conversion of SARS-CoV-2 molecular tests was observed in both the novaferon and novaferon plus LPV/r groups compared to the LPV/r group [127].

Leflunomide, a drug employed to treat autoimmune diseases, inhibits pyrimidine synthesis, a crucial element for RNA virus replication [128]. In a single-centre RCT of COVID-19 patients with prolonged viral shedding, no benefit in terms of the duration of viral shedding was observed with the combined treatment of leflunomide and interferon alfa-2a vs. interferon alfa-2a alone [129].

Sofosbuvir (SOF) and daclatasvir (DCV) are highly effective drugs employed in the treatment of hepatitis C. The results of *in silico* [130, 131] and *in vitro* studies supported the possible use of these drugs against SARS-CoV-2. Two small, open-label, RCTs (including 68 and 44 patients, respectively) performed in Iran evaluated the use of SOF and DCV in hospitalized patients with moderate and severe COVID-19 [132, 133]. In the first of these studies, the addition of SOF and DCV to standard care reduced the duration of hospital stay compared with standard alone. In the other one, distributions of mortality and ICU admission did not differ between the treatment and the standard care arms, although the comparison was hampered by reduced power. Results of both these studies need to be confirmed in larger trials, as those of other more recent RCTs preliminarily evaluating the use of SOF/DCV or SOF/ledipasvir (LDP) in COVID-19 patients [134, 135].

Question 5. GRADE tables

Recommendation:
LPV/r should not be administered to hospitalized patients with COVID-19

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
3 studies [87-89]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness, although the recommendation is also based on some results in ICU patients (although non-invasively ventilated)	Serious imprecision	No serious risk of publication bias.	Moderate

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.

Recommendation:
Pending further results from large RCTs, administration of a 5-day course of remdesivir should be considered in hospitalized patients with COVID-19 pneumonia requiring oxygen supplementation

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
5 studies [89-93]	RCTs	Serious risk of bias (subgroup analyses by severity were not pre-planned in the SOLIDARITY RCT, and partly not pre-planned in the ACTT-1 RCT)	No serious inconsistency (although results of RCTs were inhomogeneous, the direction of the effect was consistent in the population of interest)	No serious indirectness, although the recommendation is also based on some results in ICU patients (although non-invasively ventilated)	Serious imprecision	No serious risk of publication bias	Very low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.

Recommendation:

HCQ should not be administered to hospitalized patients with COVID-19

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
7 studies [32, 89, 94-96, 98, 99]	RCTs	No serious risk of bias, although it is of note that different dosages and duration of HCQ employed in the various RCTs	No serious inconsistency	No serious indirectness, although some RCTs included a (limited) number of patients under invasive mechanical ventilation	Serious risk of imprecision	No serious risk of publication bias	Moderate

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to the evaluators’ judgment.

Recommendation:

Other antiviral agents should not be administered for treating COVID-19 in hospitalized patients, unless they are administered within RCTs

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

QUESTION 6

Should antibiotics be administered to inpatients with COVID-19?

Question 6. Search strings and databases

Pubmed

(antibiotic[Text Word] OR antibacterial*[Text Word] OR antimicrobial*[Text Word] OR bacterial[Text Word] OR "antimicrobial stewardship"[Text Word] OR superinfection[Text Word] OR "secondary infection"[Text Word] OR "co-infection"[Text Word] OR procalcitonin[Text Word] OR PCT[Text Word] OR "MDR" [Text Word] OR "multi-drug resistance" [Text Word] or "nosocomial infection"[Text Word] OR "hospital acquired" [Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])*

Embase

(antibiotic:ti,ab,kw OR antibacterial*:ti,ab,kw OR antimicrobial*:ti,ab,kw OR bacterial:ti,ab,kw OR 'antimicrobial stewardship':ti,ab,kw OR superinfection:ti,ab,kw OR 'secondary infection':ti,ab,kw OR 'co-infection':ti,ab,kw OR procalcitonin:ti,ab,kw OR pct:ti,ab,kw OR mdr:ti,ab,kw OR 'multi-drug resistance':ti,ab,kw OR 'nosocomial infection':ti,ab,kw OR 'hospital acquired':ti,ab,kw) AND (coronavirus:ti,ab,kw OR 'covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)*

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bacterial" OR "stewardship" OR "co-infection" OR "antibiotic"*

– filter: report results

Question 6. Literature review details

Search strings development:

Antonio Vena

Nadia Castaldo

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

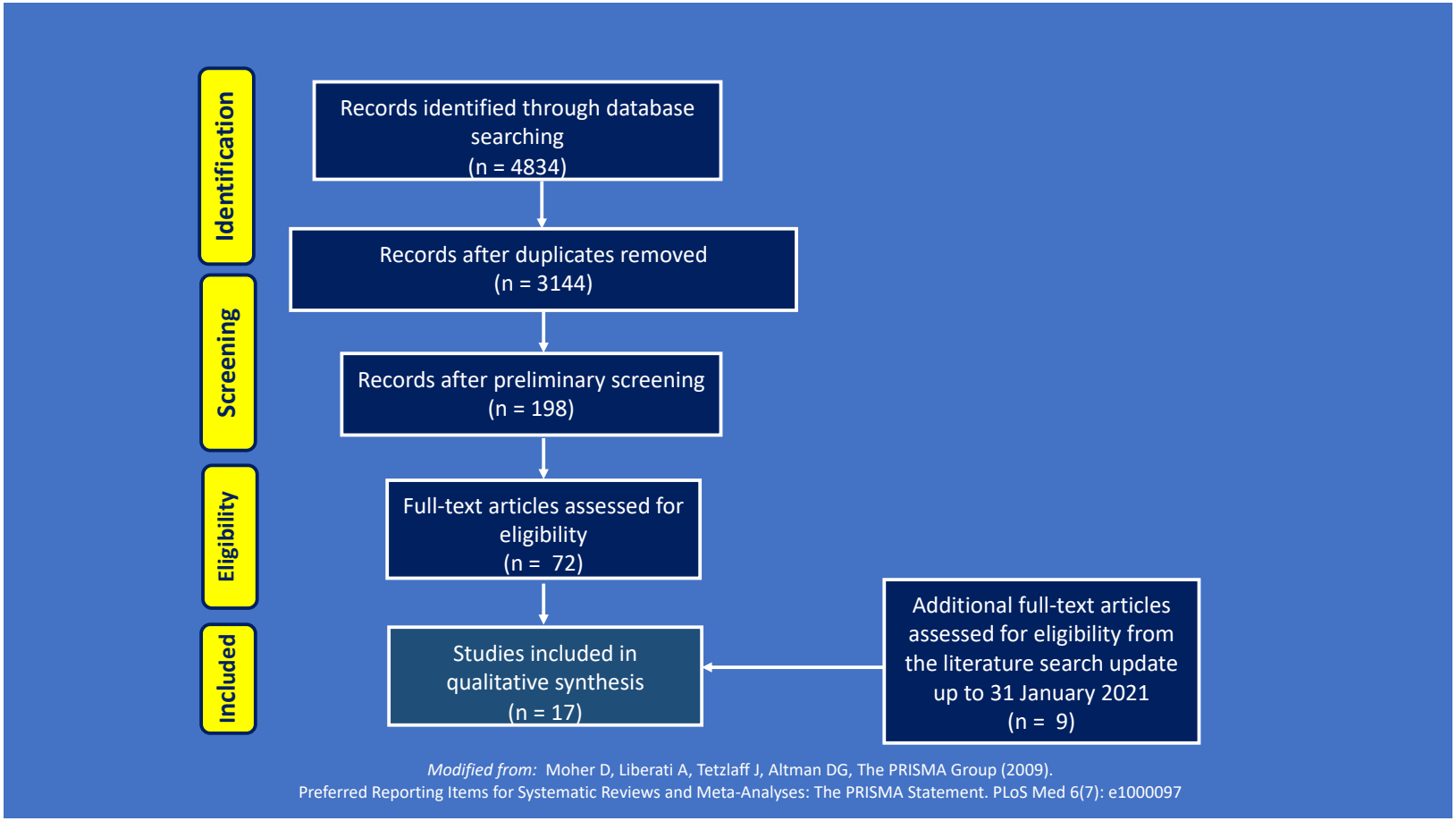
Antonio Vena

Nadia Castaldo

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 6. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 1534 de-duplicated records, with the ultimate evaluation of 9 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 2 randomized controlled trial (RCTs) were evaluated during the final literature search update up to 30 April 2021. Overall, 19 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 6. Extended evidence summary

Two RCTs evaluated the efficacy of azithromycin administration in the population of interest with respect to the endpoints of mortality and/or need for invasive mechanical ventilation.

In an open-label RCT, hospitalized patients with suspected or proven COVID-19 and severe disease (defined as presence of at least one of the following: oxygen supplementation with flow > 4 L/min; use of high-flow nasal cannula; need for non-invasive mechanical ventilation; need for invasive mechanical ventilation) were randomized to azithromycin (500 mg once daily) or standard care alone [136]. Mechanical ventilation at baseline was required in a high proportion of patients (47% and 52% of patients in azithromycin and standard care arms, respectively). The primary outcome was clinical status at 15 days assessed with the use of a 6 points ordinal scale, evaluated in the modified intention-to-treat population (i.e., patients with a confirmed diagnosis of COVID-19). In terms of proportional odds of having a higher (worse) score on the ordinal scale at day 15, azithromycin had an OR of 1.36 (95% CI from 0.94 to 1.97, p = 0.11) compared to standard care, suggesting, if any, a detrimental effect. With regard to secondary outcomes, death at day 29 was observed in 42% (90/214) and 40% (73/183) of patients in azithromycin and standard care arms, respectively (HR equal to 1.08 in a Cox regression model, with 95% CI from 0.79 to 1.47, p= 0.63). The frequency of AEs was similar between arms.

In an open-label RCT, hospitalized patients with mild to moderate COVID-19 (i.e., they were receiving either no supplemental oxygen or a maximum of 4 liters per minute of supplementary oxygen) were randomly assigned in a 1:1:1 ratio to receive: (*i*) standard care; (*ii*) standard care plus HCQ at the dosage of 400 mg twice daily for 7 days; (*iii*) standard care plus HCQ at the dosage of 400 mg twice daily plus azithromycin at the dosage of 500 mg once daily for 7 days [32]. The primary outcome was clinical status at 15 days assessed with the use of a 7 points ordinal scale, evaluated in the modified intention-to-treat population (i.e., patients with a confirmed diagnosis of COVID-19). No beneficial effect in terms of

proportional odds of having a higher score on the ordinal scale at day 15 was found for hydroxychloroquine compared to standard care (OR 1.21, with 95% CI from 0.69 to 2.11, p = 1.00) and for azithromycin plus hydroxychloroquine compared to standard care (OR 0.99, with 95% CI from 0.57 to 1.73, p = 1.00). With regard to secondary outcomes, use of invasive mechanical ventilation was necessary in 7.5% (12/159) vs. 6.9% (12/173) of patients in HCQ vs. standard care arms, respectively (OR 1.15, with 95% CI from 0.49 to 2.70), and in 11.0% (19/172) vs. 6.9% (12/173) of patients in HCQ plus azithromycin vs. standard care arms, respectively (OR 1.77, with 95% CI from 0.81 to 3.87). In-hospital death occurred in 4.4% (7/159) vs. 3.5% (6/173) of patients in HCQ vs. standard care arms, respectively (HR 1.47, with 95% CI from 0.48 to 4.53), and in 2.9% (5/172) vs. 3.5% (6/173) of patients in HCQ plus azithromycin vs. standard care arms, respectively (HR 0.64, with 95% CI from 0.18 to 2.21). Prolongation of the QTc interval was more frequent in patients treated with HCQ than in patients receiving standard care alone (14.6% and 14.7% in HCQ and HCQ plus azithromycin arms, respectively, compared to 1.7% in the standard care arm).

In the open-label RECOVERY RCT, 2582 hospitalized patients with COVID-19 were randomized to receive azithromycin, and 5181 to receive standard care alone [137]. With respect of the primary endpoint of 28-day mortality in the intention-to-treat population, 22% of patients died in both arms (rate ratio 0.97, with 95% CI from 0.87 to 1.07). In the large subgroup of patients without mechanical ventilation at baseline (n = 7319), the proportion of patients meeting the composite of invasive ventilation or death was similar in the two arms (risk ratio 0.95, with 95% CI from 0.87 to 1.03).

The effect of azithromycin administration on mortality was also assessed in an observational, retrospective multicenter study of 1438 hospitalized patients with COVID-19 [138]. Mechanical ventilation before or concurrent to treatment initiation was present in 8.9% of patients. In a multivariable Cox model, administration of HCQ plus azithromycin (HR 1.35,

with 95% CI from 0.76 to 2.40) or azithromycin alone (HR 0.56, with 95% CI from 0.26 to 1.21) were not associated with improved survival compared with standard care.

No RCTs evaluated the efficacy of general antibiotic administration in the population of interest with respect to the endpoints of mortality and/or need for invasive mechanical ventilation, and only results from observational studies were retrieved.

In a retrospective, single-center study of 274 hospitalized patients with COVID-19 who died or who recovered, mortality was 41.2% (113/274) [139]. Overall, 17/274 patients (6.2%) required invasive mechanical ventilation, although it was not specified whether it was started before or after antibiotic administration, and no distribution of invasive mechanical ventilation between antibiotic and non-antibiotic groups was presented. Use of antibiotics was registered in 144/161 (88%) and 105/113 (93%) survivors and non-survivors, respectively. No formal univariable or multivariable comparisons were performed.

In another retrospective study conducted in two centers and including 225 patients with COVID-19, 109 (48.4%) and 116 (51.6%) died or recovered, respectively [140]. Overall, 21/225 patients (9.3%) required invasive mechanical ventilation, although it was not specified whether it was started before or after antibiotic administration, and no distribution of invasive mechanical ventilation between antibiotic and non-antibiotic groups was presented. Use of antibiotics was registered in 91/109 (83.5%) and 100/116 (86.2%) survivors and non-survivors, respectively (chi-square test, p = 0.569). No formal multivariable comparison was performed.

In a retrospective, single-center study of 84 hospitalized patients with COVID-19 pneumonia and acute respiratory distress syndrome, mortality was 52.4%. (44/84) [141]. Overall, 6/84 patients (7.1%) required invasive mechanical ventilation, although it was not specified whether it was started before or after antibiotic administration, and no distribution of invasive mechanical ventilation between antibiotic and non-antibiotic groups was presented. Use of antibiotics was registered in 40/40 (100.0%) and 43/44 (97.7%) survivors

and non-survivors, respectively (difference −2.3%, with 95% CI from −8.9 to 4.4, p > 0.99). No formal multivariable comparison was performed.

In a retrospective, single-center study of 191 hospitalized patients with COVID-19 who died or who were discharged alive, mortality was 41.2% (54/191) [142]. Overall, as many as 63/191 patients (33.0%) required invasive mechanical ventilation, although it was not specified whether it was started before or after antibiotic administration, and no distribution of invasive mechanical ventilation between antibiotic and non-antibiotic groups was presented. Use of antibiotics was registered in 128/137 (93.4%) and 53/54 (98.1%) survivors and non-survivors, respectively. No formal multivariable comparison was performed.

In a retrospective, single-center study of 102 hospitalized patients with COVID-19, mortality was 16.7% (17/102) [143]. Overall, 14/102 patients (13.7%) required invasive mechanical ventilation, although it was not specified whether it was started before or after antibiotic administration, and no distribution of invasive mechanical ventilation between antibiotic and non-antibiotic groups was presented. Use of antibiotics was registered in 84/85 (98.8%) and 17/17 (100.0%) survivors and non-survivors, respectively. No formal multivariable comparison was performed.

In a retrospective, multicenter center study of 1099 hospitalized patients with COVID-19, the primary endpoint was a composite of admission to ICU, need for invasive mechanical ventilation, or death [144]. The primary endpoint was observed in 6.1% of patients (67/1099). Use of intravenous antibiotics was registered in 577/1032 (55.9%) patients who did not experience the primary composite endpoint in and 60/67 (89.6%) patients in whom the primary endpoint was registered, respectively. No formal univariable or multivariable comparisons were performed. No information about oral antibiotics administration was reported.

In a retrospective, single-center study of 275 hospitalized patients with COVID-19 who died in the hospital or were discharged alive, mortality was 43.6% (120/275) [145]. Overall, 42/275 patients (15.3%) required invasive mechanical ventilation, although it was not specified whether it was started before or after antibiotic administration, and no distribution of invasive mechanical ventilation between antibiotic and non-antibiotic groups was presented. Use of antibiotics was registered in 86/155 (55.5%) and 81/120 (67.5%) survivors and non-survivors, respectively (Fisher exact test, $p = 0.05$). Antibiotic therapy was not selected for the final multivariable model of independent predictors of mortality based on a stepwise backward selection procedure.

Other observational studies compared survival in patients receiving and not receiving antibiotics, although it was often unclear when/why the antibiotics were prescribed during the course of the disease (for example, it cannot be excluded that most antibiotics were administered to worsening patients). In a retrospective, single-center study of 836 hospitalized patients with COVID-19, mortality was 16.4% (137/836) [146]. Use of antibiotics was registered in 572/637 (89.8%) and 130/137 (94.8%) survivors and non-survivors, respectively (chi-square test, $p < 0.001$). In an observational registry of 7307 hospitalized patients with COVID-19, mortality was 24.4% (1785/7307) [147]. Use of antibiotics was registered in 5037/5522 (91.2%) and 1600/1785 (89.6%) survivors and non-survivors, respectively (chi-square test, $p = 0.044$). In a retrospective, multicenter study of hospitalized patients with COVID-19, use of antibiotics was registered in 1325/1547 (85.6%) and 412/431 (95.6%) survivors and non-survivors, respectively (Fisher exact test, $p < 0.001$) [148]. In a retrospective, single-center study of hospitalized patients with COVID-19, use of antibiotics was registered in 104/191 (54.4%) and 18/23 (78.3%) survivors and non-survivors, respectively (chi square test, $p = 0.293$) [149]. In another single-center retrospective study, antibiotics were used among 96/100 (96.0%) and 54/56 (96.4%) survivors and non-survivors of COVID-19, respectively (Fisher exact test, $p = 1.000$) [150]. Finally, in a retrospective

multicenter study, mortality was 5% (22/432). Antibiotics were used in 357/410 (87%) and 21/22 (95%) survivors and non-survivors, respectively (Fisher exact test p = 0.247) [151].

Question 6. GRADE tables

Recommendation:

We recommend against the routine use of antibiotics in all hospitalized patients with COVID-19 without proven bacterial infection

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
19 studies [32, 136, 137, 139-154]	3 RCTs for azithromycin 14 observational (either prospective or retrospective) cohort studies and 2 meta-analyses of observational studies for antibiotics in general	No serious risk of bias for azithromycin Very serious risk of bias due to confounding and possible information bias for antibiotics in general	No serious inconsistency for azithromycin Serious inconsistency for antibiotics in general (partly due to unadjusted analyses)	No serious indirectness	Serious imprecision for azithromycin Very serious imprecision due to small sample sizes of many studies for antibiotics in general	No serious risk of publication bias	Moderate for azithromycin Very low for antibiotics in general

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.

Recommendation:

We recommend collection of respiratory specimens for culture or molecular detection of respiratory pathogens, blood cultures, and urinary antigens for S. pneumoniae and Legionella spp. in hospitalized patients with COVID-19 and suspected bacterial pneumonia

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:

Empirical antibiotic treatment of suspected bacterial pneumonia alongside proper diagnostic procedures, should be considered in patients with COVID-19 with evidence of consolidative radiological lesions

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:

In the case of empirical antibiotic treatment, selection of agents to be administered should follow standard practice for the treatment of bacterial pneumonia

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

QUESTION 7

Should neutralizing monoclonal antibodies and non-steroid immunomodulators be administered to inpatients with COVID-19?

Question 7. Search strings and databases

Pubmed

("monoclonal antibodies"[Text Word] OR "monoclonal antibody"[Text Word] OR tocilizumab[Text Word] OR baricitinib[Text Word] OR eculizumab[Text Word] OR anakinra[Text Word] OR sarilumab[Text Word] OR baricitinib[Text Word] OR immunotherapy[Text Word] OR immunotherapies[Text Word] OR immunomodulatory[Text Word] OR canakinumab[Text Word] OR bamlanivimab[Text Word] OR infliximab[Text Word] OR siltuximab[Text Word] OR LY3819253[Text Word] OR LY3832479[Text Word] OR LY-CoV555[Text Word] OR REGN-CoV2[Text Word] OR VIR-7831[Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])

Embase

('monoclonal antibodies':ti,ab,kw OR 'monoclonal antibody':ti,ab,kw OR tocilizumab:ti,ab,kw OR eculizumab:ti,ab,kw OR anakinra:ti,ab,kw OR sarilumab:ti,ab,kw OR baricitinib:ti,ab,kw OR immunotherapy:ti,ab,kw OR immunotherapies:ti,ab,kw OR immunomodulatory:ti,ab,kw OR canakinumab:ti,ab,kw OR bamlanivimab:ti,ab,kw OR infliximab:ti,ab,kw OR siltuximab:ti,ab,kw OR ly3819253:ti,ab,kw OR ly3832479:ti,ab,kw OR 'ly cov555':ti,ab,kw

OR 'regn cov2':ti,ab,kw OR 'vir 7831':ti,ab,kw) AND ('covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)

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"monoclonal antibodies" OR "monoclonal antibody" OR tocilizumab OR baricitinib OR eculizumab OR anakinra OR sarilumab OR baricitinib OR immunotherapy OR immunotherapies OR immunomodulatory OR canakinumab OR bamlanivimab OR infliximab OR siltuximab OR LY3819253 OR LY3832479 OR LY-CoV555 OR REGN-CoV2 OR VIR-7831

Question 7. Literature review details

Search strings development:

Guido Granata

Emanuela Sozio

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

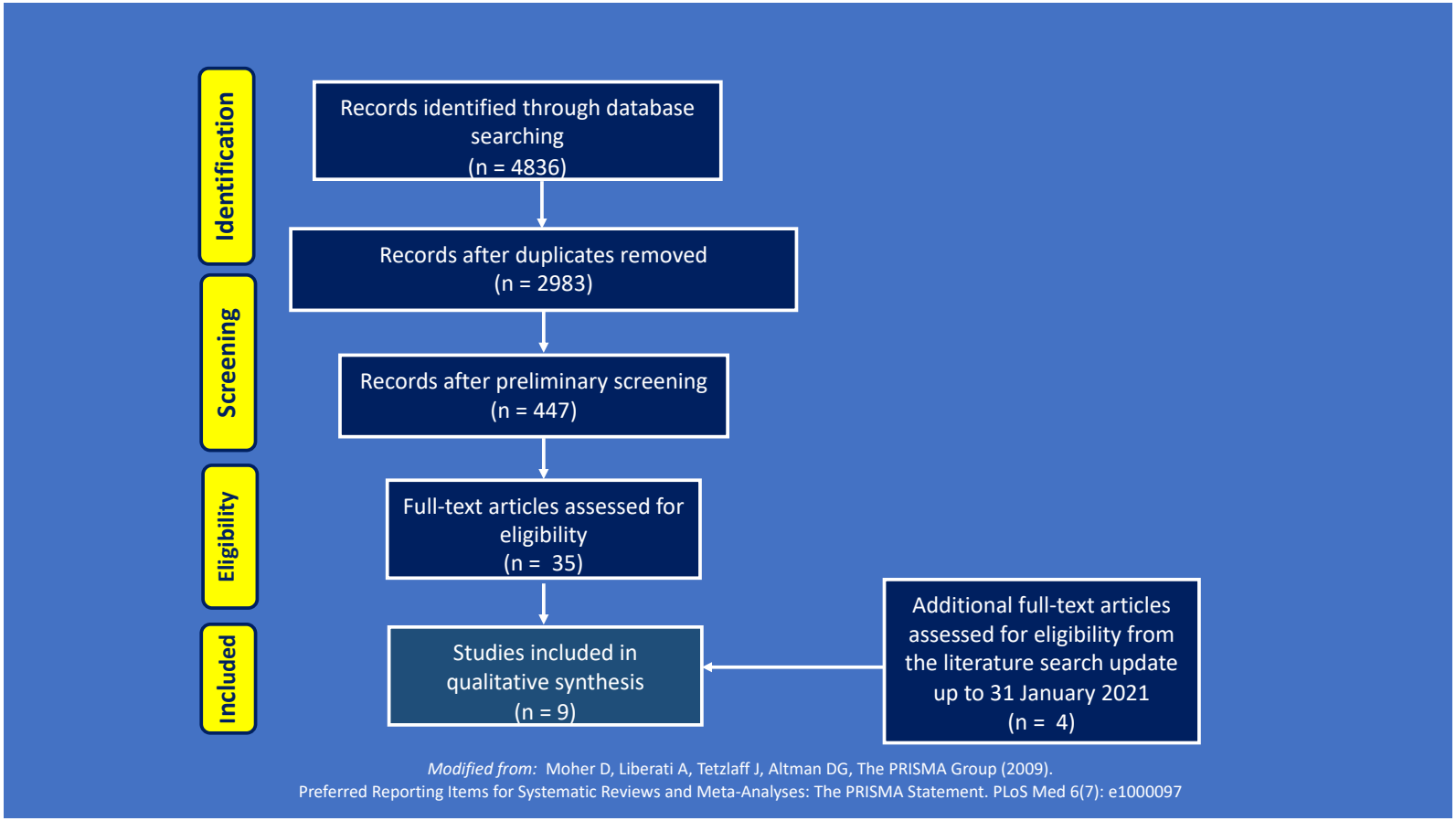
Guido Granata

Emanuela Sozio

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 7. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 1395 de-duplicated records, with the ultimate evaluation of 4 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 6 randomized controlled trials (RCT) were evaluated during the final literature search update up to 30 April 2021. Overall, 13 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 7. Extended evidence summary

Neutralizing monoclonal antibodies

The TICO platform RCT is evaluating multiple candidate therapies in hospitalized patients with COVID-19 in a multigroup, multistage, double-blind design. Preliminary results regarding efficacy of a single infusion of LY-CoV555 at the dosage of 7000 mg have been recently published [155]. The primary efficacy endpoint of the TICO RCT is sustained recovery. In prespecified preliminary analyses, two ordinal clinical outcomes (on a 7 points scale) were assessed at day 5 for futility (named pulmonary and pulmonary-plus outcomes, the former largely based on oxygen requirements, the latter capturing the range of organ dysfunction observed with the progression of the disease). No patient was under invasive mechanical ventilation at enrollment. Overall, 163 patients received LY-CoV555 and 151 received placebo. All patients received remdesivir, and when required, oxygen supplementation and steroids. The OR for patients in the LY-CoV555 arm of being in a more favorable category of the pulmonary ordinal outcome was 0.85 (with 95% CI from 0.56 to 1.29), whereas for the pulmonary-plus ordinal outcome it was 0.87 (with 95% CI from 0.57 to 1.31), thereby meeting the pre-specified criteria for futility for both the outcomes. The rate ratio for a sustained recovery (assessed in patients with available follow-up at day 28) was 1.06 (with 95% CI from 0.77 to 1.47). On Oct. 26, 2020, the trial's independent data and safety monitoring board recommended no further participants be randomized to receive LY-CoV555. This recommendation was based on a low probability that the intervention would be of clinical value in the target population. The RCT evaluating REGN-COV-2 administration in inpatients not requiring oxygen and inpatients on low-flow oxygen is ongoing.

Interleukin-6 inhibitors

In an bayesian, open-label RCT conducted in hospitalized patients with moderate or severe COVID-19 pneumonia requiring at least 3 L/min of oxygen supplementation but not ventilation (including non-invasive ventilation) or admission to the ICU, tocilizumab (two doses of 8 mg/kg intravenously on day 1 and day 3) was compared to standard care alone with respect to the primary endpoints of: (*i*) score higher than 5 on day 4 on a 10 points ordinal clinical scale; (*ii*) survival without need of ventilation (including non-invasive ventilation) at day 14 [156]. The primary analyses were conducted in the intention-to-treat population. Overall, 64 patients were randomized to tocilizumab and 67 to standard care alone. Twelve and 19 patients in tocilizumab and standard care arms, respectively, had a clinical score >5 at day 4 (median posterior absolute risk difference −9.0%, with 90% credible interval from −21.0 to 3.1). The posterior probability of negative ARD was 89.0% (thereby not meeting the prespecified efficacy threshold of 95%). At day 14, tocilizumab was associated with a reduced instantaneous risk of the composite endpoint of death or need for mechanical ventilation (median posterior HR 0.58, with 90% credible interval from 0.33 to 1.00). The posterior probability of HR less than 1 was 95.0% (thereby meeting the prespecified efficacy threshold of 95%). Tocilizumab was not associated with reduced mortality at day 28 (adjusted HR 0.92, with 95% CI from 0.33 to 2.53). Serious AEs (mostly acute respiratory distress syndrome in both arms) were observed in 20 (32%) and 29 (43%) patients in tocilizumab and standard care arms, respectively. Of note, bacterial sepsis was observed in 2 (3%) and 11 (16%) patients in tocilizumab and standard care arms, respectively.

A double-blind RCT was conducted in hospitalized patients with COVID-19, an hyperinflammatory status (based on increased laboratory inflammatory markers), and at least 2 of the following: (*i*) body temperature > 38°C; (*ii*) pulmonary infiltrates; (*iii*) need for supplemental oxygen to maintain oxygen saturation > 92% [157]. In this trial, tocilizumab (as a single dose of 8 mg/kg intravenously) was compared to placebo with respect to a

primary time-to-event endpoint of intubation or death in the modified intention-to-treat population (all randomized patients who received either tocilizumab or placebo before intubation or death). Overall, 161 patients were randomized to tocilizumab and 81 to placebo. Tocilizumab did not meet the primary endpoint of a reduced instantaneous risk of intubation or death compared to placebo (HR 0.83, with 95% CI from 0.38 to 1.81). The cause-specific HR for death and mechanical ventilation were 1.52 (with 95% CI from 0.41 to 5.61) and 0.65 (with 95% from 0.26 to 1.62), respectively. With regard to AEs, it is of note that neutropenia was more frequently observed in the tocilizumab arm than in the placebo arm (13.7% and 1.2%, respectively), whereas serious infections occurred less frequently in the tocilizumab arm than in the placebo arm (8.1% vs. 17.3%, respectively).

In another open-label RCT conducted in hospitalized patients with COVID-19 pneumonia (at enrollment patients could receive oxygen supplementation with Venturi mask or high-flow nasal cannula, but not through noninvasive/invasive mechanical ventilation), [158], the primary efficacy endpoint was a composite of ICU admission (with need for invasive mechanical ventilation), death, or clinical worsening (documented by a PaO2/FIO2 ratio < 150mmHg), assessed in the intention-to-treat population. Overall, 60 patients were randomized to tocilizumab and 63 to standard care alone. With regard to the primary efficacy endpoint, 17/60 (28.3%) and 17/63 (27.0%) patients in tocilizumab arm and standard care arm showed signs of clinical worsening within 14 days after randomization (rate ratio 1.05, with 95% CI from 0.59 to 1.86). The 30-day mortality was 3.3% (2/60) and 1.6% (1/63) in tocilizumab arm and standard care arm, respectively. With regard to safety, AEs were observed most frequently in the tocilizumab arm (23%, mostly laboratory abnormalities such as alanine aminotransferase elevation and decreased neutrophil count) than in the standard care arm (11.1%). Based on an interim analysis, the study was prematurely interrupted for futility.

The results of the EMPACTA study, a double-blind RCT assessing the efficacy of tocilizumab (one or two doses of 8 mg/kg administered intravenously) vs. placebo in hospitalized patients with COVID-19 pneumonia not requiring mechanical ventilation, have been recently published [159]. The primary efficacy, time-to-event endpoint was a composite of invasive mechanical ventilation or death by day 28, assessed in the modified intention-to-treat population (all randomized patients who received tocilizumab or placebo). Overall, 249 patients were randomized to tocilizumab and 128 to placebo. In this trial, tocilizumab met the primary efficacy endpoint in terms of reduced instantaneous risk of invasive mechanical ventilation or death (HR 0.56, with 95% CI from 0.33 to 0.97). With regard to secondary outcomes, 28-day mortality was 10.4% and 8.6% in the tocilizumab and placebo arms, respectively (weighted difference 2.0%, with 95% CI from –5.2 to 7.8). Serious AEs were observed in 15.2% and 19.7% of patients in the tocilizumab and placebo arms, respectively. Overall, 5.2% and 7.1% of patients in the tocilizumab arm and placebo arm, respectively, experience serious infections as AEs.

The results of the COVACTA study have been recently published [160]. COVACTA was a double-blind RCT assessing the efficacy of tocilizumab vs. placebo in hospitalized patients with severe COVID-19 pneumonia (evidence of bilateral radiological infiltrates and either blood oxygen saturation ≤ 93% or PaO2/FiO2 < 300 mm/Hg). Overall, 294 and 144 patients were included in the tocilizumab arm and placebo arm, respectively, in the primary study population (modified intention-to-treat, defined as randomized patients who received tocilizumab or placebo). Notably, 37.8% and 37.5% of patients in the tocilizumab and placebo arms, respectively, were already under mechanical ventilation at enrollment. Overall, tocilizumab (as intravenous administration of one or two doses of 8 mg/kg intravenously) did not meet the primary endpoint of improved clinical status at day 28 vs. the placebo arm on a 7 points ordinal scale (difference in mean value -1.00, with 95% CI from -0.25 to 0.00, p = 0.34 calculated with the van Elteren test stratified according to region

and the absence or presence of mechanical ventilation at randomization), nor the secondary endpoint of reduced 28-day mortality, which was 19.7% and 19.4% in tocilizumab and placebo arms, respectively (difference, 0.3%, with 95% CI from –7.6 to 8.2). Serious AEs were reported in 34.9% and 38.5% of patients in the tocilizumab arm and placebo arm, respectively, with similar distribution of the types of events between arms.

In an open-label RCT, 129 hospitalized patients with severe or critical COVID-19 (16% were under mechanical ventilation at baseline) were randomized to receive tocilizumab or standard of care alone, showing no benefit of tocilizumab administration with respect to the composite endpoint of mechanical ventilation or death (OR 1.54, with 95% CI 0.66 to 3.66) [161]. The RCT was halted prematurely because of an increased number of deaths in the tocilizumab arm at day 15 (17% vs. 3%).

In an open-label RCT, 180 hospitalized patients with moderate to severe COVID-19 were randomized to receive tocilizumab or standard care alone [162]. The primary endpoint was progression of COVID-19 and 5% were under mechanical ventilation at baseline. Progression of COVID-19 up to day 14 was observed in 9% and 13% of patients in the tocilizumab and standard care alone arms, respectively (difference -3.71, with 95% CI from -18.23 to 11.19).

The results of the open-label RECOVERY RCT related to the comparison of tocilizumab vs. placebo in hospitalized patients with progression of COVID-19 (defined as detection, within 21 days of allocation, of oxygen saturation < 92% on room air or receiving supplementary oxygen therapy, and serum C-reactive protein of ≥ 75 mg/L), have been recently published [163]. The primary endpoint was 28-day mortality, with a favorable effect of tocilizumab being detected (rate ratio 0.85, with 95% CI from 0.76 to 0.94), that was also consistent across pre-planned subgroups, with a more marked effect in patients already receiving steroids (rate ratio 0.79, with 95% CI from 0.70 to 0.89; p for interaction = 0.01). In patients not receiving invasive mechanical ventilation at enrollment, patients in the

tocilizumab arm were less likely to reach the secondary composite endpoint of invasive mechanical ventilation or death (35% vs. 42%; rate ratio 0.84, with 95% CI from 0.77 to 0.92). Three serious AEs (all resolved) were judged to be related to tocilizumab administration (otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess).

In a double-blind RCT of hospitalized patients with COVID-19 pneumonia, 420 subjects (of whom 12% under invasive mechanical ventilation at baseline) were randomized to sarilumab 400 mg, sarilumab 200 mg, or placebo [164]. The primary endpoint, assessed in the modified intention-to-treat population, was time to clinical improvement of two or more points on a 7-point scale. No substantial differences were observed in the median time to improvement (10 days for both sarilumab groups vs. 12 days for placebo). Of note, a potential numerical advantage in survival was observed only in critically ill patients.

Other non-steroid immunomodulators

In an bayesian, open-label RCT conducted in hospitalized patients with mild or moderate COVID-19 pneumonia, anakinra (200 mg twice daily on days 1 to 3, 100 mg twice daily on day 4, and 100 mg once daily on day 5) was compared to standard care alone with respect to two coprimary endpoints of: (*i*) score higher than 5 on day 4 on a 10 points ordinal clinical scale; (*ii*) survival without need for ventilation (including non-invasive ventilation) at day 14 [165]. The primary analyses were conducted in the intention-to-treat population. Overall, 59 patients were randomized to anakinra and 57 to standard care alone. Twenty-one patients in both arms had a clinical score >5 at day 4 (median posterior absolute risk difference −2.5%, with 90% credible interval from −17.0 to 12.0). The posterior probability of any benefit was 61.2%. At day 14, anakinra was not associated with a reduced instantaneous risk of the composite endpoint of death or need for mechanical ventilation (median posterior hazard ratio [HR] 0.97, with 90% credible interval from 0.62 to 1.51). The posterior probability of any benefit was 54.5%. Anakinra was not associated with reduced mortality at day 28

(adjusted HR 0.77, with 95% CI from 0.33 to 1.77). Serious AEs were observed in 27 (46%) and 21 (38%) patients in anakinra and standard care arms, respectively. Of note, bacterial/fungal sepsis was observed in 11 (19%) and 4 (7%) patients in anakinra and standard care arms, respectively.

In a double-blind RCT, baricitinib plus remdesivir was compared to placebo plus remdesivir in hospitalized adults with Covid-19 [166]. The primary efficacy endpoint, assessed in the intention-to-treat population, was the time to recovery, whereas the key secondary endpoint was clinical status at day 15 assessed on an 8 points ordinal scale. Overall, 515 and 518 patients were randomized to baricitinib (at the dosage of 4 mg daily administered orally or through a nasogastric tube, for 14 days or until hospital discharge) and placebo, respectively. At baseline, 10.7% and 10.5% of patients in baricitinib arm and placebo arm were under invasive mechanical ventilation. With respect to the primary endpoint, the median time to recovery was 7 and 8 days in baricitinib and placebo arms, respectively (rate ratio for recovery 1.16, with 95% CI from 1.01 to 1.32). Patients in the baricitinib arm also showed better improvement in clinical status at day 15 (OR 1.3, with 95% CI from 1.0 to 1.6). Of note, in the subgroup of patients receiving high-flow oxygen or non-invasive ventilation at enrollment, the median time to recovery was 10 and 18 days in baricitinib and placebo arm, respectively (rate ratio for recovery 1.51, with 95% CI from 1.10 to 2.08). The 28-day mortality was 5.1% and 7.8% in baricitinib arm and placebo arm, respectively (HR, 0.65; 95% CI, 0.39 to 1.09). Overall, serious AEs were less frequent in the baricitinib than in the placebo arm (16.0% vs. 21.0%).

In a small, double-blind RCT conducted in 75 hospitalized, non-ICU patients with severe COVID-19, at day 7, the need of supplemental oxygen was 9% and 42%, in colchicine and placebo arms, respectively [167]. Results of the RECOVERY RCT regarding colchicine have been released in pre-print, non-peer-reviewed form [168]. Among 11,340 hospitalized patients with COVID-19, 28-day mortality was 21% in both colchicine and

standard care alone arms (rate ratio 1.01, with 95% CI from 0.93 to 1.10). In patients not under invasive mechanical ventilation at baseline, the composite endpoint of death or invasive mechanical ventilation was registered in 25% of patients in both arms (risk ratio 1.02, with 95% CI from 0.96 to 1.09).

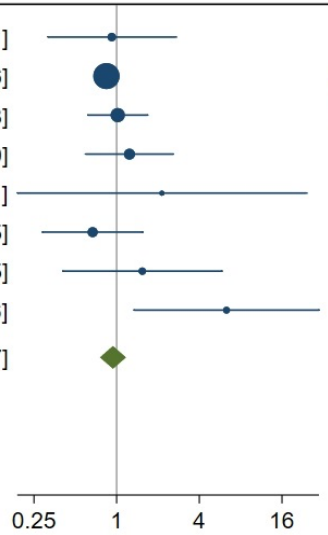
Supplementary figure S2. Impact of tocilizumab on mortality

Study	Intervention	Control	Events Intervention	Tot Intervention	Events Control	Tot Control	OR with 95% CI	Weight (%)
Hermine	tocilizumab	standard care alone	7	63	8	67	0.92 [0.31, 2.71]	3.84
Horby	tocilizumab	standard care alone	596	2022	694	2094	0.84 [0.74, 0.96]	62.00
Rosas	tocilizumab	placebo	58	294	28	144	1.02 [0.62, 1.68]	15.06
Salama	tocilizumab	placebo	26	249	11	128	1.24 [0.59, 2.60]	7.74
Salvarani	tocilizumab	standard care alone	2	60	1	63	2.14 [0.19, 24.21]	0.79
Soin	tocilizumab	standard care alone	11	91	15	88	0.67 [0.29, 1.55]	6.13
Stone	tocilizumab	placebo	9	161	3	81	1.54 [0.41, 5.85]	2.55
Veiga	tocilizumab	standard care alone	11	65	2	64	6.31 [1.34, 29.76]	1.90
Overall							0.94 [0.76, 1.17]	

Heterogeneity: $\tau^2 = 0.02$, $I^2 = 12.24\%$, $H^2 = 1.14$

Test of $\theta = 0$: $z = -0.56$, $p = 0.57$

Random-effects REML model



Supplementary figure S2 legend. Studies reporting the impact on mortality of tocilizumab in randomized controlled trials with predominance of COVID-19 patients not under invasive mechanical ventilation at enrollment. A random effects model was used to obtain the overall estimate. CI, confidence interval; OR, odds ratio.

Question 7. GRADE tables

Recommendation:

Pending further results from RCTs, we recommend against the administration of neutralizing monoclonal antibodies in hospitalized patients with COVID-19

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
2 studies [155, 169]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	No serious risk of publication bias One study halted for futility. In the other one, enrollment was halted in patients requiring high-flow oxygen or mechanical ventilation, due to a potential safety signal and an unfavourable risk/benefit profile.	Moderate

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.

Recommendation:

*We recommend considering tocilizumab administration in hospitalized patients with COVID-19 not responding to steroid treatment, with oxygen saturation < 92% on room air (including those already on supplementary oxygen), and with increased inflammatory markers** in the absence of a proven or suspected infection other than COVID-19****

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
8 studies [156-163]	RCTs	No serious risk of bias	Serious inconsistency (different direction of effect between the RECOVERY RCT and other RCTs, see supplementary figure S2)	No serious indirectness	Serious imprecision	No serious risk of publication bias	Very low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.
** In the RECOVERY trial, serum C-reactive protein ≥ 75 mg/L
*** Clinicians should be aware of the following: (*i*) the 75 mg/L cut-off is based on results of the RECOVERY RCT; (i) other markers of inflammation may be considered on a case-by-case basis (best practice recommendation); (ii) another best practice recommendation is to avoid tocilizumab administration in patients with severe immunosuppression or in those with other contraindications to tocilizumab administration (low platelet count; risk of gastrointestinal perforation; increase of transaminases > 5 times the upper limit of normal).

Recommendation:

Pending further results from RCTs, baricitinib may be considered in addition to remdesivir in patients requiring high-flow oxygen or non-invasive mechanical ventilation who are not under steroid treatment (e.g., in presence of contraindications to steroid use)

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
1 study [166]	RCT	No serious risk of bias	Unable to assess (recommendation based on one study only)	No serious indirectness	Serious imprecision	No serious risk of publication bias	Low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.

Recommendation:

Pending further results from large RCTs, we recommend against administration of other non–steroid immunomodulatory agents outside RCTs

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
2 studies [164,165]**	RCT	No serious risk of bias	Unable to assess (recommendation based on one study only for each drug)	No serious indirectness	Serious imprecision	No serious risk of publication bias	Very low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to “very serious risk of bias”, low risk of bias translated to “no serious risk of bias”, whereas moderate/unclear risk of bias translated to “serious risk of bias” or “no serious risk of bias” according to evaluators’ judgment.
** GRADE system used only for anakinra and sarilumab, best practice recommendation for other agents (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

QUESTION 8

Should convalescent plasma be administered to inpatients with COVID-19?

Question 8. Search strings and databases

Pubmed

("hyperimmune plasma"[Text Word] OR "convalescent plasma" [Text Word] OR "plasma donor" [Text Word] OR "hyperimmune immunoglobulin*" [Text Word] OR "recovered donor*" [Text Word] OR "plasma-based therap*"[Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])*

Embase

('hyperimmune plasma':ti,ab,kw OR 'convalescent plasma':ti,ab,kw OR 'plasma donor':ti,ab,kw OR 'hyperimmune immunoglobulin*':ti,ab,kw OR 'recovered donor*':ti,ab,kw OR 'plasma-based therap*':ti,ab,kw) AND ('covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)*

Cochrane COVID-19 Study Register

"convalescent plasma" OR "hyperimmune immunoglobulin"

– filter: report results

Question 8. Literature review details

Search strings development:

Guido Granata

Nadia Castaldo

Emanuela Sozio

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

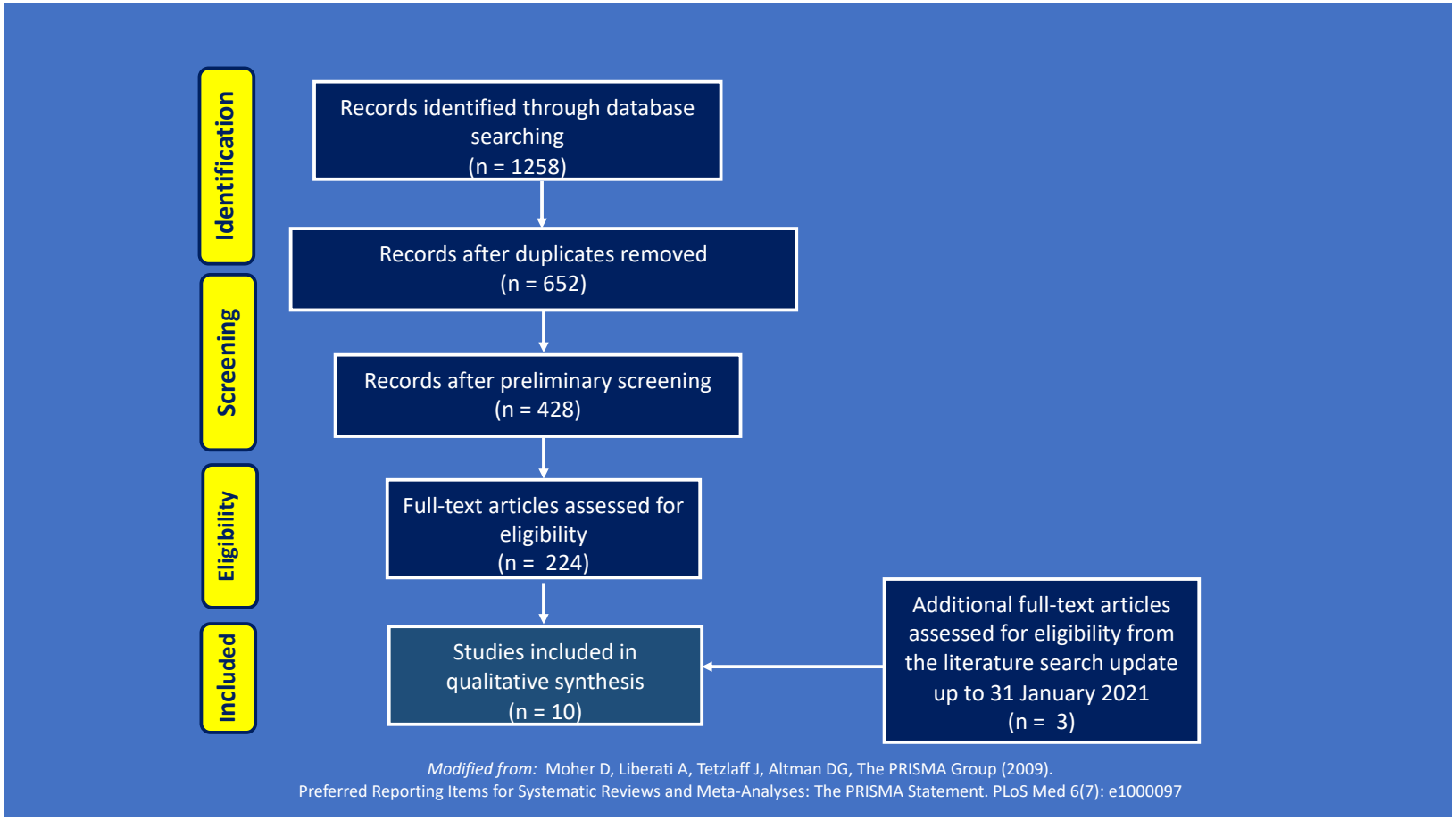
Guido Granata

Nadia Castaldo

Third reviewer for resolving possible disagreements:

Emanuela Sozio

Question 8. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 479 de-duplicated records, with the ultimate evaluation of 3 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 2 randomized controlled trials (RCTs) were evaluated during the final literature search update up to 30 April 2021. Overall, 11 of the included studies were considered for those recommendations based on the GRADE system (see GRADE tables).

Question 8. Extended evidence summary

In a double-blind RCT, hospitalized patients with COVID-19 pneumonia not requiring invasive mechanical ventilation were randomized to receive convalescent plasma or placebo, in addition to standard care [170]. The primary efficacy endpoint was 30-day clinical status, assessed on a 6 points ordinal scale. Overall, 228 and 105 patients received convalescent plasma and placebo, respectively. No substantial difference in terms of better clinical outcome at day 30 was observed for convalescent plasma compared to placebo (OR 0.52, with 95% CI from 0.52 to 1.45). The 30-day mortality was 11% in both convalescent plasma and placebo arms. The proportions of patients requiring invasive mechanical ventilation throughout the trial was 27% and 23% in convalescent plasma and placebo arms, respectively. No particular differences between arms were observed in terms of AEs, although infusion-related reactions were slightly more frequent in the convalescent plasma arm than in the placebo arm (5% vs. 2%, respectively), and five patients in the convalescent plasma arm had nonhemolytic febrile reactions (vs. none in the placebo arm).

In an open-label RCT, hospitalized patients with severe or life-threatening COVID-19 (either not requiring or requiring invasive mechanical ventilation) were randomized to receive convalescent plasma or standard care alone [171]. The primary efficacy time-to-event endpoint was clinical improvement by day 28 on a 6 points ordinal scale, assessed in the full analysis set. Overall, 52 and 51 patients received convalescent plasma and standard care alone, respectively. At baseline, the proportion of patients with invasive mechanical ventilation and/or extracorporeal membrane oxygenation was 28% and 22% in the convalescent plasma and standard care arms, respectively. No substantial difference in terms of clinical improvement was observed for convalescent plasma compared to standard care alone (HR 1.61, with 95% CI from 0.79 to 2.49). The crude 28-day mortality was 16% (8/51) and 24% (12/50) in the convalescent plasma and placebo arms, respectively (difference −8.3%, with 95% CI from −23.8% to 7.2%). In a post-hoc analysis, in the

subgroup of patients with severe disease (which did not include patients requiring invasive mechanical ventilation, since it was one of the possible entry criteria for the life-threatening subgroup), a shorter time to improvement was registered in the convalescent plasma arm than in the standard care arm (HR 2.15, with 95% CI from 1.07 to 4.32), whereas the crude 28-day mortality was 0% (0/23) and 9% (2/22) in the convalescent plasma and placebo arms, respectively (difference −9.1%, with 95% CI from −25.6% to 7.4%). Two possible transfusion-related AEs were reported in the convalescent plasma arm (chills and rash in one patient, shortness of breath, cyanosis, and severe dyspnea in the other patient). The trial was early terminated due to lack of eligible patients.

In an open-label RCT, hospitalized patients with moderate COVID-19 (defined as PaO2/FiO2 within 200 and 300 mmHg or a respiratory rate > 24 breaths per minute with oxygen saturation ≤ 93% on room air) not requiring invasive mechanical ventilation were randomized to receive convalescent plasma or standard care alone [172]. The primary efficacy endpoint was a composite of progression to severe disease (PaO2/FiO2 <100 mmHg) and 28-day mortality, assessed in the intention-to-treat population. Overall, 235 and 229 patients were included in the convalescent plasma and standard care alone arms, respectively. The primary outcome was registered in 19% and 18% of patients in the convalescent plasma and standard care arms, respectively (risk ratio 1.04, with 95% CI from 0.71 to 1.54). All-cause 28-day mortality was 15% and 14% in patients in the convalescent plasma and standard care arms, respectively (risk ratio 1.04, with 95% CI from 0.66 to 1.63). Invasive mechanical ventilation was required in 8% of patients in both arms. Mortality was registered as possibly related to convalescent plasma transfusion in 3 patients (1%).

In a double-blind RCT conducted in older patients within 72 hours after the onset of mild COVID-19 symptoms, convalescent plasma with high IgG titers (>1:1000 against SARS-CoV-2 spike protein) was compared to placebo with respect to a primary efficacy endpoint of development of severe respiratory disease (defined as a respiratory rate of ≥ 30

breaths per minute, an oxygen saturation < 93% in room air, or both) in the intention-to-treat population [173]. Overall, the development of severe respiratory disease was registered in 13/80 (16%) and 25/80 (31%) patients who received placebo (relative risk 0.52, with 95% CI from 0.29 to 0.94). The effect was larger when excluding 6 patients who developed severe disease before plasma administration (relative risk 0.40, with 95% CI from 0.20 to 0.81). Death was registered in 2% (2/80) and 5% (4/80) of patients in the convalescent plasma and placebo arms, respectively. No solicited AEs were observed after plasma administration.

In an open-label RCT, hospitalized patients with COVID-19 pneumonia and not under mechanical ventilation were randomized to receive convalescent plasma or standard care alone [174]. The primary efficacy endpoint was requirement of mechanical ventilation. Overall, 20 and 20 patients were randomized to convalescent plasma and standard care alone arms, respectively. Mechanical ventilation was required in 20% (4/20) and 30% (6/20) of patients in the convalescent plasma and standard care arms, respectively (risk ratio 0.67, with 95% CI from 0.22 to 2.0). Overall, 1/20 (5%) and 2/20 (10%) patients died in the convalescent plasma and standard care arms, respectively. Three patients receiving convalescent plasma had AEs (gastrointestinal symptoms, constipation, and desaturation) that were deemed not to be related to convalescent plasma administration.

In the open-label RECOVERY RCT, conducted in 11,558 patients randomized to convalescent plasma or standard care alone, no difference was observed in terms of 28-day mortality (primary endpoint) between high-titre convalescent plasma and usual care arms (24% vs. 24%; rate ratio 1.00, with 95% CI from 0.93 to 1.07) [175]. In patients not receiving invasive mechanical ventilation at enrollment, no substantial differences were observed in terms of the secondary composite endpoint of invasive mechanical ventilation or death (29% vs. 29%; rate ratio 0.99, with 95% CI from 0.93 to 1.05).

In an open-label RCT, available as a non-peer-reviewed pre-print manuscript, 223 hospitalized patients with COVID-19 (of whom <15% under invasive mechanical ventilation at baseline) were randomized to receive convalescent plasma or normal control plasma [176]. The primary endpoint was clinical status at day 28, with no substantial improvement being observed in the convalescent plasma arm compared with the normal control plasma arm (OR for one point improvement 1.50, with 95% CI from 0.83 to 2.68).

In an open-label RCT, available as a non-peer-reviewed pre-print manuscript, hospitalized patients with severe COVID-19 not requiring invasive mechanical ventilation were randomized to receive convalescent plasma or standard care alone [177]. The primary efficacy endpoint was the proportion of patients remaining free of mechanical ventilation on day 7. Overall, 14 and 15 patients received convalescent plasma and standard care alone, respectively. The proportion of patients free of ventilation at day 7 was 79% (11/14) and 93% (14/15) in the convalescent plasma and placebo arms, respectively. The crude 28-day mortality was 21% (3/14) and 7% (1/5) in the convalescent plasma and placebo arms, respectively. One patient in each arm showed signs of mild urticaria.

In an open-label RCT, available as a non-peer-reviewed pre-print manuscript, hospitalized patients with COVID-19 and not under mechanical ventilation for < 96 hours were randomized to receive convalescent plasma or standard care alone [178]. The primary endpoint was 60-day mortality. Overall, 43 and 43 patients were randomized to convalescent plasma and standard care arms, respectively. Many patients had autologous neutralizing antibody at baseline, and the study was discontinued prematurely after evaluation by the data safety monitoring board (DSMB) owing to a reasonable expectation of lack of effect. At the enrollment, 13/86 patients were under mechanical ventilation (15%). Overall, mortality (although not all patients were followed for 60 days when the trial was interrupted) was 14% (6/43) and 26% (11/43) in patients receiving convalescent plasma or standard care alone, respectively. According to the study protocol (pre-planned analysis),

the effect of plasma therapy on mortality was estimated by logistic regression adjusted for age, sex, intensive care unit admission, C-reactive count, absolute lymphocyte count, bilirubin and FiO2 (adjusted OR 0.95, with 95% CI from 0.20 to 4.67). No serious events related to the administration of convalescent plasma were observed.

In an open-label RCT, available as a non-peer-reviewed pre-print manuscript, hospitalized patients with COVID-19 not requiring mechanical ventilation and with ≤ 7 days from symptoms onset to enrollment were randomized to receive early convalescent plasma administration (at enrollment) or deferred convalescent plasma administration (the latter administered in the case of worsening respiratory function or at > 7 days after enrollment if still hospitalized and with COVID-19-related symptoms) [179]. The primary efficacy endpoint was a composite of mechanical ventilation, hospitalization > 14 days, or in-hospital death, assessed in the intention-to-treat population. Overall, 28 and 30 patients were included in the early and deferred convalescent plasma arms, respectively. No substantial benefit was observed with respect to the primary outcome, which was registered in 32% and 33% of patients receiving early and deferred convalescent plasma, respectively (OR 0.95, with 95% CI from 0.32 to 2.84). In-hospital mortality was 17.9% and 6.7% in patients in the early and deferred convalescent plasma arms, respectively (OR 3.04, with 95% CI from 0.54 to 17.2). Mechanical ventilation was required in 17.9% and 6.7% of patients in the early and deferred convalescent plasma arms, respectively (OR 3.04, with 95% CI from 0.54 to 17.2). Two patients developed severe respiratory deterioration within <6 hours after administration of convalescent plasma. Of note, this study was not summarized in supplementary figure S3 and ultimately not considered for drafting recommendations based on the GRADE system, since plasma could be used in both arms.

In an open-label RCT, available as a non-peer-reviewed pre-print manuscript, hospitalized patients with COVID-19 pneumonia not requiring mechanical ventilation were randomized to receive convalescent plasma or standard care alone [180]. The primary

efficacy endpoint was clinical status at day 14 according to a 7 points ordinal scale. Overall, 38 and 43 patients were included in the convalescent plasma and standard care arms, respectively. Progression to at least category 5 of the ordinal scale (non-invasive ventilation or high-flow oxygen) at day 14 was observed in 0% (0/38) and 14% (6/43) of patients in the convalescent plasma and standard care arms, respectively. The all-cause 28-day mortality was 0% and 9.3% in convalescent plasma and standard care arms, respectively. There were two suspected episodes of transfusion-related lung acute lung injury (that was nonetheless ruled out in both cases) in the convalescent plasma arm. The trial was prematurely interrupted after the first interim analysis, owing to a reduction in recruitments.

In an open-label RCT, available as a non-peer-reviewed pre-print manuscript, hospitalized patients with severe COVID-19 not undergoing mechanical ventilation were randomized to receive convalescent plasma or standard of care alone [181]. The primary endpoint was 30-day mortality. Overall, 40 and 40 patients were included in the convalescent plasma and standard care arms, respectively, with 30-day mortality being 25% (10/40) and 35% (14/40), respectively.

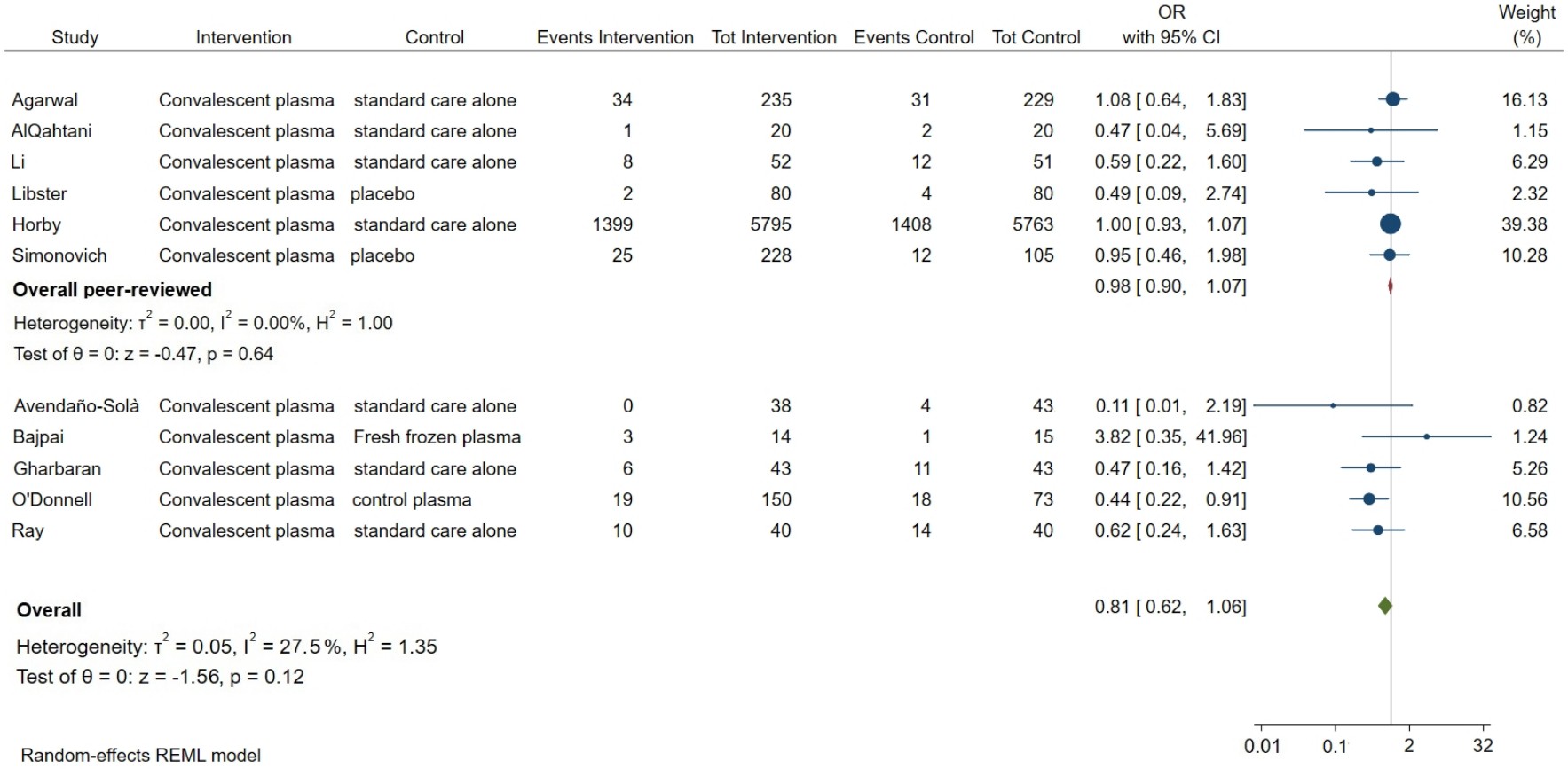
Supplementary table S2. Primary efficacy results of published randomized trials

Study, year [Ref]	Information on neutralizing antibodies titers in convalescent plasma preparations	Comparator/s	Primary endpoint	Study population	Primary analysis results
Agarwal et al., 2020 [172]	Variable neutralizing antibodies titer from undetectable to ≥1:80	Standard care alone	Composite of progression to severe disease (PaO2/FiO2 <100 mmHg) within 28 days or mortality at 28 days	Inpatients with moderate COVID-19 (either PaO2/FiO2 ratio of 200-300 mmHg or respiratory rate > 24 breaths//min with SpO2 93% or less on room air)	The primary endpoint of progression or mortality was registered in 19% (44/235) and 18% (41/229) of patients in convalescent plasma and control arms, respectively (risk difference 0.008, with 95% CI from −0.062 to 0.078; risk ratio 1.04, with 95% CI from 0.71 to 1.54)
AlQahtani et al., 2021 [174]	Variable neutralizing antibodies titers	Standard care alone	Requirement for ventilation	Inpatients with pneumonia confirmed by chest imaging and hypoxia (oxygen saturation of less than or equal 92% on air, or PO2 <60 mmHg arterial blood gas, or PaO2/FiO2 of 300 or less and the patient requiring oxygen therapy	The primary endpoint was registered in 30% (6/20) of controls and 20% (4/20) of patients receiving convalescent plasma (risk ratio 0.67, 95% CI 0.22–2.0).
Horby et al., 2021 [175]	Only plasma donations with a sample to cutoff ratio of 6·0 or more on the EUROIMMUN IgG enzyme-linked immunosorbent assay (ELISA) targeting the spike glycoprotein	Standard care alone	28-day mortality	Inpatients with COVID-19	No difference was observed in terms of 28-day mortality (primary endpoint) between high-titre convalescent plasma and usual care arms (24% vs. 24%; RR 1.00, with 95% CI from 0.93 to 1.07)
Li et al., 2020 [171]	Only plasma units with an S-RBD–specific IgG titer of at least 1:640 were used in this study	Standard care alone	Time to clinical improvement within 28 days	Inpatients with pneumonia confirmed by chest imaging and severe COVID-19 (respiratory rate ≥30 breaths/min; SpO2 93% or less on room air; or PaO2/FiO2 300 or less) or life-threatening COVID-19 (respiratory failure requiring MV; shock; or non-lung organ failure requiring ICU monitoring)	The primary endpoint of clinical improvement within 28 days was registered in 52% (27/52) and 43% (22/51) of patients in the convalescent plasma and control arms, respectively (difference 8.8, with 95% CI from −10.4 to 28.0; hazard ratio 1.40, with 95% CI from 0.79 to 2.49)
Simonovich et al., 2020 [170]	The minimum SARS-CoV-2 total antibody titer was 1:400	Placebo	Clinical status on day 30 on a 6 points ordinal scale	Inpatients with pneumonia confirmed by chest imaging and severe COVID-19 (at least one of the following: SpO2	The distribution of clinical outcomes according to the ordinal scale was similar in the convalescent plasma and placebo

				93% or less on room air; PaO2/FiO2 300 or less; or SOFA or modified SOFA score of two or more points above baseline status)	arms at day 30 (odds ratio 0.83, with 95% CI from 0.52 to 1.35)
Libster et al., 2020 [173]	The minimum SARS-CoV-2 spike protein antibodies titer was 1:1000	Placebo	Development of severe disease (respiratory rate of at least 30 breaths /min or more, SpO2 93% or less on room air, or both)	Low-complexity inpatients and outpatients with COVID-19 of 75 years or older with at least one baseline chronic comorbidity, in which convalescent plasma or placebo were administered within 72 h of onset of symptoms	The primary endpoint of severe disease was registered in 16% (13/80) and 31% (25/80) of patients in convalescent plasma and placebo arms, respectively (relative risk 0.52, with 95% CI from 0.29 to 0.94)

CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; RBD, receptor binding domain; SOFA, sequential organ failure assessment.

Supplementary figure S3. Impact of convalescent plasma on mortality



Supplementary figure S3 legend. Studies reporting the impact on mortality of convalescent plasma in randomized controlled trials with predominance of COVID-19 patients not under invasive mechanical ventilation at enrollment. A random effects model was used to obtain the overall estimate. CI, confidence interval; OR, odds ratio.

Question 8. GRADE tables

Recommendation:

Pending further results from RCTs, currently we do not support the administration of convalescent plasma in hospitalized patients with COVID-19 outside RCTs

Number of studies	Study design	Risk of bias*	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
11 studies [170-178, 180, 181]	RCTs	Serious risk of bias (decision based on the fact that more than >40% of studies were still to be peer-reviewed, only 2 studies were double-blind, and the median time elapsed from onset of symptoms to randomization was as long as 30 days in the RCT by Li and colleagues)	No serious inconsistency	No serious indirectness	Serious imprecision (small sample in the majority of RCT)	No serious risk of publication bias	Low

* For observational studies, the risk of bias was assessed by means of the Newcastle-Ottawa Scale (NOS) [23], whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines [24]. High risk of bias translated to "very serious risk of bias", low risk of bias translated to "no serious risk of bias", whereas moderate/unclear risk of bias translated to "serious risk of bias" or "no serious risk of bias" according to evaluators' judgment.

Recommendation:

Pending further results from RCTs, currently we do not support the administration of anti-COVID-19 hyperimmune immunoglobulin preparations in hospitalized patients with COVID-19 outside RCTs

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

QUESTION 9

Should continuous positive airway pressure (CPAP)/non-invasive ventilation (NIV) be employed for treating inpatients with COVID-19 with acute hypoxemic respiratory failure?

Question 9. Search strings and databases

Pubmed

(helmet[Text Word] OR "noninvasive"[Text Word] OR "non-invasive"[Text Word] OR "positive pressure"[Text Word] OR NIV[Text Word] OR HFNC[Text Word] OR CPAP[Text Word] OR NIPPV[Text Word] OR "nasal intermittent positive pressure ventilation"[Text Word] OR "high flow nasal cannula"[Text Word] OR "non-invasive ventilation"[Text Word] OR "noninvasive ventilation"[Text Word] OR "non-invasive support"[Text Word] OR "noninvasive support"[Text Word] OR "continuous positive airway pressure"[Text Word] OR "positive airway"[Text Word]) AND (COVID-19[Text Word] OR "SARS-CoV-2"[Text Word] OR "2019-nCOV"[Text Word] OR "novel coronavirus" [Text Word])*

Embase

(helmet:ti,ab,kw OR 'positive pressure':ti,ab,kw OR niv:ti,ab,kw OR hfnc:ti,ab,kw OR cpap:ti,ab,kw OR nippv:ti,ab,kw OR 'nasal intermittent positive pressure ventilation':ti,ab,kw OR 'high flow nasal cannula':ti,ab,kw OR 'non-invasive ventilation':ti,ab,kw OR 'noninvasive ventilation':ti,ab,kw OR 'non-invasive support':ti,ab,kw OR 'noninvasive support':ti,ab,kw OR 'continuous positive airway pressure':ti,ab,kw OR 'positive airway':ti,ab,kw) AND ('covid*

19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)

Cochrane COVID-19 Study Register

“"non-invasive" OR "noninvasive" OR "positive pressure" OR "high-flow nasal cannula" OR "continuous positive airway pressure"

– filter: report results

Question 9. Literature review details

Search strings development:

Andrea Gramegna

Dejan Radovanovic

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

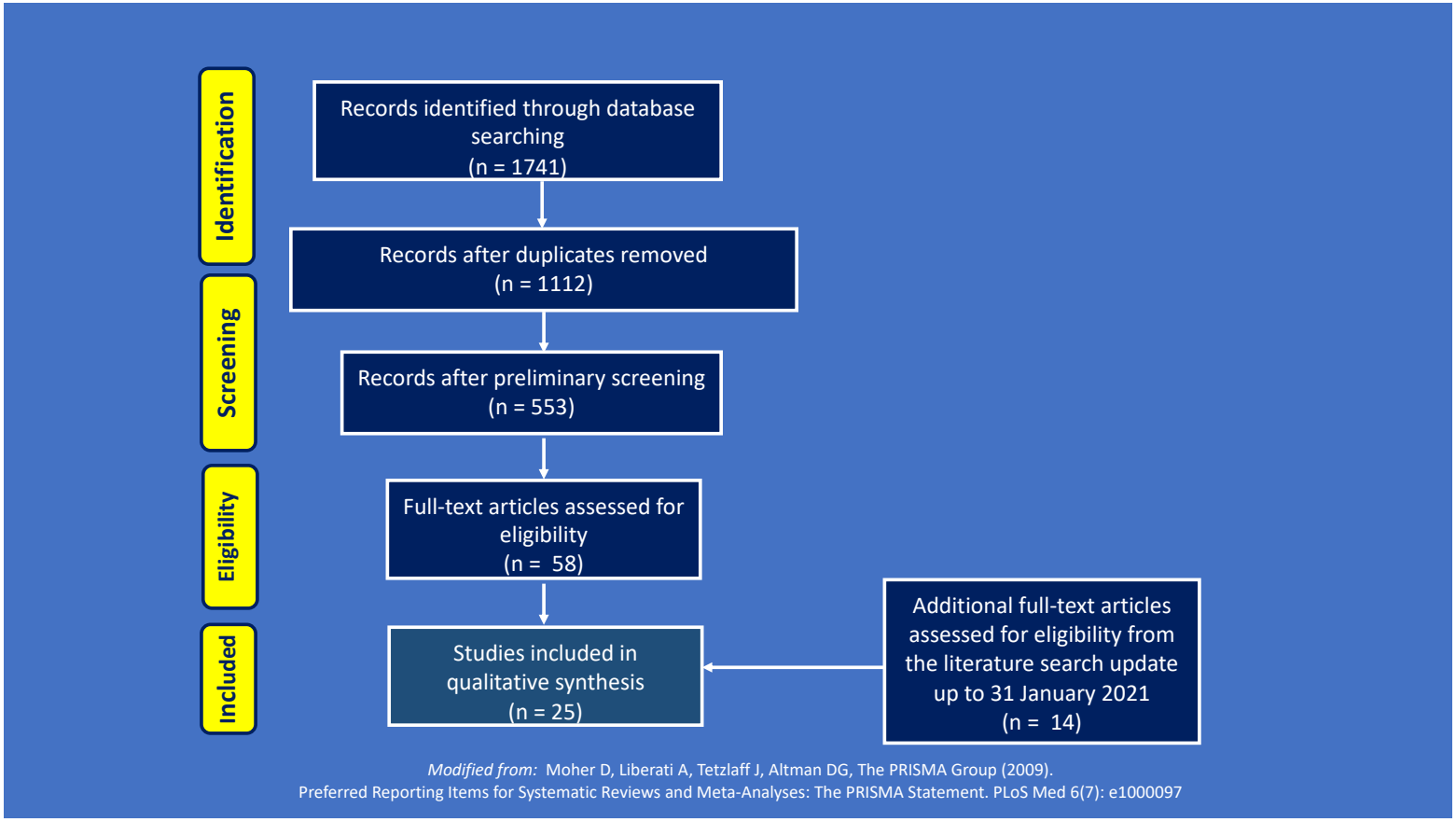
Andrea Gramegna

Dejan Radovanovic

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 9. Workflow of study selection process



Search update

An updated search performed up to 31 January 2021 to retrieve studies published after 20 November 2021 led to the screening of further 381 de-duplicated records, with the ultimate evaluation of 5 additional papers for potential inclusion in qualitative synthesis (see figure above). Finally, 1 randomized controlled trial (RCT) was evaluated during the final literature search update up to 30 April 2021.

Question 9. Extended evidence summary

Included studies

Very strict criteria were applied for the selection of studied to be included in the analysis. Small physiological or proof of concept studies, or, in general, studies with ≤ 20 treated patients, with unclear or pooled outcomes (e.g., for patients treated with non-invasive and invasive mechanical ventilation), were excluded from the final analysis. A final pool of 25 studies was included. When present or specified, patients for which CPAP/NIV was considered the ceiling treatment and that received a “do not intubate” (DNI) order were considered separately when evaluating relevant clinical outcomes. All studies had an observational design, 18 (72.0%) were single center while 7 (28.0%) were multicenter. No RCT were retrieved.

Nine studies (36.0%) [182-190] were conducted in high-dependency respiratory units (HDRU) or in mixed HDRU/general wards settings, 7 (28.0%) in general/medical wards [191-197], and 7 (28.0%) in ICU (with or without other non-ICU wards) [198-204]. Only two studies (one including also general wards) majorly involved the emergency department [205, 206]. The number of patients exposed to CPAP/NIV ranged from 24 [194] to 798 [197], with a mean age that ranged from 52 [194] to 81 years [184]. The proportion of males was always higher when compared to females and spanned from 52-54% [184, 198] to 80-88% [194, 195, 205].

CPAP was the most frequently employed non-invasive ventilatory approach and was reported alone in 13 studies (52.0%) [182, 185-187, 189, 192-195, 200, 201, 203, 204], while NIV only was employed in 4 studies (16.0%) [191, 196, 198, 202]. The remaining 8 manuscripts reported the use of both NIV and CPAP [183, 184, 188, 190, 197, 199, 205, 206]. Excluding patients in whom it was not specified whether they received CPAP or NIV, a total 1607 patients were exposed to CPAP, which was delivered by high-flow generators (with Helmet or Boussignac interfaces) in 6 studies (25.0%) [182, 183, 187, 192, 200, 205],

while ventilators with facial masks were employed in 5 studies (20.0%) [186, 187, 194, 200, 204]. Other studies did not report the delivery systems and the interfaces used for CPAP or reported more than 1 interface [184, 185, 188, 189, 193, 195, 197, 199, 201, 203]. Excluding patients in whom it was not specified whether they received CPAP or NIV, a total 715 patients underwent a NIV trial, with only one study reporting the ventilator used [191]. The study by Rahim et al. included 126 patients that underwent CPAP/NIV without distinguishing between the two approaches [199]. A clear distinction of the number of patients receiving CPAP or NIV among those ultimately retained in the analysis was not possible in the studies by Bellani et al and by Potalivo et al [197, 206].

Indications and settings

Criteria for initiating CPAP were different in all studies. The severity of respiratory failure was used by Aliberti et al. (PaO2/FiO2 < 300 mmHg while receiving an FiO2 of 50-100%) [182], De Vita et al. (respiratory distress despite Venturi mask up to FiO2 50% and PaO2/FiO2 < 200 mmHg) [189], Brusasco et al. (PaO2/FiO2 < 200 mmHg, or PaO2 < 60 mmHg, or respiratory rate > 30/min on room air) [192], and Duca et al. (PaO2 < 60 mmHg, or respiratory rate > 30/min while on 100 FiO2 nonrebreather mask) [205]. A variable threshold for peripheral oxygen saturation (SpO2) of 90% [200], 92% [187] and 94% [183, 184, 195] while receiving oxygen at inspired fractions ranging from approximately 40% [184, 187, 204], to 100% [195, 200] was sometimes coupled with the alternative presence of respiratory distress [200], or tachypnea [202]. In a few cases criteria for initiating the CPAP therapy were limited to the presence of respiratory failure [194, 201, 206], or to increased oxygen requirements with unspecified target SpO2. Indications for CPAP were not specified in 5 cases [186, 193, 197, 199, 203].

Criteria for NIV included: the presence of chronic respiratory failure on top of a SpO2 < 94% with < 40% FiO2 [184], a SpO2 < 92%while receiving O2 [190, 191, 202], the

evidence of respiratory acidosis or fatigue/distress [188, 190, 191, 205], or as an alternative to CPAP in case of shortage of CPAP helmets [183]. In 5 studies, clear indications for NIV were not provided [196-199, 206].

The PEEP value used during CPAP in the majority of studies ranged from 5-6 to 10-12 cmH2O, only in two cases going up to 14 [184] and 15 cmH2O [205]. Only a few manuscripts indicated the NIV setting. For example, Avdeev and colleagues reported a median value of pressure support of 9.9 (9.8-10.3) cmH2O [191], while Duca et al reported that patients treated with NIV were exposed to higher PEEP values (16 cmH2O, range 12-20), compared with CPAP [205]. PEEP values were missing in 11 studies.

Patients eligible for CPAP had generally a moderate to severe respiratory failure, with PaO2/FiO2 values before the initiation of the non-invasive support ranging between a median of 90 (IQR, 37.5-232) mmHg [201] and 170 (IQR, 112-224) mmHg [202]. In three studies data on respiratory failure were not reported [185, 198, 199].

Primary outcomes

The majority of studies (n = 15, 60%) had composite primary endpoints based on CPAP/NIV failure, intended as the proportion of patients that during the study period were intubated or died while on invasive mechanical ventilation or receiving CPAP/NIV in those with a DNI order. Five studies (20%) had descriptive and broad outcomes regarding the use of non-invasive support and the impact of patients' characteristics on clinical outcomes. Differential mortality in patients exposed to CPAP or NIV was reported in all studies, except for five cases (20%), in which mortality data were pooled between patients treated with CPAP or NIV [184, 191, 197, 199, 206]. The latter was also true for endotracheal intubation rate/need for invasive mechanical ventilation, which were present in all studies, but five (20%): Avdeev and colleagues did not differentiate intubated patients between CPAP and NIV groups [191], one study included only DNI patients [184], and in four cases data on intubation for the

denominators of interest was missing [188, 193, 199, 203]. Complications related to CPAP or NIV application were infrequently reported [182, 183, 185].

Outcomes and safety of CPAP

Mortality rates in patients treated with CPAP ranged from 14%-23% [182, 1186, 192, 194, 195] to 43-55% [195, 201], but possibly reached 84% as ceiling treatment [204]. Endotracheal intubation and therefore need for invasive mechanical intubation was observed in 41% to 63% of patients treated with CPAP [186, 189, 200, 201], but in some cases the proportion was as low as 11% [192]. In the studied conducted by Avdeev et al. [191] and Burns et al. [184], COVID-19 patients hospitalized with acute respiratory failure were treated either with CPAP (n = 45 and n = 23, respectively) or with NIV (n = 16 and n = 5). Pooling outcomes for the CPAP and NIV groups, Avdeev and colleagues found a mortality of 23% and an intubation rate of 28% [191], and Bellani and colleagues found a mortality of 25% and an intubation rate of 18% [197] while pooled results from Burns et al demonstrated a 50% mortality among DNI patients [184]. Aliberti and coworkers reported a 1.9% occurrence of pneumothorax/pneumomediastinum in patients exposed to CPAP treatment [182], while Franco et al. reported none [183]. Tolerance to CPAP was generally under-reported, with available data on proportion of CPAP interruption ranging from 0% [195] to 44% [194].

Outcomes and safety of NIV

Mortality in patients treated with NIV was reported in 4 studies. Karagiannidis and colleagues reported a comparable mortality between patients treated with NIV (44.8%) and those treated with NIV that were eventually exposed to invasive mechanical ventilation (49.6%) in a large multicenter retrospective study conducted in Germany (n = 286/1727 treated with NIV) [198]. Mortality was 52% (n = 13/25) in the study by Carpagnano and colleagues [188].

A much lower mortality was observed in the study by Mukhtar and colleagues, conducted in Egypt on a sample of 55 patients, of which 39 (71%) underwent a NIV trial. Mortality was 10%, while the intubation rate was unclear, as only data regarding directly intubated patients was available [202]. Sivaloganathan and coworkers performed a retrospective analysis of patients admitted with respiratory failure and COVID-19 pneumonia in UK, including 82 patients exposed to NIV, of which 24 received a DNI order and for which NIV represented the ceiling treatment [196]. Mortality was 5% in non-DNI patients (but 17 were still hospitalized at the moment of writing) and 83% among DNI patients. Among patients eligible for endotracheal intubation, 46% were intubated. Complications and intolerance specifically related to NIV was missing in the selected studies.

Comparison of CPAP vs. NIV and of CPAP/NIV vs. other ventilatory supports

None of the studies was aimed at comparing CPAP or NIV outcomes with other respiratory approaches. Indirect comparisons for mortality could be extrapolated in four studies. Duca and colleagues reported patients' characteristics, severity of respiratory failure at presentation and the respiratory support used in their emergency department during the first Italian pandemic wave in 2020 [205]. The authors showed comparable mortality rates for patients treated with CPAP (54,9%) and with NIV (57.1%). The intubation rate was 36.6% for the CPAP group and 0% for the NIV group. But the latter result is limited by the small number of patients treated with NIV (n=7), of which 4 died because received a DNI order [205]. Franco et al. conducted a multicenter study including ICU patients with COVID-19 pneumonia and acute respiratory failure treated with CPAP (n=330) or NIV (n=177) [183]. The study showed similar mortality for the two groups (30.3 vs. 30.5%; unadjusted p-value = 0.20, adjusted p-value = 0.88), and similar intubation rates (24.8 vs. 27.7%; unadjusted p-value = 0.80, adjusted p-value = 0.65) [183]. Mortality was lower in patients treated with CPAP (52%, 13/25) than in those treated with NIV (52%, 13/25) in the study by Carpagnano

and colleagues, although the two approaches could have been used subsequently [188]. Oranger and coworkers compared two historical cohorts treated with either O2 (n = 14, first cohort) or CPAP (n = 38, second cohort). Mortality was higher in patients treated with O2 as the ceiling treatment (2 deaths vs. none), and the intubation rate lower (42.8% vs. 23.7%; p = 0.043) [187]. There are several issues that may limit the generalizability of the study results, namely the short follow up period (7 days), the small sample size of the first cohort, and the limited ceiling treatment in patients treated with only O2 in the first cohort of patients [187]. Finally, Rahim et al retrospectively analyzed data from 204 COVID-19 patients admitted to the ICU with respiratory failure, of which 126 were treated either with CPAP or NIV [199]. The authors found that patients treated non-invasively had a lower mortality (66.7%) compared with intubated patients (93.6%). However, the unreported criteria for CPAP or NIV initiation, the unknown proportion of patients treated with CPAP or NIV, and the number of patients that were intubated after a CPAP/NIV trial, largely limit the interpretation of such results [198].

Supplementary table S3. Summary of included studies

Study, year [ref]	Design	Population/subgroup of interest for the present review (No. patients)	Primary/major endpoint/s of interest for the present review*	Mortality	Intubation
			Definition **No./total (%)**	***Follow-up**** **No./total (%)**	***Follow-up**** **No./total (%)**
Aliberti et al., 2020 [182]	Multicenter Prospective	COVID-19 patients with pneumonia-related respiratory failure undergoing CPAP treatment (157)	*CPAP failure (defined as the occurrence of either intubation or death due to any cause)* 70/157 (45%)	*30 days* 36/157 (23%)	*30 days* 34/157 (22%)
Alviset et al., 2020 [200]	Single center Retrospective	COVID-19 patients treated with CPAP due to respiratory failure (49)	*Discontinuation of CPAP (for various reasons ranging from improvement to death)* 49/49 (100%)	*Not specified* 18/49 (37%)	*Not specified* 24/41*** (59%)
Arina et al., 2020 [201]	Single center Retrospective	COVID-19 ICU patients with moderate-to-severe respiratory failure who received initial management with CPAP (93)	*CPAP success (defined as hospital survival with CPAP alone)* 32/93 (34%) *CPAP failure (defined as either death when CPAP was a ceiling of treatment, or need for mechanical ventilation regardless of hospital outcome)* 61/93 (66%)	*Not specified* 47/93 (51%)	*Not specified* 40/93 (43%)
Avdeev et al., 2020 [191]	Multicenter Retrospective	COVID-19 patients with respiratory failure receiving NIV/CPAP in general wards (61)	*NIV/CPAP failure (defined as intubation or death during the hospital stay)* 17/61 (28%)	*Not specified* 15/61 (25%)	*Not specified* 17/61 (28%)

Bellani et al., 2020 [197]	Multicenter Prospective	COVID-19 patients with respiratory failure receiving NIV/CPAP in general wards (798)	*NIV/CPAP failure (defined as intubation or death during the hospital stay)* 300/798 (38%)	*In-hospital* Reported as 25% in the study cohort	*Not specified* 123/798 (15%)
Brusasco et al., 2020 [192]	Single center Retrospective	COVID-19 patients with moderate-to-severe respiratory failure who received initial management with CPAP (64)	*Survival without invasive mechanical ventilation* 53/64 (83%)	*28 days* 9/64 (14%)	*28 days* 7/64 (11%)
Burns et al., 2020 [184]	Single center Retrospective	Severely hypoxic COVID-19 patients deemed unsuitable for invasive ventilation and treated with NIV/CPAP (28)	*Mortality* 14/28 (50%)	*Not specified* 14/28 (50%)	-
Carpagnano et al., 2020 [188]	Single center Retrospective	Patients with COVID-19 and mild-to-moderate ARDS treated with NIV/CPAP (61)	*Mortality* CPAP: 12/36 (33%) NIV: 13/25 (52%)	*In-hospital* CPAP: 12/36 (33%) NIV: 13/25 (52%)	-
De Vita et al., 2020 [189]	Multicenter Retrospective	Patients with COVID-19 treated with CPAP outside the ICU (367)	*Intubation* 150/367 (41%)	-	*Not specified* 150/367 (41%)
Duca et al., 2020 [205]	Single center Retrospective	Patients with COVID-19 admitted to the ED and requiring CPAP/NIV (78)	*CPAP/NIV failure (defined as death or intubation)* CPAP: 65/71 (92) NIV: 4/7 (57)	*Not specified* CPAP: 54/71 (76%) NIV: 4/7 (57%)	*Not specified* CPAP: 26/71 (37%) NIV: 0/7 (0%)
Faraone et al, 2021 [190]	Single center Retrospective	COVID-19 patients treated with NIV/CPAP in general wards (50)	*NIV/CPAP failure (defined as switch to invasive mechanical ventilation and acute hypoxemic respiratory failure-related death)* 28/50 (56%)	*In-hospital* 25/50 (50%)	*Not specified* 9/25*** (36%)
Franco et al., 2020 [183]	Multicenter Prospective	Patients with COVID-19 requiring CPAP/NIV outside the ICU (507)	*Death or intubation* CPAP: 156/330 (47) NIV: 94/177 (53)	*30 days* CPAP: 100/330 (30%) NIV: 54/177 (31%)	*30 days* CPAP: 82/322*** (25%) NIV: 49/169*** (29%)
Hallifax et al. 2020 [185]	Single center Retrospective	Patients with COVID-19 requiring CPAP/NIV outside the ICU (51)	*Death or intubation* CPAP: 37/48 (77%)	*Not specified* CPAP: 28/48 (58%)	*Not specified* CPAP: 11/48 (23%)

			NIV: not reported	NIV: not reported	NIV: not reported
Karagiannidis et al., 2020 [198]	Multicenter Retrospective	Patients with COVID-19 requiring NIV (286)	*Mortality and NIV failure with subsequent invasive mechanical ventilation, assessed separately (see columns on the right)*	*In-hospital* 135/286 (47%)	*Not specified* 141/286 (49%)
Knights et al., 2020 [193]	Single center Retrospective	Hospitalized patients requiring CPAP as ceiling treatment (17)	*Mortality* 7/17 (41)	*Not specified* 7/17 (41%)	-
Mukhtar et al., 2020 [202]	Single center Retrospective	COVID-19 ICU patients treated with NIV (30)	*Mortality* 3/30 (10%)	*In-hospital* 10/39 (26%)	*Not specified* 9/39 (23%)
Nightingale et al., 2020 [194]	Multicenter Retrospective	COVID-19 patients with respiratory failure undergoing CPAP treatment outside the ICU (24)	*Death or intubation* 10/24 (42%)	*Not specified* 5/24 (21%)	*Not specified* 9/24 (38%)
Noeman-Ahmed et al., 2020 [186]	Single center Retrospective	COVID-19 patients with respiratory failure undergoing CPAP treatment in an acute respiratory care unit (52)	*CPAP outcome (see columns on the right)*	*Not specified* 18/52 (35%)	*Not specified* 21/41*** (51%) patients failed CPAP trial (not specified if all ultimately intubated)
Oranger et al., 2020 [187]	Single center Retrospective	COVID-19 patients with respiratory failure undergoing CPAP treatment in a pulmonology unit (38)	*Intubation (in patients without DNI order)* 9/38 (24%)	*7 days* 0/38 (0%)	*7 days* 9/38 (24%)
Potalivo et al., 2020 [206]	Multicenter Retrospective	Proven/suspected COVID-19 inpatients who required NIV/CPAP (71)	*NIV/CPAP outcome (see columns on the right)*	*60 days* 17/71 (24%)	*60 days* 25/71 (35%)
Rahim et al., 2020 [199]	Single center Retrospective	COVID-19 ICU patients treated with CPAP/NIV (126)	*Mortality* 84/126 (67%)	*In-ICU* 84/126 (67%)	*Not specified*
Ramirez et al., 2020 [195]	Single center Prospective	COVID-19 patients with ARDS undergoing CPAP treatment outside the ICU (90)	CPAP failure (defined as intubation/ICU admission or death) 35/90 (39)	*Not specified* 17/90 (19%)	*Not specified* 29/90 (32%)

Sivaloganathan et al., 2020 [196]	Single center Prospective	COVID-19 patients with respiratory failure undergoing NIV treatment (82)	*CPAP outcome (see columns on the right)*	*Not specified* 23/82 (28%)	*Not specified* 27/82 (33%)
Thompson et al., 2020 [203]	Single center Retrospective	Hospitalized COVID-19 patients undergoing CPAP treatment	*Mortality* 13/39 (33%)	*Up to 30 days after discharge* 13/39 (33%)	-
Walker et al., 2020 [204]	Multicenter Retrospective	Hospitalized COVID-19 patients undergoing CPAP (60)	*Mortality* CPAP as ceiling treatment: 16/19 (84%) *CPAP failure (defined as death or intubation)* CPAP not as ceiling treatment: 25/44 (57%)	*Not specified* CPAP as ceiling treatment: 16/19 (84%)	-

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; DNI, do not intubate; ICU, intensive care unit; NIV, non-invasive ventilation.

* When the primary endpoint was not specified, we reported composite outcomes of death/intubation, whenever indicated in the study

** "Not specified" follow-up also refers to those study in which follow-up was interrupted on a given date

*** DNI patients excluded from the denominator

Question 9. GRADE tables

Recommendation:

Unless contraindicated, non-invasive ventilatory support by means of NIV or CPAP is feasible and safe in patients with acute respiratory failure secondary to COVID-19, and should be considered for patients in whom standard oxygen supplementation is not or no longer sufficient and who do not require immediate intubation

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:

CPAP delivery systems allowing for PEEP titration should be preferred, and PEEP should not exceed 10 cmH2O

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

QUESTION 10

When can an improved patient with COVID-19 be discharged from an acute care hospital?

Question 10. Search strings and databases

Pubmed

(discharge [Text Word]) AND (predict* [Text Word] OR criter*[Text Word] OR prognos*[Text Word]) AND (coronavirus[MeSH Terms] OR COVID-19[Text word] OR "SARS-CoV-2"[Text word] OR "2019-nCOV"[Text word] OR "novel coronavirus" [Text word])*

Embase

(discharge:ti,ab,kw) AND (predict*:ti,ab,kw OR criter*:ti,ab,kw OR prognos*:ti,ab,kw) AND (coronavirus:ti,ab,kw OR 'covid 19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'novel coronavirus':ti,ab,kw)*

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discharge AND predict OR criter* OR prognos* - filter: report results*

– filter: report results

Question 10. Literature review details

Search strings development:

Andrea Lombardi

Silvia Corcione

Alberto Enrico Maraolo

Language restrictions:

None

Search period:

From Inception of January 2020 to 20 November 2020. The search was subsequently updated to 31 January 2021, and then to 30 April 2021 (the latter update was restricted to the addition of results from novel randomized controlled trials potentially impacting recommendations).

Screening and selection of retrieved evidence (independently):

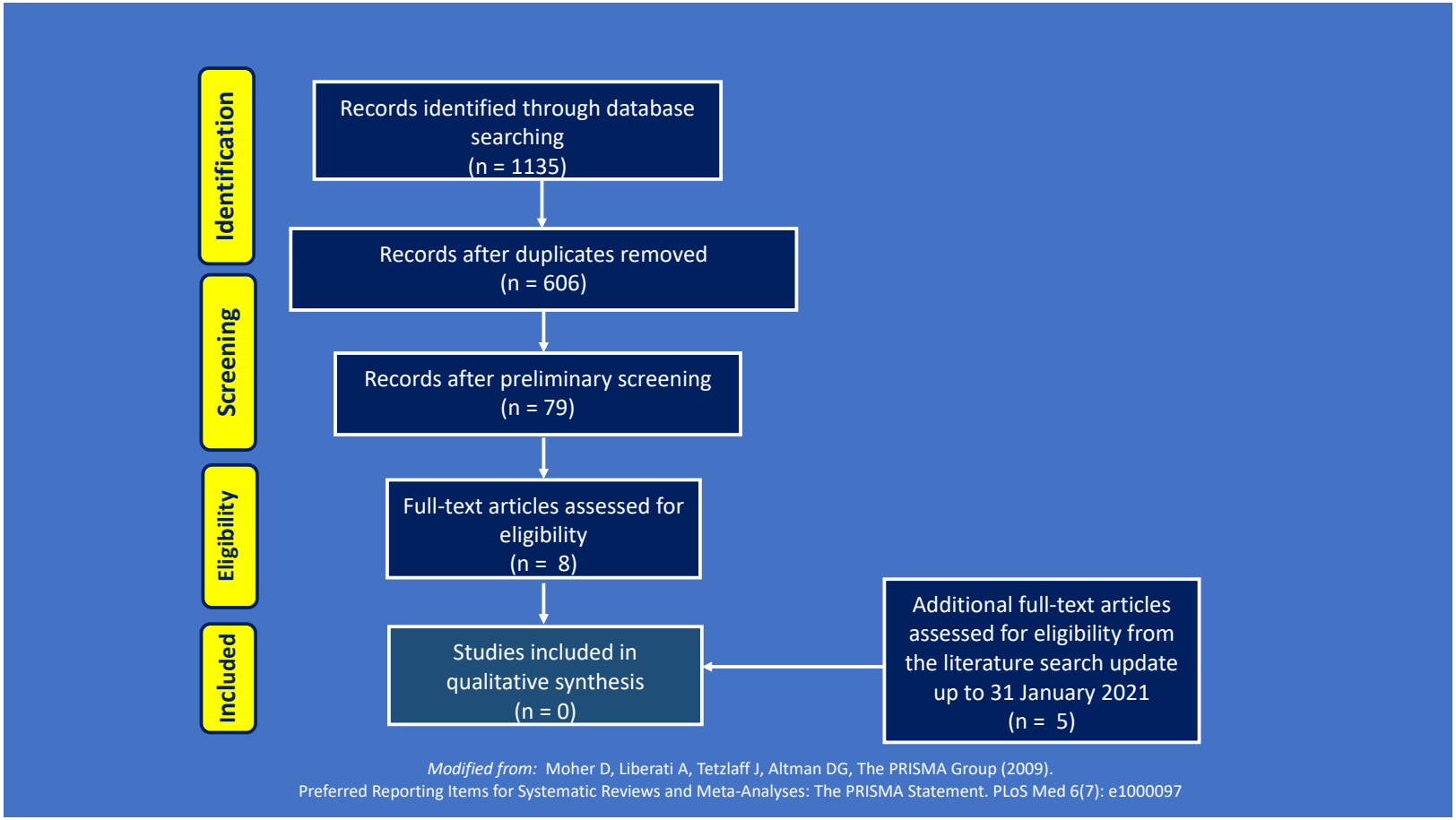
Andrea Lombardi

Silvia Corcione

Third reviewer for resolving possible disagreements:

Daniele Roberto Giacobbe

Question 10. Workflow of study selection process



Search update

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Question 10. GRADE tables

Recommendation:

Clinically stable patients with COVID-19 who no longer require isolation (or who can be isolated outside the hospital) should be discharged from acute care hospitals when oxygen supplementation is no longer required or with a maximum requirement of low-flow oxygen at 2 L/min through nasal cannula (with the exception of patients already under oxygen supplementation at home at baseline or patients requiring initiation of long-term oxygen therapy after discharge evaluation), in line with common practice with other types of non-contagious lower respiratory tract infections, and provided there are no complications or other reasons that require continuation of hospitalization

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

Recommendation:

For patients with COVID-19 still requiring isolation but who could be discharged from a clinical standpoint, isolation outside the hospital (at home, in community facilities, or in long-term facilities, according to the specific need for non-acute care of any given patient) should be supported and made feasible for as many patients as possible

Best practice recommendation (based on expert opinion only; the retrieved evidence was deemed as insufficient for developing a recommendation based on the GRADE system)

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