

Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial

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A Trial of methylprednisolone in COVID-19

Summary: This randomized controlled trial evaluated the use of short-term methylprednisolone in patients with COVID-19 in Brazil. Results showed no overall reduction in mortality in 28 days. Patients over 60 years presented a lower mortality in a subgroup analysis.

ABSTRACT

Background

Steroid use for COVID-19 is based on the possible role of these drugs in mitigating the inflammatory response, mainly in the lungs, triggered by SARS-CoV-2. This study aimed at evaluating the efficacy of methylprednisolone (MP) among hospitalized patients with suspected COVID-19.

Methods

Parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial was performed with hospitalized patients aged ≥ 18 years with clinical, epidemiological and/or radiological suspected COVID-19, at a tertiary care facility in Manaus, Brazil. Patients were randomly allocated (1:1 ratio) to receive either intravenous MP (0.5 mg/kg) or placebo (saline solution), twice daily, for 5 days. A modified intention-to-treat (mITT) analysis was conducted. The primary outcome was 28-day mortality. ClinicalTrials Identifier NCT04343729.

Findings

From April 18 to June 16, 2020, 647 patients were screened, 416 randomized, and 393 analyzed as mITT, MP in 194 and placebo in 199 individuals. SARS-CoV-2 infection was confirmed by RT-PCR in 81.3%. Mortality at day 28 was not different between groups. A subgroup analysis showed that patients over 60 years in the MP group had a lower mortality rate at day 28. Patients in the MP arm tended to need more insulin therapy, and no difference was seen in virus clearance in respiratory secretion until day 7.

Conclusion

The findings of this study suggest that a short course of MP in hospitalized patients with COVID-19 did not reduce mortality in the overall population.

Keywords: SARS-CoV-2; corticosteroid; inflammation; Coronavirus; Brazil

Clinical Trials: NCT04343729.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, has caused catastrophic health, social and economic disruptions worldwide. The spectrum of disease associated with this infection ranges from asymptomatic or mild self-limiting infection to rapidly progressing life-threatening disease, with higher mortality rates in older adults with underlying chronic diseases.¹⁻³ Respiratory failure is common among critically-ill patients, often requiring invasive mechanical ventilation (IMV).³ Given the poor outcome of patients progressing to critical disease, there is a desperate need to identify drugs that could potentially improve their prognosis.

Given the high pro-inflammatory profile of severe COVID-19, many options have been proposed as immune modulators of the disease.^{4,5,6} In a retrospective study of 201 patients in China, administration of methylprednisolone (MP) seemed to reduce the risk of death in patients with acute respiratory distress syndrome (ARDS).⁷ The effect of short-term low dose corticosteroids has been shown in a preliminary report suggesting that although systemic corticosteroids might not improve ICU mortality in critical patients, their use in the first days of disease could enhance oxygen saturation and arterial oxygen tension/inspiratory oxygen fraction.⁸

More recently, a quasi-experimental study showed that an early short course of MP in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.⁹ The premise for the use of corticosteroids relies on their potential role in counterbalancing the hyperinflammatory response in the lung, as well as antithrombotic effect¹⁰, therefore preventing progression to ARDS.^{11,12} One recent small randomized clinical trial (RCT) has shown benefit in the use of steroids.¹³ The RECOVERY study released preliminary data showing benefit in patients

randomized to receive dexamethasone in a large robust randomized controlled trial conducted among 15% of patients hospitalized with COVID-19 in the UK.¹⁴

Review of the potential benefits of corticosteroids for the treatment of other viral pneumonias due to SARS-CoV-1, influenza, and Middle East Respiratory Syndrome (MERS)-CoV, are informative, but sufficiently robust data for their use in COVID-19 outside clinical trials are lacking.^{12,15} The latter are needed to provide solid evidence for clinical decision-making and to further shed light on the benefits or harm of corticosteroid drugs use in COVID-19 infection. Thus, this trial aimed at evaluating the efficacy of MP, compared to placebo treatment, in preventing death in patients admitted to a public reference center for management of COVID-19 patients in Manaus, one of the first epicenters of the disease in Brazil.

Methods

Study Design and Site

Metcovid was a parallel, double-blind, randomized, placebo-controlled phase IIb clinical trial, which ran between April 18 and June 16, 2020, aiming to assess the efficacy of MP in the treatment of hospitalized patients with suspected SARS-CoV-2 infection. This trial was conducted at *Hospital e Pronto-Socorro Delphina Rinaldi Abdel Aziz*, in Manaus, Western Brazilian Amazon; the largest public reference unit dedicated exclusively to the treatment of severe COVID-19 cases in town, with an intensive care unit of 100 beds capacity. Manaus is the capital of the Amazonas state, the geographically largest Brazilian state with ~2.5 million inhabitants. At the beginning of the study, autochthonous SARS-CoV-2 transmission had already been recorded at the study site, and Manaus became a major site of SARS-CoV-2 transmission in Brazil within a few weeks. This trial was registered under ClinicalTrials Identifier NCT04343729.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. The protocol was approved by the *Brazilian Committee of Ethics in Human Research*. Random online clinical monitoring and quality control were performed. An independent Data and Safety Monitoring Board (DSMB), with intensive care clinicians and experts in infectious diseases, was set up to review preliminary and final analyses. The trial was reported according to the *Consolidated Standards of Reporting Trials* (Consort) guideline.¹⁶ The detailed protocol is available as Supplement 1.

Participants

Hospitalized patients were included if they had clinical AND/OR radiological suspicion of COVID-19 (history of fever AND any respiratory symptom, e.g., cough or dyspnea AND/OR ground glass opacity OR pulmonary consolidation on CT scan), aged 18 years or older at the time of inclusion, with SpO₂ ≤ 94% at room air OR in use of supplementary oxygen OR under IMV. Children under 18 years of age were not included due to the known lower morbidity/mortality from COVID-19.¹⁷ Patients were excluded if they had a history of hypersensitivity to MP, HIV/AIDS, chronic use of corticosteroids or immunosuppressive agents, pregnant or breastfeeding, decompensated cirrhosis or chronic renal failure. Patients were enrolled before laboratory confirmation of COVID-19 to avoid treatment delays. For the final primary analyses, all patients were included regardless of the confirmed etiology, based on clinical, epidemiological, AND/OR radiological criteria. All patients and/or legal representatives of patients unable to consent were informed about objectives and risks of participation. They were given time to carefully read and then sign an informed consent form (ICF). After recovery, patients also signed ICF.

Procedures

Eligible participants were allocated with a 1:1 ratio to receive either intravenous sodium succinate MP (0.5 mg/kg), twice daily for 5 days, or placebo (saline solution). As per hospital protocol, all patients meeting ARDS criteria used pre-emptively intravenous ceftriaxone (1g 2x for 7 days) plus azithromycin (500 mg 1x for 5 days) or clarithromycin (500 mg 2x for 7 days), starting on day 1.

Clinical parameters were measured daily by the hospital clinical staff from day 1 until discharge or death. Other laboratory tests were performed at the clinician's discretion. Invasive mechanical ventilation (IMV) was recommended when $\text{PaO}_2/\text{FiO}_2 < 150$, as per hospital protocol, and ARDS Network high PEEP/low FiO_2 strategy was followed. The hospital has all source documents recorded online, using electronic medical/pharmaceutical recording system (*Medview* version 710801 and *Esthor*). Clinical laboratory analyses and routine CT scanning are also available locally. Data were electronically recorded in the source document, and then transferred into an electronic database (REDCap), in tablet computers, at bedside in the wards, and were further validated by external trial monitoring staff. An experienced radiologist reviewed CT scans.

Outcomes

The primary outcome was 28-day mortality. Secondary endpoints included early mortality (days 7 and 14), need for orotracheal intubation by day 7, proportion of patients with oxygenation index ($\text{PaO}_2/\text{FiO}_2$) < 100 by day 7. Post-hoc exploratory analyses were mortality in subgroups (enrolled already in IMV or not, age and some laboratorial predictors of severity). Subgroup analyses were based on the same direction of prespecified hypotheses (benefit of MP), consistency across other

studies, and strong preexisting biological rationale supporting the apparent subgroup effect¹⁸.

Length of hospitalization, radiological presence of fibrosis or Bronchiolitis Obliterans with Organizing Pneumonia (BOOP) after day 7¹⁹, need for insulin or increase in the dosage in diabetic patients, positive blood culture (Bactec®) and presence of viral RNA in the naso/oropharyngeal swab at day 7, were also analysed. As per protocol, day 120 visit will focus on respiratory sequelae of surviving patients, therefore, data will not be presented here.

Randomization and Blinding

An independent statistician prepared an electronically generated randomization list with 14 blocks of 30 participants per block, generated via R software version 3.6.1 (Blockrand package). The list was accessible only to nonblinded pharmacists in the study. Participants were randomized by the study pharmacist to their designated treatment regimen at the time of inclusion and were subsequently identified throughout the study only by their allocated study number. Nonblinded pharmacists prepared the dilutions in the wards and distributed syringes to the nursing staff labeled as MP/placebo.

Laboratory Analysis

Hematology and biochemistry analyses were performed in automated machines. Plasma samples from Day1 were diluted (1:2 or 1:5) and used for measurement of human IL-6 by ELISA following the manufacturer's recommendations (R&D Systems, DY206). The optical density was measured using an ELISA plate reader (BioTek, BioTek Instruments Inc, USA). The concentration in each sample was determined based upon standard curves using a four-parameter logistic (4-PL) curve-fit generated by

Graphpad Prism 5.0 Software. Ferritin was measured by chemiluminescence. Two nasopharyngeal or one oropharyngeal swabs (per institutional protocol) were used to extract viral RNA with the QIAamp Viral RNA mini kit according to the manufacturer's recommendations. Subsequently, all swab specimens were tested for SARS-CoV-2 using the one-step multiplex RT-qPCR kit produced by *Instituto de Biologia Molecular do Paraná* (IBMP, Curitiba, Brazil), following the manufacturer's recommendations and targeting the virus nucleocapsid (N) (HEX) and ORF-1ab (FAM) genes and an endogenous human gene as the internal control (ROX). For all assays, specimens were considered positive if both viral targets, N1 and N2, showed cycle thresholds (CT) lower than 40.0. Swab specimens were collected on days 1 and 7. Viral screening results were not available on time so as to guide any clinical decision, because a state-level laboratory centralized all the exams (results were available usually after 7 days).

Statistical Analysis

The sample for the primary outcome (reduction in lethality rate) was calculated assuming a 50% lethality rate among critically ill patients,⁷ and that MP would reduce lethality by 50%. Preliminary data from our reference hospital, in the beginning of the outbreak, suggested the risk of mortality to be approximately 50%, given that many of the admitted patients arrived in very severe clinical conditions. Thus, considering a test of differences in proportions between two groups of the same size, 80% power and 5% alpha, 378 participants were needed (189 per group). Adding 10% for losses, a final sample size of 416 participants was obtained. Sample calculation was performed using the R software version 3.6.1 (TrialSize and gsDesign packages).

A modified intention to treat (mITT) analysis was conducted (all patients who have used at least one dose of the investigational drug, even with protocol deviations were included). The ITT analysis

(excluding only patients who have withdrawn informed consent) was also performed and presented in supplementary tables. Descriptive statistics were used for demographic, laboratory and clinical data. For qualitative variables, Chi-square test was performed. T-test or Mann-Whitney test were used for means and median comparisons, respectively. Survival models, using Kaplan-Meier estimate curves, assessed the cumulated proportion of deaths. The unadjusted hazard ratio (HR), with respective 95% CI, was calculated using Cox regression analysis. Statistical analyses were performed using Stata® 13.0 software, and two-tailed $P \leq 0.05$ was considered significant.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Population Characteristics

Out of 647 eligible patients, 416 were randomized from April 18 to June 16, 2020. After *a posteriori* exclusion of patients who did not take any dose, and ICF withdrawals after drug treatment was started, 393 completed follow up (194 in the MP arm and 199 in the placebo arm); Figure 1 shows the trial profile. There were no major differences in baseline characteristics between intervention and placebo groups (Table 1). Median number of administered doses was 10 (IQR 4-10). No patient received anti-IL-6, anti-IL-1, remdesivir or convalescent plasma therapy, as none of these interventions was available in the site.

Outcomes

In the mITT strategy, no significant difference was seen between patients regarding major primary, secondary and exploratory outcomes (Table 2). In Supplementary Table 2, the same analyses were performed with the ITT strategy, with similar findings. Overall 28-day mortality was 76/199 (38.2%) in the placebo group vs 72/194 (37.1%) in the MP group ($P=0.629$) while we observed a reduced mortality in the steroid group in post-hoc analysis including patients over 60 years old (Figures 2 and 3A-B). Notably, patients >60 years old had higher C-reactive protein median (IQR) values than those ≤ 60 years [81.3 (67.5-149.8) vs 74.7 (53.3-89.1); $P=0.0028$]. In patients under 60 years, despite not significant, there was a change in the direction of the effect, with more fatal outcomes in the MP group (Figure 3B). The risk of death was increased on average 43% in parallel with the increase in the age group (by decade), regardless of the treatment (HR=1.43; 95%IC=1.26-1.60, $P=0.0001$). Table 3 shows post-hoc defined subgroups analysis.

The radiological presence of BOOP and pulmonary fibrosis during follow up did not differ between groups. Patients receiving MP tended to need more insulin due to hyperglycemia, had no more sepsis or positive blood culture collected on day 7, and a similar proportion was RT-qPCR positive at day 7. After randomization, over the hospitalization period, in patients evolving with shock under treatment with norepinephrine, hydrocortisone was used as per clinical discretion, considering that they were blinded for the interventional drug. Not being an *a priori* exclusion criterion, these patients were also included in the mITT analysis, and no difference was seen between groups (8.7% in MP x 7.0% in placebo).

Discussion

We found no evidence of improved survival in the overall population with a short course of intravenous MP in patients hospitalized for COVID-19. However, a subgroup analysis found a lower mortality in patients over 60 years who received MP, and these patients were the ones who also presented a more pronounced systemic inflammatory status as documented by high C-reactive protein values.

At present, remdesivir and dexamethasone are the two robust evidence-based therapies that are now used widely²⁰. Corticosteroid have been widely used in critically ill patients.²¹ Until recently, all the evidence regarding the benefits of corticosteroid in COVID-19 come from observational studies in which there was no clear definition of criteria followed regarding their use.^{7,22-29} The corticosteroid dosages used in the literature are heterogeneous.¹⁵ MP is a non-expensive corticosteroid widely available in public hospitals that has been used more than other corticosteroids in trials in ARDS patients for five days.^{30,31} A different time and duration of corticosteroid administration might have affected the observed outcome. For severe community-acquired pneumonia, five days of MP were enough to decrease treatment failure in high initial inflammatory response.³¹ Long use duration might be associated with increased prevalence of osteonecrosis of the femoral head, especially in younger adult males.³² We had no chance to evaluate this complication in our study. Glucocorticoid pulse therapy also does not seem to be more beneficial than lower doses in COVID-19.³³

The observed high mortality, compared to other studies^{14,34}, may be related to the study site, a reference hospital receiving transferred patients in very critical conditions, and a late start of MP treatment in the evolution of severe disease. However, a clinically relevant effect in the exploratory analysis performed in patients over 60 years of age was seen, which might be enough to recommend the intervention. In this trial, the elderly had higher CRP levels when compared to younger patients. This might explain the better response to steroids in this group, as already observed in the

community acquired pneumonia trial which showed improved outcomes in the group of patients with high CRP levels receiving steroids²⁶.

A recent systematic review of corticosteroid studies showed delayed viral clearance for SARS-CoV-1 and MERS-CoV.¹⁵ Therefore, if such drugs are used in early disease, they probably need to be used for longer than five days or until clinical improvement is observed, because of the risk of increased viral shedding leading to more inflammation after the steroid is suppressed. This hypothesis needs to be tested. Longer virologic follow up is needed in further trials, as high-dose corticoids have shown to impact the long-term viral shedding³⁵.

Data from a large RCT using dexamethasone 6 mg once daily for 10 days (RECOVERY trial) point to mortality benefit, mostly in critical COVID-19 patients.¹⁴ As dexamethasone, MP also has minimal mineralocorticoid activity, preventing potential safety problems with fluid retention (sodium/water imbalance), a common feature of severe ARDS. Regimen differences between the two trials may explain the results. In contrast to the RECOVERY trial, MP was weight-based dosed in our study (0.5mg/kg twice daily, for 5 days). Thus, equivalence calculation between the total dosing regimens in both studies demonstrates a higher daily total corticoid dosage in Metcovid. Moreover, MP has a shorter biological half-life (24-36h) than dexamethasone (36-54 h). The RECOVERY trial, which administered treatment for twice as long as our study, led to higher corticosteroid bioavailability. In Metcovid, in patients under 60 years, a proxy of less inflamed and therefore less severe subjects, a possible harm was seen with MP, as already pointed out in the RECOVERY study, in which patients not receiving oxygen also had a trend towards increased mortality when using dexamethasone. We hypothesize that one possible explanation is that early use of corticoids in COVID-19 could lead to increase in viral load, with worse outcomes. However, the overall mortality and mortality among ventilated patients were higher in the current study compared to RECOVERY. Therefore, the

comparison between studies is not straightforward, especially because there are differences in health care systems and norms of practice in two different sites. Subjects demographics and severity at enrollment might also explain higher mortality in Metcovid, and differences with RECOVERY data.

Available observational data suggest a higher potential to secondary bacterial or fungal infections following use of corticosteroids in viral syndromes, as previously observed in influenza,³⁶ and impaired immune response in respiratory syncytial virus.³⁷ In our study, sepsis was not higher in patients using MP, as shown by microbiological surveillance using blood cultures and clinical criteria. However, all patients were hospitalized and receiving a combination of ceftriaxone plus a macrolide, which may have confounded the adequate evaluation of such potential side effect of the corticosteroid use. Corticosteroid drugs have been used in septic shock to restore effective blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance.^{38,39}

For ethical reasons, patients in septic shock were allowed to receive open label steroids for the treatment of shock (only hydrocortisone was used), and this could have reduced the separation between groups in the final analysis. Despite not significant, treatment group had longer median time from ventilation to treatment assignment, what might have increased the mortality in this group, allowing for less significant differences.

Regarding pulmonary mid-term complications, BOOP could complicate SARS-CoV-2. Although BOOP seems to improve with corticosteroids when associated with other viral diseases,⁴⁰ such effect was not seen in our series. Furthermore, fibrosis was also similar between groups; therefore MP did not

seem to change such pulmonary complication. Nevertheless, one major limitation of this study was the relatively small number of patients submitted to CT scan during follow-up.

This study had some strengths, including that it was: (1) double-blind; (2) placebo-controlled; (3) performed in a public hospital setting; and (4) compliant with good clinical practices. It also had limitations as follows: (1) single center; (2) low sample size to estimate small differences between the arms and subgroup analyses; (3) high overall mortality as compared to other settings; (4) late administration of the drug in some patients.

In conclusion, the use of MP during only 5 days in hospitalized patients with COVID-19 was not sufficient to improve prognosis, as opposed to RECOVERY trial, in which dexamethasone was successfully used for 10 days. Our exploratory analysis showed that MP reduces mortality in hospitalized patients older than 60 years with COVID-19. Caution is needed in the use of steroids in less severe patients, as a trend towards more harm was seen in the lower age group.

NOTES

Authors' Contributions:

MVGL and WMM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

The authors declare no competing interests.

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Figures legends

Figure 1. Trial profile. Eligible participants were allocated at a 1:1 ratio to receive MP (0.5 mg/kg/day) or placebo twice daily, for 5 days. MP, Methylprednisolone; mITT, modified intention to treat

Figure 2. Time from randomization to death in all patients. Survival analysis until day 28, in overall enrolled patients. MP, Methylprednisolone; HR, Hazard Ratio

Figure 3. Time from randomization to death in a subgroup of patients ≤ 60 years of age (A) and > 60 years (B). Survival analysis until day 28. MP, Methylprednisolone; HR, Hazard Ratio

Table 1. Demographic, clinical, laboratory, and radiological findings of patients at baseline.

Variables	Total n=393	Placebo n=199	MP n=194
Age, years, mean (SD)	55 (15)	57 (15)	54 (15)
Gender (women), %	139/393 (35.4)	71/199 (35.7)	68/194 (35.1)
Race, %			
White	58/393 (14.8)	28/199 (14.1)	30/194 (15.5)
Admixed*	294/393 (74.8)	147/199 (73.9)	147/194 (75.8)
Black	23/393 (5.9)	17/199 (8.5)	6/194 (3.1)
Asian	6/393 (1.5)	3/199 (1.5)	3/194 (1.5)
Amerindian	12/393 (3.1)	4/199 (2.0)	8/194 (4.1)
Diabetes, %	106/364 (29.1)	52/184 (28.3)	54/180 (30.0)
Hypertension, %	178/364 (48.9)	87/184 (47.3)	91/180 (50.6)
Alcohol use disorder, %	98/363 (27.0)	46/183 (25.1)	52/180 (28.9)
Heart disease, %	25/363 (6.9)	11/183 (6.0)	14/180 (7.8)
Asthma, %	9/364 (2.5)	3/184 (1.6)	6/180 (3.3)
Rheumatic diseases, %	33/363 (9.1)	16/183 (8.7)	17/180 (9.4)
Liver diseases, %	20/362 (5.5)	13/182 (7.1)	7/180 (3.9)
Previous tuberculosis, %	8/362 (2.2)	4/183 (2.2)	4/179 (2.2)
COPD, %	2/364 (0.5)	0/184 (0.0)	2/180 (1.1)
ICU at admission, %	126/348 (36.2)	63/177 (35.6)	63/171 (36.8)
Invasive mechanical ventilation, %	133/393 (33.8)	67/199 (33.7)	66/194 (34.0)
Non-invasive oxygen therapy, %	188/393 (47.8)	90/199 (45.2)	98/194 (50.5)
Body temperature >37.8, %	28/393 (7.1)	12/199 (6.0)	16/194 (8.2)
Heart rate, bpm, mean (SD)	91.3 (18.5)	89.8 (18.7)	92.9 (18.2)
Respiratory rate, rpm, mean (SD)	25.5 (7.8)	25.8 (8.5)	25.2 (7.0)
Mean blood pressure, mmHg, mean (SD)	95.3 (17.2)	94.9 (17.6)	95.7 (16.8)
Body mass index, kg/m ² , median (IQR)	29.0 (25.6-32.9)	28.9 (25.7-34.1)	29.0 (25.4-32.4)

Capillary refill time >2s, %	134/384 (34.9)	67/195 (34.4)	67/189 (35.4)
PaO ₂ /FiO ₂ , median (IQR)	158 (120-213)	156 (120-227)	160 (118-200)
Positive blood culture, %	7/269 (2.6)	3/135 (2.2)	4/134 (3.0)
White blood cell, 10 ³ /mm ³ , mean (SD)	12.3 (6.1)	12.2 (6.1)	12.4 (6.1)
Hemoglobin, g/dL, mean (SD)	12.0 (1.9)	12.0 (1.8)	11.9 (2.0)
Neutrophils, %, mean (SD)	84.8 (75.8-90.6)	84.2 (74.9-90.0)	85.9 (77.0-91.0)
Lymphocytes, %, mean (SD)	9.0 (4.7-15.4)	9.3 (4.9-17.6)	8.2 (4.7-14.5)
Platelet count, 10 ³ /mm ³ , mean (SD)	300.6 (122.7)	298.7 (121.5)	302.5 (124.1)
Blood glucose, mg/dL, median (IQR)	197.7 (87.6)	195.2 (86.9)	200.3 (88.6)
Alanine aminotransferase, U/L, median (IQR)	74.3 (92.0)	76.9 (58.7)	71.7 (116.6)
Creatinine, mg/dL, median (IQR)	1.0 (0.8-1.6)	0.9 (0.8-1.6)	1.0 (0.8-1.6)
Creatine kinase, U/L, median (IQR)	87.7 (47.8-224.4)	86.9 (45.1-208.5)	92.9 (51.5-266.0)
Creatine kinase MB, U/L, median (IQR)	22.6 (16.2-36.8)	22.3 (17.7-33.6)	23.0 (15.0-38.6)
Lactate dehydrogenase, U/L, median (IQR)	631.0 (353.0-979.0)	658.0 (333.0-950.0)	617.5 (375.0-1043.0)
D-dimer, ng/mL, median (IQR)	1016.7 (451.6-3734.2)	845.3 (394.8-3592.5)	1251.8 (503.9-4673.0)
C-reactive protein, mg/L, median (IQR)	77.7 (57.4-112.9)	76.1 (53.6-106.5)	79.6 (58.0-125.3)
IL-6, pg/mL, median (IQR)	74.6 (19.8-183.9)	71.5 (15.2-172.3)	75.4 (25.8-187.4)
Ferritin, ng/mL, median (IQR)	941 (528-1650)	853 (483-1545)	966 (582-1710)
Ground-glass opacity infiltration, %	296/310 (95.5)	153/160 (95.6)	143/150 (95.3)
Consolidation, %	266/310 (85.8)	137/160 (85.6)	129/150 (86.0)
Pleural effusion, %	52/310 (16.8)	23/160 (14.4)	29/150 (19.3)
qSOFA score ≥2, %	146/393 (37.2)	70/199 (35.2)	76/194 (39.2)
Days from illness onset to randomization, median (IQR)	13.0 (9.0-16.0)	13.0 (9.0-17.0)	13.0 (9.0-16.0)
Days from IMV to randomization, median (IQR)	3.0 (2.0-6.0)	3.0 (2.0-6.0)	4.0 (2.0-6.0)
SARS-CoV-2 PCR +, %	318/391 (81.3%)	157/198 (79.3%)	161/193 (83.4%)

BMI, body mass index (calculated as weight in kilograms divided by height in squared meters); IQR, interquartile range; COPD, Chronic Obstructive Pulmonary Disease; qSOFA, quick sequential organ failure

assessment; IMV, invasive mechanical ventilation. Mean blood pressure(MBP) calculated as $MBP = [\text{systolic blood pressure} + (2 \times \text{diastolic blood pressure})]/3$.

* Admixed population refers to subjects with different ethnic backgrounds.

For some variables, patients' unconsciousness did not allow for complete personal history data collection

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Table 2. Primary, secondary and post hoc exploratory outcomes

Variable	Total n=393	Placebo n=199	MP n=194	HR (95%CI) / Absolute Difference (95% CI)	P
Primary outcome					
28-day mortality, %	148/393 (37.7%)	76/199 (38.2%)	72/194 (37.1%)	0.924 (0.669 - 1.275)	0.629
Secondary and exploratory outcomes					
7-day mortality, %	79/393 (20.1%)	47/199 (23.6%)	32/194 (16.5%)	0.677 (0.432 - 1.061)	0.089
14-day mortality, %	116/393 (29.5%)	63/199 (31.7%)	53/194 (27.3%)	0.821 (0.570 - 1.183)	0.290
Presence of viral RNA in the naso/oropharyngeal swab on day 5, %	135/283 (47.7%)	66/139 (47.5%)	69/144 (47.9%)	0.43 (-11.1 - 11.9)	0.942
Presence of viral RNA in the naso/oropharyngeal swab on day 7, %	111/212 (52.4%)	50/95 (52.6%)	61/117 (52.1%)	-0.49 (-13.7 - 12.8)	0.943
Need for IMV until day 7, %	34/188 (18.1%)	16/95 (16.8%)	18/93 (19.4%)	2.6 (-8.6 - 13.6)	0.654
Proportion of patients with oxygenation index (PaO ₂ /FiO ₂)<100 until day 7, %	34/111 (30.6%)	13/51 (25.5%)	21/60 (35.0%)	9.51 (-7.70 - 25.59)	0.279
Pulmonary fibrosis after day 7, %	15/56 (26.8%)	3/22 (13.6%)	12/34 (35.3%)	21.7 (-2.4 - 40.7)	0.074
BOOP after day 7, %	36/56 (64.3%)	17/22 (77.3%)	19/34 (55.9%)	-21.4 (-42.1 - 4.3)	0.103
Positive blood culture on day 7, %	16/196 (8.2%)	7/88 (8.0%)	9/108 (8.3%)	0.3 (-8.1 - 8.3)	0.923

Need for insulin therapy until day 28, %	189/347 (54.5%)	86/174 (49.4%)	103/173 (59.5%)	10.1 (-0.4 - 20.3)	0.059
Sepsis until day 28	151/393 (38.4%)	77/199 (38.7%)	74/194 (38.1%)	-0.6 (-10.1 - 9.0)	0.911
Length of hospitalization (days), median (IQR)	9 (7 - 13)	9 (7 - 12)	10 (7 - 13)	-	0.296

HR: Hazard Ratio; CI: Confidence interval

IQR, interquartile range; BOOP=Bronchiolitis Obliterans with Organizing Pneumonia; IMV, invasive mechanical ventilation

Table 3. Death on day 28 per post-hoc defined subgroups

Subgroup	Placebo n=199	MP n=194	HR (95%CI)	<i>P</i>
Age > 60 years	52/84 (61.9%)	34/73 (46.6%)	0.634 (0.411 - 0.978)	0.039
Invasive mechanical ventilation	57/67 (85.1%)	53/66 (80.3%)	0.808 (0.555 - 1.176)	0.266
Non-invasive oxygen therapy	19/90 (21.1%)	18/98 (18.4%)	0.818 (0.429 - 1.558)	0.541
qSOFA ≥ 2	52/70 (74.3%)	53/76 (69.7%)	0.850 (0.579 - 1.246)	0.404
Lymphocytes $\leq 876 \times 10^9/L$	54/87 (62.1%)	45/88 (51.1%)	0.693 (0.466 - 1.029)	0.056
IL-6 >77 pg/mL	57/82 (69.5%)	51/81 (63.0%)	0.755 (0.517 - 1.102)	0.319
Ferritin >940 ng/mL	52/83 (62.7%)	47/90 (52.2%)	0.738 (0.497 - 1.096)	0.304
C-reactive protein >80 mg/L	35/65 (53.8%)	34/74 (45.9%)	0.745 (0.465 - 1.195)	0.344
SARS-CoV-2 positive PCR	69/157 (43.9%)	70/161 (43.5%)	0.953 (0.683 - 1.329)	0.777

HR: Hazard Ratio; CI: Confidence interval; Cut-off levels were defined as lower and higher than the median.

Figure 1

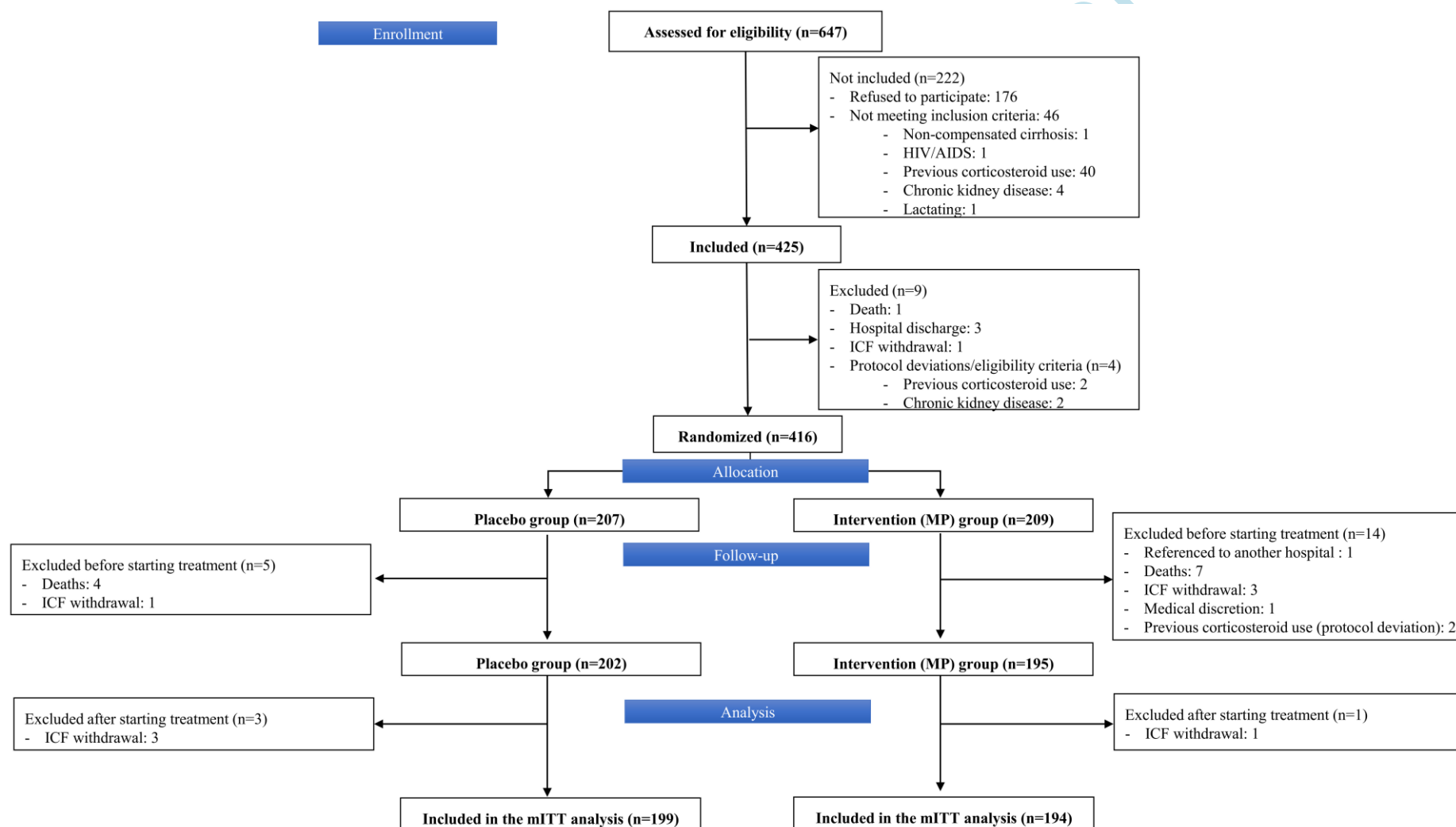


Figure 2

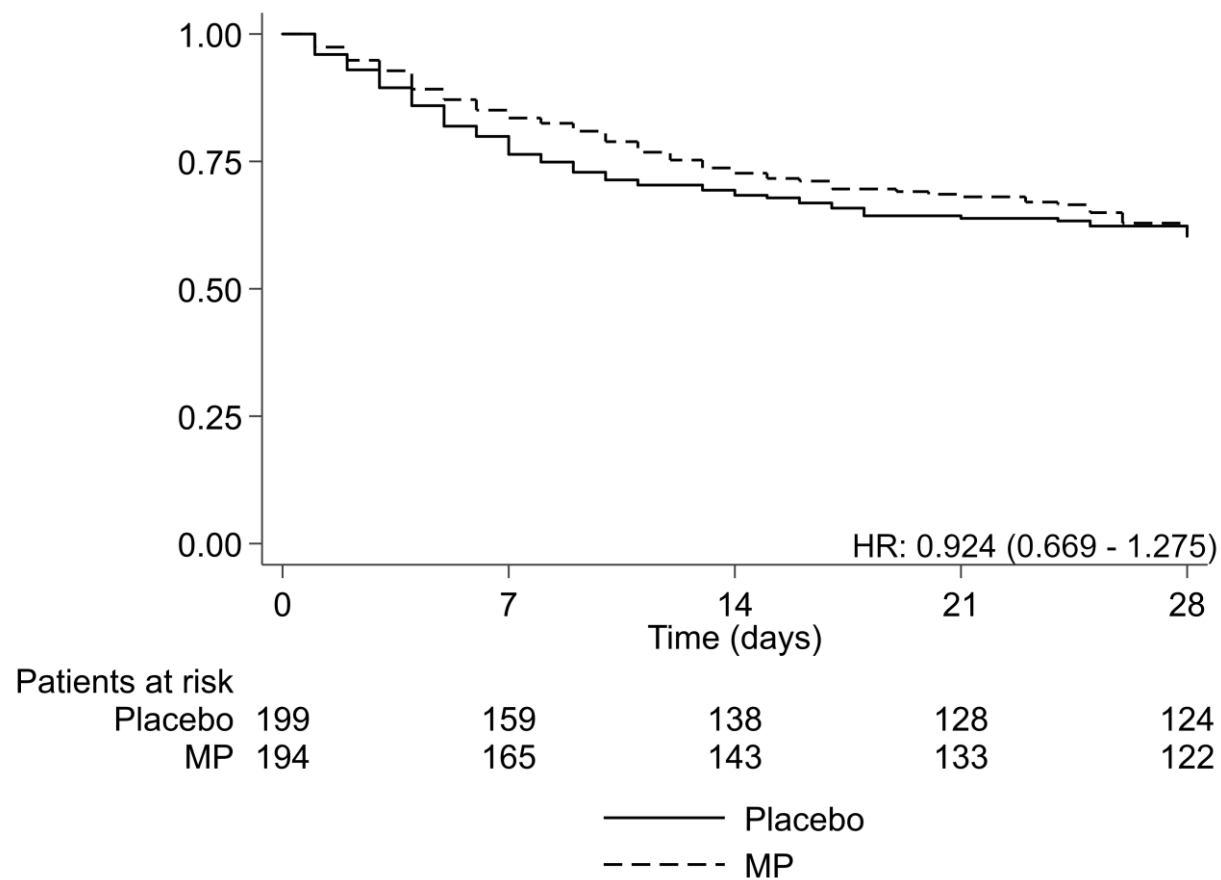


Figure 3

