# Should corticosteroids be used as an adjunct in the treatment of COVID-19?

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## KEY FINDINGS

Contradictory results from low-quality observational studies do not support the routine use of corticosteroids as an adjunct in the treatment of COVID-19 beyond their usual indication. Caution must be exercised to weigh risks and benefits of their use.

- Corticosteroids are potent anti-inflammatory hormones that may temper the severe inflammatory response to COVID-19.
- They have been historically used during the SARS-CoV and MERS-CoV outbreaks to subdue lung inflammation caused by the cytokine storm characteristic of coronavirus infections.
- At present, there are no published clinical trials on the use of corticosteroids for COVID-19.
- Evidence from low-quality observational studies show contradictory results with possibility for both harm and benefit with the use of corticosteroids as an adjunct in the treatment of COVID-19.
- Our meta-analysis of 4 retrospective studies (n=1291) on the outcome of mortality in severe COVID-19 was inconclusive OR 1.48 [95% 0.56, 3.91, I2=59%]. However, a subgroup analysis of COVID-19 patients without ARDS showed significant increase risk for mortality OR 2.52 [95% 1.17, 5.42, I2=0%] .
- Our meta-analysis of 2 retrospective studies (n=97) on duration of oropharyngeal viral clearance in corticosteroid-exposed and unexposed groups showed inconclusive results due to high degree of heterogeneity with mean difference of 3.38 days [95%CI -1.42, 8.18, $I^2$ = 96%].
- Several observational studies showed potential benefits (shortened duration of fever and shortened duration of oxygen supplementation while other observational studies potential harm (prolonged duration of symptoms, prolonged hospital stay, increased risk for ICU admission and delayed fecal nucleic acid clearance)
- As of April 27, 2020, there are currently 16 planned and on-going clinical trials about this topic, with 1 completed trial awaiting results.
- WHO 2020 guidelines in the clinical management of severe acute respiratory infection (SARI) when COVID 19 is suspected recommends **against** the routine use of systemic corticosteroids for treatment. The Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) **recommends** the use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and ARDS (weak recommendation and low quality evidence). The 2020 Philippine Society of Microbiology and Infectious Disease (PSMID) Clinical Practice Guideline on Sepsis and Septic Shock, **recommends** the use of corticosteroids among critically-ill patients with refractory shock.

## RESULTS

There are currently no published clinical trials on the efficacy of corticosteroids as an adjunct in the treatment of COVID-19.

We found six retrospective observational studies done from December 2019 to February 2020 all done in China (1 case control and 5 case series) that evaluated the use of corticosteroids in COVID-19 and its association with different clinical outcomes.

Meta-analysis of 6 studies

Death (4 studies)

Our meta-analysis of four observational studies (17)(18)(22)(24) comparing the mortality rate of COVID-19 patients who received corticosteroids (n=311) to those who did not (n=980), showed an inconclusive overall OR 1.48 [95% 0.56, 3.91, $I^2$=59%]. However, a subgroup analysis that included only COVID-19 patients without ARDS showed a significant increase in mortality OR 2.52 [95% 1.17, 5.42, $I^2$=0%] among those who received corticosteroids [Figure 1].

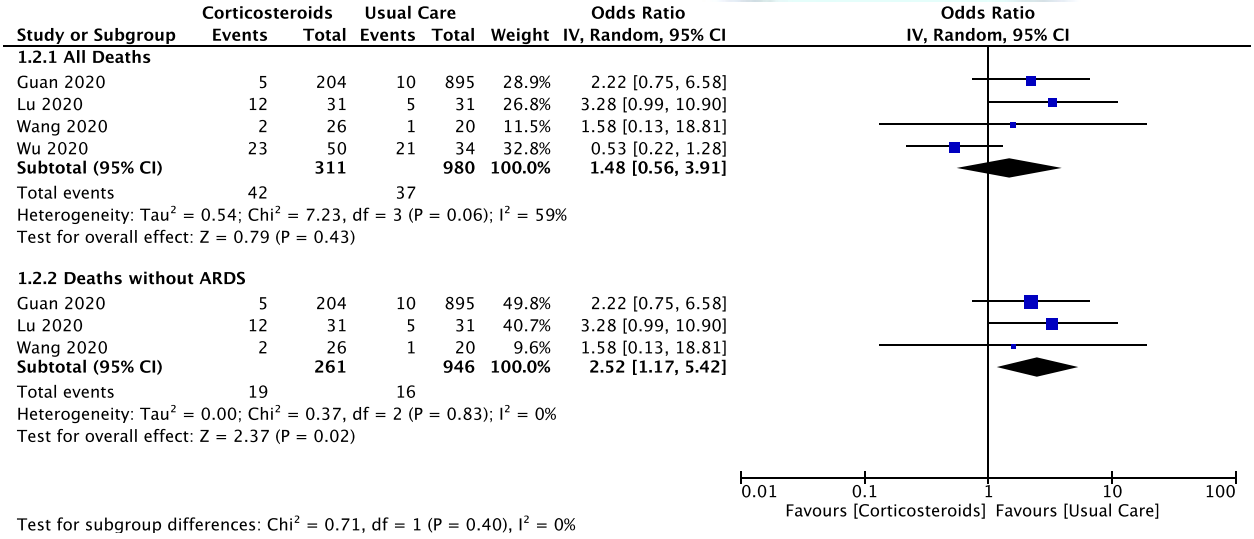


Figure 1. Forest plot of use of corticosteroids and risk of death

Viral Clearance (2 studies)

*Oropharyngeal Nucleic Acid Detection*

The risk of prolonged viral shedding detected by SARS-CoV-2 nucleic acid determination among recovered patients was reported in 2 retrospective studies (8)(23). Pooled mean difference of the duration of viral shedding among those who received corticosteroids to those who did not was inconclusive because of significant heterogeneity with mean difference of 3.38 days [95%CI -1.42, 8.18, $I^2$ = 96%] [Figure 2 ].

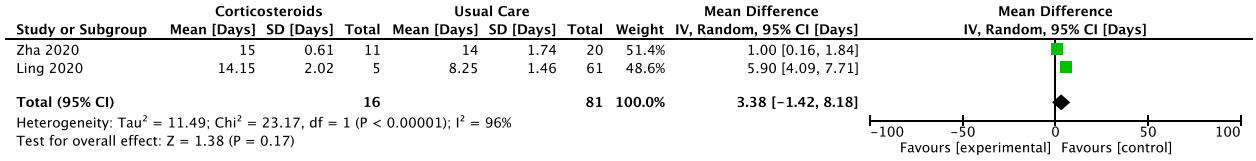


Figure 2. Forest plot on the use of corticosteroids and oropharyngeal nucleic acid clearance time in days

*Fecal Nucleic Acid Detection*
Ling et al. retrospectively demonstrated that corticosteroids significantly prolonged fecal nucleic acid clearance times with a mean difference of 8.75 days [95% 7.42, 10.08, p<0.0001] when patients given corticosteroids were compared to those who were not.

Other Outcomes
Duration of symptoms (1 study)
Zha et al.(8), retrospectively reported median duration of symptoms in 11 corticosteroid patients as 8 days (IQR 5-12) vs 20 non-corticosteroid patients with resolution of symptoms in a median of 6.5 days (IQR 4-9.25). When converting their data to mean and (SD) following the method by Hozo (21), use of corticosteroids significantly lengthened the duration of symptoms with a mean difference of 1.69 days [95% 0.31, 3.07, p=0.02], favoring the non-steroid group.

Duration of fever (1 study)
Wang et al (18) when retrospectively comparing 26 COVID-19 patients given corticosteroids to 20 who were not showed that the mean difference of fever duration was -2.33 days [95% -2.66, -2.00, p<0.00001], favoring corticosteroid use to shorten the duration of this endpoint.

Oxygen supplementation (1 study)
The duration of oxygen support among non-intubated COVID-19 patients was significantly shortened by the use of steroids in the study by Wang et al. (n=46) (18), giving a mean difference -4.90 days [95% -5.72, -4.08, p<0.0001]. This is one of the bases of the conditional recommendation of the Surviving Sepsis Guidelines on the use of steroids for COVID-19 patients.

Clinical Recovery (1 study)
In a retrospective study of COVID19 patients (8), methylprednisolone given 40mg once or twice a day within 24 hours of (n=15) did not show any significant difference in clinical recovery compared to those who did not receive it (n=14) OR 8.16 [95%, 0.41,162.92].

Composite Outcome of Death, ICU Admission and Mechanical Ventilation (1 study)
In another retrospective study by Guan et al. (22), corticosteroid-use was shown to significantly increase the risk of their primary composite outcome (death, mechanical ventilation and ICU admission) compared to those who did not receive corticosteroids [OR 5.59 [95% 3.36, 9.27]. However, on secondary analysis of their data showed that only ICU admission among the other outcome measures was found to be the significant [OR 7.66, 95% 4.36, 13.46].

Length of hospital stay (1 study)
Use of corticosteroid significantly prolonged hospital stay in the study by Zha et al. (8), with a mean difference of 2.50 days [95% 1.79, 3.21] compared to those who did not receive corticosteroids..

In summary based on low-quality data, there is inconclusive results for the use of corticosteroids as adjunctive therapy in relation to mortality, clinical recovery and duration of viral shedding. Corticosteroid use may significantly prolong duration of symptoms, hospital stay, fecal nucleic acid clearance and increase risk of ICU admission. In addition, corticosteroid may significantly decrease the duration of fever and the duration of use of oxygen supplementation. These results should be interpreted with caution, considering the limitations of retrospective study designs, small sample size and multiple confounders unaccounted for in these studies.

## CONCLUSION

- Evidence from low-quality observational studies show contradictory results with possibility for both harm and benefit with the use of corticosteroids as an adjunct in the treatment of COVID-19.

- Meta-analysis of observational studies showed possibility of significant higher risk for mortality among COVID-19 patients without ARDS who received corticosteroids.
- Potential benefits from low-quality evidence in single retrospective cohorts include shortened duration of oxygen support and to shortened duration of fever.
- Possible harm on the use of glucocorticoids include: 1) prolonged of duration of symptoms, 2) increased risk of ICU admission, 3) prolonged duration of hospital stay and 4) prolonged fecal nucleic acid clearance.
- Limitations of current recommendations are due to lack of well-designed RCTs and high-risk of bias in included studies, with care given to interpretation and applying results.
- Sixteen ongoing trials may give more insight to these recommendations once completed in 2020.

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## Table 1. Characteristics of included studies

| No. | Title/Author | Study design | Country | Population | Exposure | | Outcomes | Key findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | Intervention Group(s) | Comparison Group(s) | | |
| 1 | Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19)/Zha, L et al. (5) | Case series | China | 31 patients with severe respiratory COVID-19 | 11 Corticosteroid patients (Methylprednisolone 40mg OD to BID x 5 days | 20 Non-corticosteroid patients | Primary outcome: Virus clearance Secondary outcomes: Duration of clinical recovery Duration of Symptoms Length of Hospital Stay | No statistically significant differences in virologic and clinical outcomes between corticosteroid and non-corticosteroid groups. |
| 2 | The persistence and clearance of viral RNA in 2019 novel coronavirus disease survivors /Ling Y et al. (7) | Case series | China | 66 convalescent COVID-19 patients | Viral RNA detection in throat swabs, stool, urine and serum specimen with multiple regression to determine factors affecting viral shedding duration | | Corticosteroid exposure; other factors affecting viral shedding duration | 5 patients out of the 66 received corticosteroids. The duration of viral RNA detection for throat swabs and feces in the corticosteroid treatment group was longer than that in the non-corticosteroid group (15 days vs 8 days ($p = 0.13$), and 20 days vs 11 days ($p < 0.001$, respectively. The use of corticosteroids may delay the clearance of virus and should be avoided during viral replication. |
| 3 | Adjuvant corticosteroid therapy for critically ill patients with COVID-19 /Lu, X et al. (4) | Case control | China | 62 patients (31 pairs in propensity-score matching | 28-day mortality after admission | | With or without corticosteroid exposure | Corticosteroid used on multivariate analysis was not associated with overall mortality. |
| 4 | Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China/Wang Y et al. (2) | Case series | China | 46 COVID-19 patients | With corticosteroids | Without corticosteroids | Demographic and clinical characteristics | Average number of days with fever was lower in the corticosteroid group (2.06 vs 4.39, p=0.01). Oxygen saturation improvement was faster for the corticosteroid group, with lesser days on supplemental oxygen (8.2 vs 13.5, p<0.001) |
| 5 | Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, | Case series | China | 201 patients with COVID-19 | Development of ARDS and death among patients with ARDS Pneumonia Severity Index | | Methylprednisolone No Methylprednisolone Other risk factors | The administration of methylprednisolone appears to have reduced the risk of death among patients with ARDS (HR 0.38; 95%CI, 0.20-0.72, p=0.003) |

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| | China/Wu C et al. (1) | | | | | | | |
| 6 | Clinical Characteristics of Coronavirus Disease 2019 in China/Guan, W (3) | Case series | China | 1099 patients with COVID -19 | With corticosteroids | Without corticosteroids | Primary composite endpoint of death, use of mechanical ventilation, ICU admission | Corticosteroid use was done more frequently for patients with severe disease than non-severe disease (44.5% vs. 13.7%). Secondary analysis of data showed RR 4.80 [95% CI 3.05, 7.56, p<0.00001] in the primary composite outcome favoring non-usage of corticosteroids |
| 7 | Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study/Du, Y et al. (8) | Case series | China | 85 fatal cases of COVID-19 | N/A | N/A | Medical history, exposure history, symptoms, laboratory findings Imaging and clinical management | 65 (76.5%) of the 85 included patients received glucocorticoids. Eosinophilopenia may indicate poor prognosis. Use of corticosteroids did not improve patients' outcome |
| 8 | COVID-19 in a patient with long-term use of glucocorticoids: A study of a familial cluster/Han, Y et al. (9) | Case series | China | 5 cases of COVID-19 belonging to a single family with the index case having SLE on prednisone 7.5mg/day, and seeming atypical symptoms | Index case with SLE on prednisone maintenance therapy | 2 patients who are household contacts of index case | Epidemiological data, incubation period, clinical characteristics | Use of corticosteroids may lead to absence of symptoms, or prolongation of asymptomatic phase (28 days in this case series), with possible delay in viral shedding. |
| 9 | Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms/Jin X et al. (10) | Case series | China | 651 patients with COVID-19 | 74 patients with GI symptoms | 577 patients without GI symptoms | Epidemiological, clinical and virological characteristics of patients with COVID-19 with GI symptoms | No significant difference in the use of glucocorticoid therapy between the two groups. |
| 10 | Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China/Zhen F et al. (11) | Case series | China | 25 pediatric patients with COVID-19 | N/A | N/A | Demographic data, epidemiological history, underlying diseases, clinical manifestations, laboratory and radiological data, treatments and outcomes | Only 2 critical patients were given corticosteroids |
| 11 | Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing/Wan, S et al. (12) | Case series | China | 135 adult patients with COVID-19 | N/A | N/A | Epidemiological, clinical features, laboratory findings, radiological characteristics, treatment and clinical outcomes | 36 patients (26.7%) received corticosteroids. More patients in the severe group were given corticosteroids. |

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| 12 | The clinical characteristics of pneumonia patients co-infected with 2019 novel coronavirus and influenza virus in Wuhan, China/Ding Q et al (13) | Case series | China | 5 COVID-19 patients with simultaneous influenza virus infection | N/A | N/A | Medical history, clinical symptoms, laboratory findings, chest computed tomography (CT) scans and treatment and outcomes data | 3 out of the 5 patients with COVID-19 and influenza co-infection were given corticosteroids. All patients were discharged without ICU care |
| 13 | Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia/Zhou W et al. (14) | Case series in a correspondence article | China | 15 confirmed critical COVID-19 patients | With Corticosteroids | Without Corticosteroids | ICU mortality, oxygen saturation, arterial oxygen tension, invasive mechanical ventilation | Inconclusive data re: the role of corticosteroids in the treatment of critically-ill COVID-19 patients |
| 14 | Medical treatment of 55 patients with COVID-19 from seven cities in northeast China who fully recovered: a single-center, retrospective, observational study/Fan L et al. (15) | Case series | China | 55 COVID-19 patients | N/A | N/A | Clinical manifestations, laboratory and radiological findings, total patient recovery rate | 7 patients (13%) received glucocorticoids during the rapid progression of their disease. Glucocorticoids were unnecessary for patients with mild disease, their use in treating patients with severe disease is still controversial |

## Table 2. Characteristics of clinical trials

| Number (Reference) | Clinical Trial ID / Title | Status | Start and estimated primary completion date | Study design | Country | Population | Intervention Group(s) | Comparison Group(s) | Outcomes |
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| 1 (16) | ChiCTR2000029386/ Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: a randomized controlled trial | Recruiting | Jan 29, 2020-Jan 29, 2021 | RCT, Parallel assignment | China | 1. Male or female over 18 years of age;<br>2. Novel coronavirus infection is confirmed by pathogenic detection;<br>3. The diagnosis of severe coronavirus pneumonia will have to meet at least one of the following criteria:<br>(1) Respiratory distress, RR>30 times/minute<br>(2) In the state of no oxygen at rest, the patient's SPO2<=93%<br>(3) Oxygenation Index | Methylprednisolone, intravenous injection, 1-2mg/kg/d for 3 days. | Without any glucocorticoid therapy | Primary Outcome:<br>SOFA Score<br>Secondary Outcomes:<br>1. Duration of hospitalization<br>2. Proportion of mechanical ventilation use<br>3. Mortality |

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| | | | | | | (PaO2/FiO2) <=300 mmHg (1mmHg=0.133kPa);<br>(4) Respiratory failure requiring mechanical ventilation;<br>(5) Sepsis;<br>(6) Other organ failure requiring ICU care.<br>4. Be willing to give the informed consent. | | | |
| 2 (17) | ChiCTR2000029656/ A randomized, open-label study to evaluate the efficacy and safety of low-dose corticosteroids in hospitalized patients with novel coronavirus pneumonia (COVID-19) | Not yet recruiting | Feb 14, 2020 to April 14, 2020 | RCT, parallel assignment | China | 1. Adults (defined as age >= 18 years);<br>2. Patients with new type of coronavirus infection confirmed by PCR / serum antibodies;<br>3. The time interval between symptom onset and random enrollment is within 10 days. The onset of symptoms is mainly based on fever. If there is no fever, cough or other related symptoms can be used;<br>4. Imaging confirmed pneumonia;<br>5. In the state of no oxygen at rest, the patient's blood oxygen saturation SPO2 <= 94% or shortness of breath (breathing frequency >= 24) or oxygenation index <= 300mmHg. | Methylprednisolone on top of standard therapy | Standard therapy alone | Primary outcomes:<br>1. ECG<br>2. Chest imaging<br>3. Vital Signs<br>4. Complications<br>5. NEWS 2 Score |
| 3 (18) | ChiCTR2000030481/ The clinical value of corticosteroid therapy timing in the treatment of novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial | Recruiting | March 1, 2020 to April 30, 2020 | RCT, parallel assignment | China | Patients who are more than 18 years are definitely diagnosed with COVID-19. [That is, the diagnosis of 2019-nCoV-infected pneumonia patients was diagnosed according to the diagnostic criteria for novel coronavirus pneumonia | Early corticosteroid Middle-late corticosteroid | No corticosteroid | Primary outcome: Duration of COVID-19 nucleic acid RT-PCR test results of respiratory specimens (such as throat swabs) or blood specimens change to negative.<br>Secondary outcomes:<br>1. Improvement of clinical symptoms |

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| | | | | | | diagnosis and treatment program (trial version 5) issued by the National Health and Health Commission on February 5, 2020. | | | 2. Improvement of imaging tests<br>3. Occurrence of complications during admission<br>4. Mechanical ventilation time<br>5. ICU stay<br>6. Duration of admission<br>7. 21-day all-cause mortality<br>8. Steroid side effects<br>9. Lab indicators |
| 4 (19) | jRCTs031190269/ A multicenter, open-label, randomized controlled trial to evaluate the efficacy and safety of inhaled ciclesonide for asymptomatic and mild patients with COVID-19 | Recruiting | March 27, 2020 | RCT | Japan | 1) Patient who have given written consent to participate in the study 2) Age is over 20 years old, regardless of gender. 3) SARS-CoV-2 PCR positive 4) Patients who can be hospitalized during study drug administration 5) Patients who can inhale ciclesonide using inhalation assist device | Inhaled Ciclesonide 400mcg TID x 7 days | Not stated | Primary Outcome: Pneumonia incidence on day 8 of ciclesonide inhalation<br>Secondary Outcomes:<br>1. Changes in clinical findings<br>2. Changes in laboratory findings<br>3. SARS CoV 2 virus genome amount<br>4. Incidence rates of adverse events |
| 5 (20) | NCT04244591/ Glucocorticoid Therapy for | Completed | January 28, 2020 to | RCT, parallel | Multi-center, China | Adult PCR confirmed novel | Methylprednisolone 40 mg q12h for 5 | Standard of care | Primary Outcome: Murray lung injury score |

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| | Novel CoronavirusCritically Ill Patients With Severe Acute Respiratory Failure | | April 25, 2020 | assignment | | coronavirus infection<br>Symptoms developed more than 7 days<br>PaO2/FiO2 < 200 mmHg<br>Positive pressure ventilation (non-invasive or invasive) or high flow nasal cannula (HFNC) higher than 45 L/min for less than 48 hours<br>Requiring ICU admission | days + Standard of care | | Secondary Outcome:<br>1. P/F ratio<br>2. SOFA score<br>3. Mechanical ventilation support<br>4. Clearance of corona virus<br>5. All-cause mortality |
| 6 (21) | NCT04323592/ Efficacy of Methylprednisolone for Patients With COVID-19 Severe Acute Respiratory Syndrome | Recruiting | March 23, 2020 to May 20, 2020 | Cohort | Italy | SARS-CoV-2 positive<br>Age >17 years and < 80 years<br>P/F < 250 mmHg<br>Bilateral pneumonia (infiltrates/interstitial)<br>CRP >10mg/dL (or >100mg/L)<br>Alternatively to 4-5-6 criteria a diagnosis of ARDS according to the Berlin definition (JAMA 2012) | Methylprednisolone | Historical control | Composite primary end-point<br>[ Time Frame: 28 days ]<br>Death or ICU admission or Invasive mechanical ventilation (yes/not, at least one of three of the composite end-point)<br>death<br>[ Time Frame: 28 days ]<br>Yes/no<br>Admission to ICU<br>[ Time Frame: 28 days ]<br>yes/no<br>Endotracheal intubation (invasive mechanical ventilation)<br>Secondary Outcomes:<br>reduction of C-reactive protein or CRP<br>[ Time Frame: 14 days and 28 days ]<br>mg/L<br>Reduction of mechanical ventilation<br>[ Time Frame: 28 days ]<br>number of days free from mechanical ventilation (invasive or not) |
| 7 (22) | NCT04327401/ COVID-19-associated ARDS Treated With Dexamethasone: Alliance | Not yet recruiting | April 1, 2020 to August 30, 2020 | RCT, parallel assignment | Multi-center, Brazil | >18 years old<br>Probable or confirmed infection by SARS-CoV2<br>Moderate/severe ARDS defined by | Dexamethasone 20mg IV 1x/day for 5 days, followed by 10mg IV 1xd for 5 days + standard | Standard treatment (according to the treatment protocol for 2019-nCoV infection) | Primary Outcome:<br>Ventilator-free days<br>Secondary Outcomes:<br>1. Clinical status |

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| | Covid-19 Brasil III | | | | | the Berlin criteria (PaO2/FiO2 ≤200mmHg with PEEP ≥5cmH20) Development of moderate/severe ARDS in less than 24h before randomization | treatment (according to the treatment protocol for 2019-nCoV infection) | | 2. All-cause mortality after 28 days<br>3. Duration of mechanical ventilation<br>4. SOFA Score |
| 8 (23) | NCT02735707/ Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia | Recruiting | April 13, 2016 to June 2022 | RCT, factorial assignment | Multicenter, Multi-country | Adult patients admitted to an ICU for severe CAP within 48 hours of hospital admission with: i. symptoms or signs or both that are consistent with lower respiratory tract infection AND ii. Radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate) 2. Requiring organ support with one or more of: i. Non-invasive ii. Invasive ventilatory support; iii. Receiving infusion of vasopressor or inotropes | Fixed-dose Hydrocortisone 50mg IV every 6 hours for up to 7 days | No Hydrocortisone | Primary Outcome: Mortality 60 days after randomization Secondary Outcomes:<br>1. ICU Mortality<br>2. ICU Length of Stay<br>3. Hospital Length of Stay<br>4. Ventilator Free Days<br>5. Organ failure Free Days<br>6. All-cause Mortality<br>7. Health-related Quality of Life<br>8. Tracheostomy<br>9. Destination at Hospital Discharge<br>10. Readmission Index |
| 9 (24) | NCT04263402/ The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia | Recruiting | February 10, 2020 to July 1, 2020 | RCT, parallel | China | Adult 18 years or above with severe pneumonia: Shortness of breath,RR≥30 bpm; In a resting state:SPO2≤93 %; PaO2/FiO2≤300 mmHg. 2.2019-nCoV nucleic acid test was positive. | Methylprednisolone <40mg/day | Methylprednisolone 40-80mg/day | Primary Outcomes:<br>1. Rate of disease remission<br>2. Rate and time of entering the critical stage<br>Secondary Outcomes: |

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| | | | | | | 3.CT of the lung conformed to the manifestation of viral pneumonia. | | | 1. Rate of normal temperature<br>2. Rate of respiratory symptoms remission<br>3. Rate of lung imaging recovery<br>4. Rate of laboratory indicator recovery<br>5. Rate of undetectable viral RNA |
| 10 (25) | NCT04273321/ Efficacy and Safety of Corticosteroids in COVID-19 | Recruiting | February 18, 2020 to May 30, 2020 | RCT | China | Age more than 18 years old with the clinical diagnosis and/ or etiological diagnosis diagnostic criteria of Novel coronavirus pneumonia (COVID-19) admitted in the general wards and able to sign informed consent | Methylprednisolone 1mg/kg/day | No Methylprednisolone | Primary Outcome: Treatment failure in 14 days<br>Secondary Outcomes:<br>1. Clinical cure in 14 days<br>2. Viral load<br>3. Mortality at Day 30<br>4. ICU admission rate at Day 30 |
| 11 (26) | NCT04325061/ Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19 | Not yet recruiting | March 27, 2020 to October 30, 2020 | RCT, parallel assignment | Multi-center, Spain | Age 18 years or older;<br>positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay for COVID-19 in a respiratory tract sample;<br>intubated and mechanically ventilated;<br>acute onset of ARDS, as defined by Berlin criteria as moderate-to-severe ARDS,3 which includes: (i) having | Dexamethasone (20 mg/iv/daily/from Day 1 of randomization during 5 days, followed by 10 mg/iv/daily from Day 6 to 10 of randomization | Standard Intensive Care | Primary Outcome: All-cause mortality at 60 days<br>Secondary Outcome: Ventilator-free days |

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| | | | | | | pneumonia or worsening respiratory symptoms, (ii) bilateral pulmonary infiltrates on chest imaging (x-ray or CT scan), (iii) absence of left atrial hypertension, pulmonary capillary wedge pressure <18 mmHg, or no clinical signs of left heart failure, and (iv) hypoxemia, as defined by a PaO2/FiO2 ratio of ≤200 mmHg on positive end-expiratory pressure (PEEP) of ≥5 cmH2O, regardless of FiO2. | | | |
| 12 (27) | NCT04329650/ Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID19 Pneumonia | Note yet recruiting | April 1, 2020 to May 20, 2020 | RCT, parallel assignment | Spain | Age ≥ 18 years old. Hospitalized patient (or documentation of a hospitalization plan if the patient is in an emergency department) with illness of more than 5 days of duration with evidence of pneumonia by chest radiography / tomography computed chest and meets at least one of the following requirements: Non-critical patient with pneumonia in radiological progression and / or Patient with progressive respiratory failure at the last 24-48 hours. Laboratory confirmed SARS-CoV-2 infection (by PCR) or other commercialized analysis or public health in any | Siltuxumab 11mg/kg | 250mg/24 hours of methylprednisolone during 3 days followed by 30mg/24 hours during 3 days will be administered by intravenous infusion. | Primary Outcome: Proportion of patients requiring ICU Admission |

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| | | | | | | sample collected 4 days before the randomization or COVID-19 criteria following the defined diagnostic criteria at that time in the center.<br>Patient with a maximum O2 support of 35% | | | |
| 13 (28) | EudraCT2020-001457-43/Dexamethasone and oxygen support strategies in ICU patients with Covid-19 pneumonia (COVIDICUS) | Ongoing | March 27, 2020 to October 2020 | RCT, double-blind, parallel group | France | Age ≥ 18 years<br>Admitted to ICU within 48 hours<br>Confirmed or highly suspected COVID-19 infection<br>Acute hypoxemic respiratory failure (PaO2 <70 mmHg or SpO2<90% on room air or tachypnea>30/min or labored breathing or respiratory distress; need for oxygen flow >=6L/min)<br>Any treatment intended to treat the SARS-CoV-2 infection (either as a compassionate use or in the context of a clinical trial, i.e remdesivir, lopinavir/ritonavir, favipiravir, hydroxychloroquine and any other new drug with potential activity). | Dexamethasone 20mg IV | Standard therapy | Primary Outcome:<br>1. All-cause mortality at 60 days after randomization,<br>2. Time to need for mechanical ventilation<br>Secondary Outcome:<br>1. Cycle threshold for SARS-CoV-2 PCR at baseline, Day 7 and Day 10<br>2. Proporation of patietns with any healthcare-associated infection at 28 days post randomization<br>3. Number of days alive without mechanical ventilation at 28 days |

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| | | | | | | | | | 4. Number of days without renal replacement therapy at 28 days |
| 14 (29) | EudraCT 2020-001306-35/Protective role of inhaled steroids for COVID-19 infection | Ongoing | March 27, 2020 to | RCT, open | France | Patient ≥ 18 years old<br>Laboratory proved infection by COVID-19 within 2 days<br>-Hospitalization is required (based on investigator judgement)<br>Patient affiliated to a social security regime<br>Patient able to give free, informed and written consent | Symbicort | Standard of care | Primary Outcome:<br>Time to clinical improvement<br>Secondary Outcomes:<br>1. Mortality Rate at Day 30<br>2. Time in days from randomization to death<br>3. Number of days alive outside ICU within 30 days<br>4. Number of days alive free of invasive or non-invasive ventilation within 30 days<br>5. Number of days alive with oxygen therapy within 30 days<br>6. Minimal Oxygen rate within 30 days |

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| | | | | | | | | | 7. P/F ratio at randomization and at Day 7<br>8. Number of days alive outside hospital within 30 days<br>9. CRP levels at randomization and Day 7<br>10. Safety outcomes |
| 15 (30) | EudraCT 2020-001500-41/A prospective, randomized, factorial design, interventional study to compare the safety and efficacy of combinations of blockade of interleukin-6 pathway and interleukin-1 pathway to best standard of care in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome | Ongoing | April 4, 2020 | RCT, open-label, parallel, factorial | Belgium | COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome | Anakinra, Tocilizumab, Siltuximab | Standard therapy with salvage steroid therapy | Primary Outcome: Time to clinical improvement |
| 16 (31) | EudraCT 2020-001307-16/ Efficacy and Safety of corticoids in patients with adult respiratory distress syndrome (ARDS) | Ongoing | April 8, 2020 | RCT, open-label | Spain | Diagnosis of SARS-CoV-2 by testing the polymerase chain reaction performed on a respiratory sample; Pneumonia confirmed by radiological | Methylprednisolone | Standard therapy | Primary Outcome: All-cause mortality at 28 days post-randomization<br>Secondary Outcomes:<br>Mortality at 7 and 14 days<br>Days without mechanical ventilation |

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| | secondary to COVID-19 | | | | | imaging test; ARDS Criteria: (i) bilateral infiltrates; (ii) PO2/FiO2 <300 mmHg; And (iii) reasonable clinical exclusion of heart cause (requires all). Verbal consent of the patient | | | Duration of hospitalization Adverse reactions in the first 28 days |