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Title page

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Title

Effect of intravenous pulses of methylprednisolone 250 mg versus dexamethasone 6 mg in hospitalized adults with severe COVID-19 pneumonia: an open-label randomized trial.

Short running title

High doses of methylprednisolone for COVID-19

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Abstract

Background: The efficacy and safety of high vs. medium doses of glucocorticoids for the treatment of COVID-19 patients has shown mixed outcomes in controlled trials and observational studies. We aimed to evaluate the effectiveness of methylprednisolone 250 mg bolus vs. dexamethasone 6 mg in patients with severe COVID-19.

Methods: A randomized, open-label, controlled trial was conducted between February and August 2021 at four hospitals in Spain. The trial was suspended after the first interim analysis since the investigators considered that continuing the trial would be futile. Patients were randomly assigned in a 1:1 ratio to receive dexamethasone 6 mg once daily for up to 10 days or methylprednisolone 250 mg once daily for 3 days.

Results: Of the 128 randomized patients, 125 were analysed (mean age 60 ± 17 years; 82 males [66%]). Mortality at 28 days was 4.8% in the 250 mg methylprednisolone group vs. 4.8 % in the 6 mg dexamethasone group (absolute risk difference, 0.1% [95% CI, -8.8 to 9.1%]; *P*=0.98). None of the secondary outcomes (admission to the intensive care unit, non-invasive respiratory or high-flow oxygen support, additional immunosuppressive drugs, or length of stay) or prespecified sensitivity analyses were statistically significant. Hyperglycaemia was more frequent in the methylprednisolone group at 27.0 vs. 8.1 % (absolute risk difference, -18.9% [95% CI, -31.8 to - 5.6%]; *P*=0.007).

Conclusions: Among severe but not critical patients with COVID-19, 250 mg/d for 3 days of methylprednisolone compared with 6 mg/d for 10 days of dexamethasone did not result in a decrease in mortality or intubation.

Keywords: COVID-19; Methylprednisolone; Dexamethasone; Mortality; Intubation, intratracheal.

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Introduction

Dexamethasone was identified in a key article published on June 22, 2020, as the first drug able to reduce mortality in severe or critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (COVID-19)[1]. Since then, dexamethasone with the Randomized Evaluation of COVID-19 Therapy (RECOVERY) regimen (6 mg/day for 10 days) has been included in most guidelines for the treatment of COVID-19. Although different glucocorticoids (GCs) such as methylprednisolone have been widely used as off-label therapy since the start of the COVID-19 pandemic[2], and up to three GCs have been evaluated in clinical trials (dexamethasone, methylprednisolone and hydrocortisone)[3], we are uncertain whether other GCs or different dosages or timings could be more effective than the classic dexamethasone regimen[4].

Dysregulation of the immune response and hyperinflammation are linked to severe pneumonia in COVID-19. Some fundamental mechanisms are neutrophil dysfunction, cytokine increase[5], complement hyperactivation[6] and macrophage hyperactivation[7]. Due to their profound immunomodulatory actions[8], GCs have anti-inflammatory and immunosuppressive properties and are applied in multiple inflammatory conditions. The main mechanism of GCs, the genomic pathway, is mediated through the activation of intracellular glucocorticoid receptors (GRs). GCs diffuse across the cell membrane and bind to the GR in the cytosol. Both form a complex in which GR is reorganized and transduced into the nucleus, where it binds to DNA and stimulates target gene expression to switch off multiple inflammatory genes. This results in decreased production of proinflammatory proteins (transrepression) and switches on other genes that increase the expression of regulatory-including anti-inflammatory proteins (transactivation)[9]. This is intended to be the predominant effect when low to medium doses of GCs (less than 160 mg hydrocortisone equivalent, as in the RECOVERY regimen) are used. In higher concentrations (doses higher than 400–500 mg of hydrocortisone equivalent, as in methylprednisolone pulses), GCs have additional rapid effects on the synthesis of anti-inflammatory proteins and post-genomic effects. These effects are mediated by the interaction of the GC with GRs localized in the plasma membrane instead of in the cytoplasm, by nonspecific interactions with the cellular membrane and by interaction with non-classic receptors also associated with the plasma membrane. GCs modify the polarity and permeability of the cellular membranes of immune cells. These membrane-initiated GC signals are the non-genomic pathways[10]. In non-genomic pathways, gene expression is not affected, at least initially or directly. The activation of these non-genomic pathways with higher doses of GCs (bolus) has been beneficial in the treatment of several immune-mediated diseases, such as giant cell arteritis[11], multiple sclerosis[12], rheumatoid arthritis[13], lupus nephritis[14], primary immune thrombocytopenia[15], inflammatory demyelinating polyradiculoneuropathy[16] and nonspecific interstitial pneumonia[17].

The comparison of high doses of dexamethasone with the RECOVERY regimen in COVID-19 has shown mixed outcomes in randomized controlled studies[18–24]. A recent systematic review[25] suggested the possibility that medium-to-high doses of GCs may benefit patients with severe COVID-19.

The MP3-pulses-COVID-19 trial was conducted to evaluate the efficacy and safety of higher doses of GCs, able to initiate immunomodulatory non-genomic GC actions, in patients with severe but not critical COVID-19 pneumonia. The hypothesis was that methylprednisolone 250 mg pulses compared with the RECOVERY dexamethasone regimen would reduce mortality and/or intubation at 28 days in these patients.

Methods

Trial design

The MP3-pulses-COVID-19 trial was an investigator-initiated, multicentre, parallel-group, low-intervention, phase IV, open-label, randomized clinical trial. The trial protocol was approved by the Spanish Agency of Medicines and Medical Devices (AEMPS), the Ethical Committee for Drug Research (CEIm) of the Hospital Universitario de Salamanca and the CEIms at each trial site. The trial was registered with EUDRA CT (2020-005026-28) and Clinicaltrials.gov (NCT04780581). The study was sponsored by the Institute of Health Science Research of Castilla y Leon (IECSCYL) and the Institute for Biomedical Research of Salamanca (IBSAL). Safety monitoring was conducted by the Spanish Clinical Research Network (SCReN). Informed consent was obtained from the patients or their legal surrogates according to Spanish regulation.

Trial sites and patients

Patients were screened and randomized between February 1, 2021, and August 15, 2021, at four hospitals in Spain.

Eligible patients were those aged 18 years or older, hospitalized with confirmed SARS-CoV-2 infection, with evidence of pulmonary involvement on radiology, and who required supplementary oxygen. Patients were excluded if their situation was so serious that the doctor in charge thought they could die within 24 hours; if they required one of the following ventilatory supports at the time of randomization: a) high-flow oxygen devices, b) non-invasive mechanical ventilation, c) invasive mechanical ventilation, d) extracorporeal membrane oxygenation (ECMO); or if the patient had been treated in the 2 weeks before randomization with glucocorticoids or inflammation-modifying drugs. The complete inclusion and exclusion criteria are detailed in the Supplement.

Randomization

Randomization was performed using a centralized, computer-generated allocation, stratified by trial site and by age under 70 years. Eligible patients were randomly allocated in a 1:1 ratio to methylprednisolone pulses or the dexamethasone RECOVERY regimen. The study was open-label, so treatment assignments were not concealed from patients or clinicians.

Interventions

A daily intravenous pulse with methylprednisolone 250 mg (equivalent to approximately 1250 mg of hydrocortisone or 46.9 mg of dexamethasone) for 3 days or a daily dose of 6 mg of dexamethasone (equivalent to approximately 160 mg of hydrocortisone or to 32 mg of methylprednisolone) for up to 10 days was administered. For the dexamethasone group, the first 3 days of treatment were intravenous (7.2 mg of dexamethasone phosphate). From days 4 to 10, dexamethasone could be administered intravenously or orally according to clinician judgement. No placebo was used from days 4 to 10 for patients in the methylprednisolone group. Dexamethasone could be stopped in patients who recovered and were discharged from hospital.

All other interventions for COVID-19 treatment were at the discretion of the clinicians according to the standard of care (SOC) in each hospital (detailed in Supplement).

Outcomes

The primary outcome was the mortality rate at 28 days. The secondary outcomes were (1) the proportion of patients admitted to the intensive care unit at 28 days, (2) the proportion of patients with non-invasive respiratory support requirement (high-flow oxygen or non-invasive mechanical ventilation requirements) at 28 days, (3) the proportion of patients with tracheal intubation at 28 days, (4) the proportion of patients who needed additional immunosuppressive drugs, (5) the length of stay in hospital and (6) the clinical status at every visit according to the World Health Organization (WHO) 10-category scale[26]. Due to the lower number of fatalities registered in the trial, a non-prespecified composite outcome, defined as the mortality rate at 90 days or tracheal intubation, was also analysed.

The safety outcomes included three prespecified adverse events likely related to GC use: (1) secondary infections, (2) hyperglycaemia and (3) psychotic states. In addition, any severe adverse event (SAE) was registered.

Sample size calculation

We initially estimated that 290 patients were required for the trial to have 80% power to show an absolute reduction of 12% in mortality rate at 28 days at a 2-sided α level of 5%, assuming that 23% in the 6 mg dexamethasone group would die. The estimation of the mortality rate of 23% in the dexamethasone group was based on the data from two previous clinical trials[1,27], and the mortality estimation of 11% in the methylprednisolone pulses group was based on three observational studies[28–30].

Two interim analyses for efficacy and security outcomes were planned after the recruitment of 100 and 200 patients, respectively.

Statistical analysis

Categorical variables were presented as number and proportion, and continuous variables were presented as mean and standard deviation. A modified intention-to-treat comparison was conducted. We excluded from analysis the participants who were excluded before the initiation of therapy. In addition, a per protocol analysis was performed in patients who received at least two doses of the GC.

For the primary outcome of 28-day mortality, we used the log-rank statistic to test the null hypothesis of equal survival curves. Time-to-event secondary outcomes and the composite outcome were compared between the two groups with the Kaplan–Meier approach. Differences in categorical data were analysed using the Cochran–Mantel–Haenszel test. Differences in continuous variables were analysed using Student's t-test.

Prespecified analyses of primary, secondary and composite outcomes were performed in subgroups defined by two characteristics at the time of randomization: (1) days since symptom onset (<7 vs. ≥7 days) and (2) the presence of a hyperinflammatory state. We considered that a patient had a hyperinflammatory state when we found any of the following laboratory parameters: a) ferritin ≥1000 mg/dL, b) interleukin-6 (IL-6) ≥20 pg/mL, c) D-dimer ≥1000 mg/dL or d) C-reactive protein (CRP) ≥150 mg/L. Due to the imbalance in vaccination status between the groups, a post hoc, non-prespecified analysis according to vaccination at the time of randomization was performed.

A predefined sensitivity analysis excluding patients with do-not-intubate orders was performed.

Estimates of rate and risk ratios are shown with 95% confidence intervals. All p-values are 2-sided and shown without adjustment for multiple testing, and $P<0.05$ was considered statistically significant. The analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY, USA: IBM Corp.).

Results

Between February 10, 2021, and August 31, 2021, a total of 158 patients were assessed for eligibility, and 128 were randomized: 64 were randomized to receive 250 mg/d of methylprednisolone (high GC dose) for 3 consecutive days, and 64 were randomized to receive 6 mg/d of dexamethasone (medium GC dose) for 10 consecutive days (Figure 1). Of these, 125 were included in the full modified intention-to-treat analysis (mean age, 60±17 years; 83 [66%] were men). The final sample size was smaller than originally planned because the study was terminated after the first interim analysis based on investigators expecting the study to be futile and because of ongoing recruitment challenges (see discussion section).

The patient characteristics at baseline and the use of respiratory support, anticoagulants, antibacterials and antivirals were similar in both groups (Table 1). An imbalance existed in vaccination status between trial arms (22% of vaccinated patients in the high GC dose arm vs. 11% in the medium GC dose arm). Most of the patients were vaccinated 3 weeks or less before randomization. Post hoc analyses were performed according to vaccination status to assess whether this difference affected trial outcomes. No differences were found in this analysis.

One patient was administered an erroneous trial intervention. The rest of the patients received the trial intervention according to randomization. The duration of the treatment was 3 days for 97% of patients in the methylprednisolone group (61/63). The mean number of dexamethasone doses was 9 ± 2 days (9.7% received 5 or fewer doses, 17.7% received 6 to 8 doses and 72.6% received 9 to 10 doses).

Primary outcome

At 28 days after randomization, 3 (4.8%) patients in the methylprednisolone group and 3 (4.8%) in the dexamethasone group had died (absolute risk difference, 0.1% [95% CI, -8.8 to 9.1%]; *P*=0.98) The results were similar in the per protocol analysis (eTable s1 in the Supplement) and the pre-planned sensitivity analysis (eTable s2a–s2d in the Supplement). The causes of death are detailed in eTable s3 in the Supplement.

Secondary outcomes

None of the secondary outcomes was statistically significant: admission to intensive care unit within 28 days, non-invasive respiratory support within 28 days, high-flow oxygen support within 28 days, additional immunosuppressive drugs within 28 days or length of stay (Table 2). The non-prespecified composite outcome of the mortality rate at 90 days or tracheal intubation was not significant either. At 90 days after randomization, 10 (15.9%) patients in the methylprednisolone group and 9 (15%) in the medium GC dose group were intubated or had died (composite outcome; absolute risk difference, -0.9% [95% CI, -13.8 to 12.3%]; *P*=0.83). The survival curves for mortality at 90 days and the composite endpoint of mortality or intubation are shown in Figure 2. No differences existed between the groups.

The pre-planned subgroup analysis and the post hoc analysis by vaccination status are shown in Figure 3. No differences were found. The rest of the subgroup analyses are shown in eTables s2a–s2d in the Supplement.

The differences in clinical status at every visit according to the WHO 10-category scale are shown in Figure 4. Data on surrogate markers of inflammatory and radiographic changes are shown in eTables s4a–s4b in the Supplement.

Adverse events likely related to glucocorticoids and serious adverse events

At 28 days, 7 (11.1%) patients in the methylprednisolone group and 8 (12.9%) in the dexamethasone group had secondary infections (absolute risk difference, 1.8% [95% CI, -10.1 to 13.7%]; *P*=0.76). The infection detail and microbiological data of every patient are in eTable s5 in the Supplement. Hyperglycaemia was more frequent in the methylprednisolone group (27.0%) vs. the dexamethasone group (8.1%; absolute risk difference, -18.9% [95% CI, -31.8 to -5.6%]; *P*=0.007). All the episodes of hyperglycaemia were transient, lasting less than 12 hours after glucocorticoid administration. All the episodes were controlled by administering short-acting subcutaneous insulin. No patient needed long-term treatment with additional specific measures for glycaemia control. There were 116 adverse events, 68 of which were registered as SAEs. The adverse events are detailed in eTable s6 in the Supplement.

Discussion

In this multicentre, open-label, randomized clinical trial including adults with severe COVID-19, treatment with 250 mg/d of methylprednisolone (equivalent to approximately 1250 mg of hydrocortisone) compared with 6 mg/d of dexamethasone (equivalent to approximately 160 mg of hydrocortisone) did not result in a significant reduction in mortality at 28 days. None of the secondary outcomes or prespecified sensitivity analyses were statistically significant. Hyperglycaemia was the only adverse event more frequently associated with the higher dose of GC.

Systemic GCs have been demonstrated to improve survival when administered to patients needing oxygen supplementation, from moderately to critically ill. However, the optimal GC dose is yet to be discovered. Medium-dose regimens, such as the RECOVERY trial regimen of 6 mg of dexamethasone once daily[1], have been compared with high-dose regimens in some clinical trials with different results, from favourable to unfavourable (eTable 7a–7c in the Supplement)[18–24]. Importantly, none of the published clinical trials has shown clinically significant differences in the occurrence of SAEs between medium- and high-dose regimens. Hyperglycaemia was more frequent in the methylprednisolone group in our study. This adverse event was not associated with an increased risk of infections or other complications. Their transient nature and the use of insulin therapy to quickly maintain blood glucose justify the lack of impact of the hyperglycaemia episodes.

One difference between the present study and others is the lower mortality rate. This low rate might be explained by the type of patients studied: we excluded critical patients and those requiring high-flow oxygen devices or non-invasive mechanical ventilation. In addition, because vaccination started in January 2021 for older people in Spain, the median age of patients admitted to hospital for COVID-19 dropped significantly in this period, with a resulting mortality rate decrease. The median age in our previous trial[27] and the RECOVERY trial[1] was 70 years and 66 years, respectively, nearly 10 years older than the patients in the current trial, which had a median age of 60 years. Additionally, the changes in COVID-19 variants of concern (VOC) could play a role in the mortality rate decrease. Alpha and Delta were the VOC dominant in our region during the study period[31].

One of the strengths of this study is the homogeneity of the sample, with all patients in group 5 of the WHO clinical progression scale. The use of a high-dose bolus of methylprednisolone does not seem to be an advantage in these patients when compared with dexamethasone 6 mg, but it could be an alternative to the RECOVERY scheme of GCs. However, the study design does not allow non-inferiority analysis, so this cannot be definitively confirmed. The use of a short course

of 3 days of methylprednisolone bolus could predominantly activate the non-genomic pathway because the genomic pathway is slower and needs several days for complete activation. Future research could be framed by the hypothesis of a potential role of the combination of an initial extra short course of high-dose pulse GC therapy for induction (1 to 3 days), followed by a short course of moderate-dose GC for maintenance (10 days or until hospital discharge) to potentiate the anti-inflammatory effect by the activation of both genomic and non-genomic pathways. However, the results of a recent study also seem to rule out a possible benefit of this treatment scheme[24].

Limitations

This trial has several limitations. First, the sample size was not achieved due to the early termination of the study. The sample size estimation for the primary outcomes was based on data from the first waves of COVID-19. The impact of vaccination programmes in early 2021 in Spain dramatically changed the characteristics of hospitalized patients with COVID-19. As older persons were prioritized for vaccination, an impressive decline occurred in the number of hospital admissions for patients aged over 70 years, resulting in a spectacular decrease in mortality rates. Considering this, our initial estimation for sample size calculation was outdated. In addition to the flaw in sample size calculation, the study was prematurely terminated according to pre-defined criteria. The first pre-defined criterion was the inability to enrol an acceptable number of patients. In the summer of 2021, a marked decrease occurred in the number of hospitalized patients and the severity of the admitted patients in Spain due to a high percentage of people vaccinated and the end of the fifth wave of COVID-19. Due to the inability to include new patients in the study, the monitoring committee decided to conditionally stop the trial in August 2021. In addition to this pre-defined criterion to prematurely discontinue the study, the futility analysis for the primary outcome of the first 100 recruited patients found a conditional power lower than the 20% pre-defined threshold for futility. After careful clinical consideration, the principal investigators and the monitoring committee considered that continuing the trial would be unlikely to change the results. The decision to stop the trial was communicated in writing to the CEIm of the Hospital Universitario de Salamanca and to the AEMPS. The recruitment period was closed on August 15, 2021, and the trial was definitively stopped on November 11, 2021. A second limitation is that the open-label design and investigator-reported data on adverse events and infections may have led to bias in the description of these events. Third, an imbalance in vaccination status existed between the two randomized groups. No differences were found in the post hoc analysis according to vaccination status, and the imbalance is not likely to have affected the trial outcomes.

Conclusions

Among severe, but not critically ill, patients with COVID-19, 250 mg/d of methylprednisolone compared with 6 mg/d of dexamethasone did not result in a statistically significant reduction in mortality at 28 days. However, the trial may have been underpowered to identify a significant difference.

Access to data

The data that support the findings of this study are available from the corresponding author, Corral-Gudino, Luis, upon reasonable request.

Author contributions

Corral-Gudino, Luis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had final responsibility for the decision to submit for publication.

1. Substantial contributions to:

    a. Conception and design (Corral-Gudino, Luis; López-Franco, Esperanza)

    b. Acquisition of data (Corral-Gudino, Luis; Cuascovich, Ivan; Martín-González, Jose Ignacio; Muela-Molinero, Alberto; Abadía-Otero, Jésica; González-Fuentes, Roberto; Ruíz-de-Temiño, Ángela; Tapia-Moral, Elena; Cuadrado-Medina, Francisca; Martín-Asenjo, Miguel; Miramontes-González, Pablo; Delgado-González, Jose Luis; Ines, Sandra; Abad-Manteca, Laura; Usategui-Martín, Iciar; Ruiz-Albi, Tomás; Miranda-Riaño, Sara; Rodríguez-Fortúnez, Patricia; Rodríguez-Jiménez, Consuelo)

    c. Analysis and interpretation of data (Corral-Gudino, Luis; Cuascovich, Ivan; Martín-González, Jose Ignacio; Muela-Molinero, Alberto; Marcos, Miguel)

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Legends for figures

Figure 1. Screening, randomization, and follow-up of patients in the MP3-pulses-COVID-19 trial

Figure 2. Primary and composite outcome curves to day 90

Figure 3. Mortality within 90 days or intubation absolute risk difference in the three predefined subgroups and post hoc vaccination comparison

Figure 4. WHO (World Health Organization) clinical progression scale at every visit

Tables

Table 1. Baseline participant characteristics, COVID data and medications

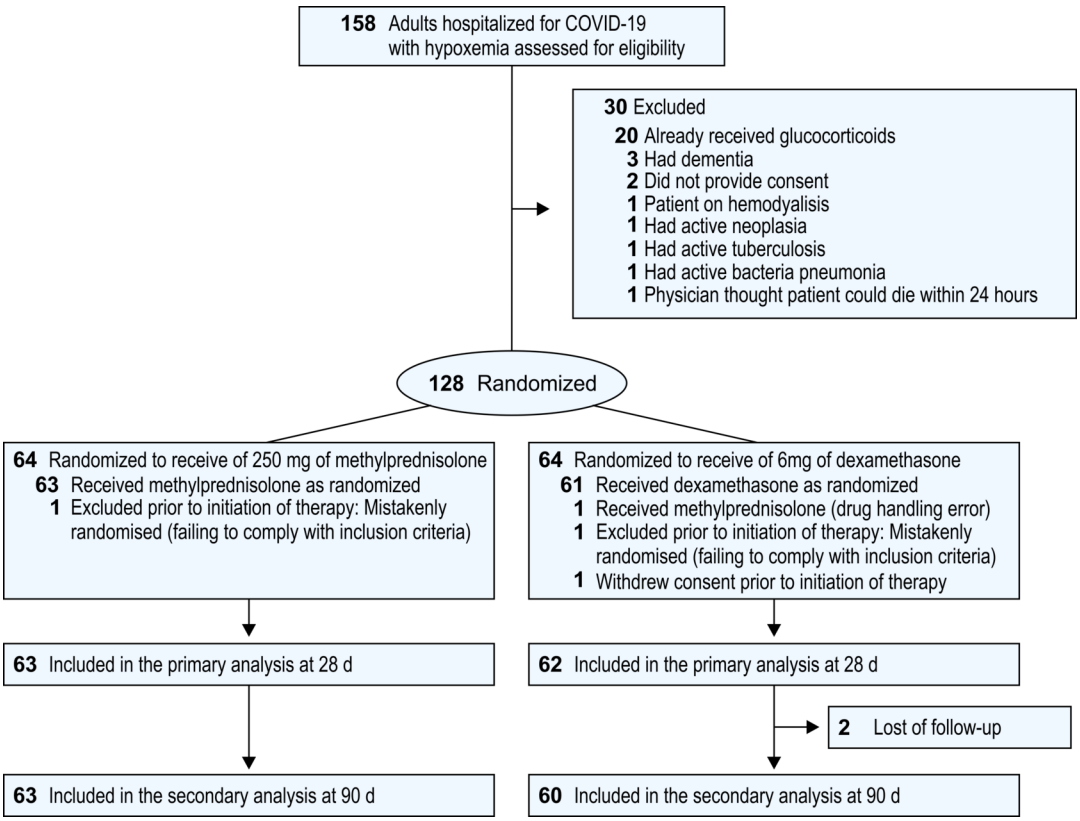
	MP 250 mg pulses (Equivalent to 1250 mg of hydrocortisone)	DXM 6 mg (Equivalent to 160 mg of hydrocortisone)	Total
n	63	62	125
Age, years, mean ± SD	60 ± 17	59 ± 16	60 ± 17
Sex (male, %)	43 (68%)	40 (65%)	83 (66%)
Comorbidities			
Barthel Index, mean ± SD	99 ± 4	99 ± 6	99 ± 5
Hypertension, n (%)	31 (49%)	22 (36%)	53 (42%)
Diabetes, n (%)	13 (21%)	10 (16%)	23 (18%)
Dyslipidaemia, n (%)	16 (25%)	22 (36%)	38 (30%)
Heart failure, n (%)	4 (6%)	4 (6%)	8 (6%)
Cardiac ischaemia, n (%)	4 (6%)	5 (8%)	9 (7%)
Stroke, n (%)	4 (6%)	5 (8%)	9 (7%)
COPD, n (%)	1 (2%)	2 (3%)	3 (2%)
Asthma, n (%)	3 (5%)	0 (0%)	3 (2%)
Hypoventilation, n (%)	3 (5%)	0 (0%)	3 (2%)
Chronic kidney disease, n (%)	2 (3%)	4 (7%)	6 (5%)
Liver disease, n (%)	1 (2%)	1 (2%)	2 (2%)
Neoplasia, n (%)	7 (11%)	4 (6%)	11 (9%)
Transplant, n (%)	0 (0%)	0 (0%)	0 (0%)
HIV, n (%)	0 (0%)	1 (2%)	1 (1%)
Autoimmune disease, n (%)	1 (2%)	1 (2%)	2 (2%)
Dementia (mild), n (%)	0 (0%)	1 (2%)	1 (1%)
Current smoker, n (%)	0 (0%)	5 (8%)	5 (4%)
Charlson score, mean ± SD	0.6 ± 1.1	0.6 ± 1.2	0.6 ± 1.2
Clinical Frailty Scale			
Very fit to managing well	59 (94%)	60 (97%)	119 (95%)
Vulnerable to moderately frail	4 (6%)	2 (3%)	6 (5%)
Severely frail to terminally ill	0 (0%)	0 (0%)	0 (0%)
Days from symptom onset to inclusion, mean ± SD	8 ± 4	7 ± 5	7 ± 5
Days from diagnosis to inclusion, mean ± SD	5 ± 7	5 ± 4	5 ± 5

Days from hospital admission to inclusion, mean ± SD	1 ± 4	1 ± 1	1 ± 3
COVID-19 characteristics			
Fever, n (%)	47 (75%)	43 (69%)	90 (72%)
Arthralgia/myalgia, n (%)	21 (33%)	19 (31%)	40 (32%)
Cough, n (%)	47 (75%)	43 (69%)	90 (72%)
Thoracic pain, n (%)	8 (13%)	7 (11%)	15 (12%)
Nausea, n (%)	13 (21%)	10 (16%)	23 (18%)
Diarrhoea, n (%)	18 (29%)	16 (27%)	34 (27%)
Hyposmia/hypogeusia, n (%)	10 (16%)	13 (21%)	23 (18%)
Headache, n (%)	15 (24%)	9 (15%)	24 (19%)
PaFI (PaO_2/FIO_2), mean ± SD	247 ± 50	266 ± 67	258 ± 60
Creatinine, mg/dL, mean ± SD	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.3
AST, U/L, mean ± SD	43 ± 58	43 ± 44	43 ± 52
Lymphocytes/μL, mean ± SD	0.955 ± 0.435	1.019 ± 0.521	0.987 ± 0.479
CRP, mg/dL, mean ± SD	120 ± 168	118 ± 119	119 ± 145
D-dimer, mg/dL, mean ± SD	846 ± 840	992 ± 1048	919 ± 948
Ferritin, mg/dL, mean ± SD	814 ± 698	772 ± 474	793 ± 595
IL-6, mg/dL, mean ± SD	59 ± 141	53 ± 125	56 ± 132
X-ray Brixia score, mean ± SD	7.0 ± 3.2	7.5 ± 4.0	7.2 ± 3.6
Vaccinated, n (%)			
Non-vaccinated	49 (78%)	56 (89%)	105 (84%)
BNT162b2 (Pfizer®)			
≤3 weeks before randomization	8 (13%)	5 (8%)	13 (10%)
>3 weeks before randomization	2 (3%)	0 (0%)	2 (2%)
ChADOx1-S (AstraZeneca®)			
≤3 weeks before randomization	2 (3%)	0 (0%)	2 (2%)
>3 weeks before randomization	2 (3%)	0 (0%)	2 (2%)
Ad25COVS1 (Janssen®)			
>3 weeks before randomization	0 (0%)	1 (2%)	1 (1%)
Total			
≤3 weeks before randomization	10 (16%)	5 (8%)	15 (12%)
>3 weeks before randomization	4 (6%)	1 (2%)	5 (4%)
Therapy			
Oxygen support			
Nasal cannula, face mask, n (%)	62 (98%)	61 (98%)	123 (98%)
Non-rebreather, n (%)	1 (2%)	1 (2%)	2 (2%)
Anticoagulation			
None, n (%)	1 (2%)	1 (2%)	2 (2%)
LMWH-SDPA, n (%)	50 (79%)	53 (86%)	103 (82%)
LMWH-IDPA n (%)	6 (10%)	4 (7%)	10 (8%)
LMWH-AD or SDTA, n (%)	6 (10%)	4 (7%)	10 (8%)
Antibiotics, n (%)	34 (54%)	27 (44%)	61 (49%)
Remdesivir, n (%)	7 (11%)	8 (13%)	15 (12%)

AST: Aspartate aminotransferase; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; DXM: Dexamethasone; ITPD: Intermediate-dose prophylactic anticoagulation (dose higher than SDPA and lower than SDTA); MP: Methylprednisolone; LMWH: Low–molecular weight heparins; OA: Oral anticoagulants; SDPA: Standard-dose prophylactic anticoagulation; SDTA: Standard-dose therapeutic anticoagulation.

Table 2. Primary and secondary outcomes and predefined adverse events likely related to glucocorticoid use

	MP 250 mg pulses (Equivalent to 1250 mg of hydrocortisone)	DXM 6 mg (Equivalent to 160 mg of hydrocortisone)	Absolute risk difference (95% CI)	OR (95% CI)	P-value
Primary outcome					
Mortality within 28 d, n/total (%)	3/63 (5%)	3/62 (5%)	0.1% (-8.8 to 9.1%)	1.0 (0.2 to 5.1)	0.984
Secondary outcome					
Admission to intensive care unit within 28 d, n/total (%)	10/63 (16%)	9/62 (15%)	-1.4% (-14.2 to 11.5%)	1.1 (0.4 to 3.0)	0.833
Tracheal intubation within 28 d, n/total (%)	8/63 (13%)	7/60 (12%)	-1.0% (-13.0 to 11.1%)	1.1 (0.4 to 3.3)	0.809
Non-invasive respiratory support within 28 d, n/total (%)	3/63 (5%)	2/62 (3%)	-1.5% (-10.2 to 6.9%)	1.5 (0.2 to 9.3)	0.661
High-flow oxygen support within 28 d, n/total (%)	6/63 (10%)	8/62 (13%)	3.4% (-8.2 to 15.1%)	0.7 (0.2 to 2.2)	0.549
Additional immunosuppressive drugs within 28 d, n/total (%)	14/63 (22%)	14/62 (23%)	0.4% (-14.2 to 14.9%)	1.0 (0.4 to 2.3)	0.962
Mortality within 90 d, n/total (%)	6/63 (10%)	4/60 (7%)	-2.9% (-13.4 to 7.7%)	1.5 (0.4 to 5.5)	0.572
Length of stay, mean ± SD	13 ± 15	13 ± 12	-0.3 days (-5 to 5)	---	0.908
Adverse events					
Secondary infections within 28 d, n/total (%)	7/63 (11%)	8/62 (13%)	1.8% (-10.1 to 13.7%)	0.8 (0.3 to 2.5)	0.758
Hyperglycaemia within 28 d, n/total (%)	17/63 (27%)	5/62 (8%)	-18.9% (-31.8 to -5.6%)	4.2 (1.4 to 12.3)	0.007
Psychotic states within 28 d, n/total (%)	1/63 (2%)	0/62 (0%)	-1.6% (-8.5 to 4.4%)	---	0.319
Composite outcome (post-hoc addition)					
Mortality within 90 d or tracheal intubation within 28 d	10/63 (16%)	9/60 (15%)	-0.9% (-13.8 to 12.3%)	1.1 (0.4 to 2.8)	0.833



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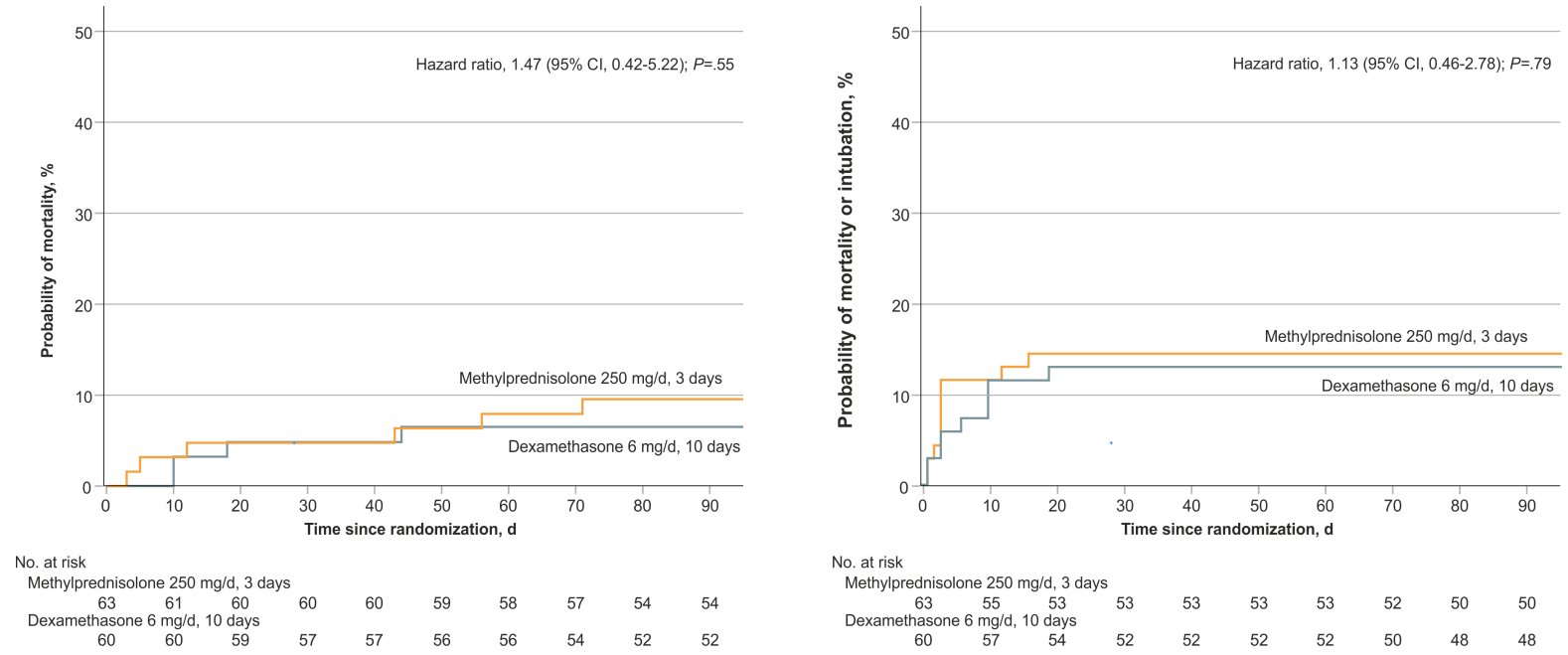

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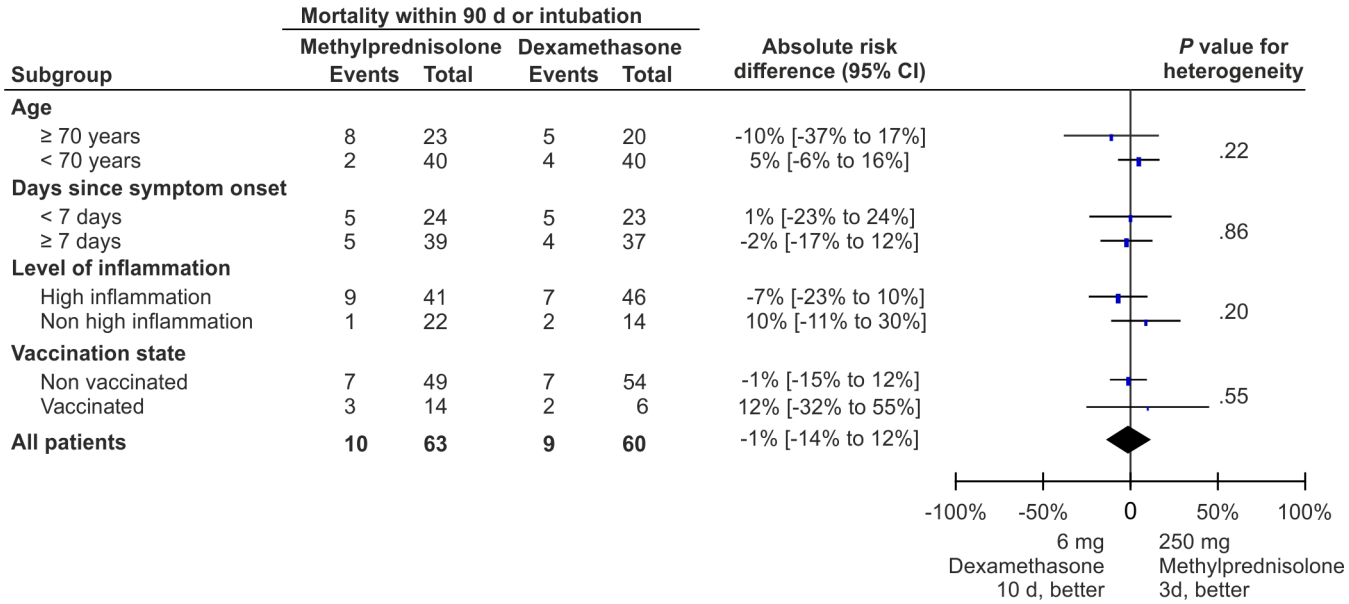

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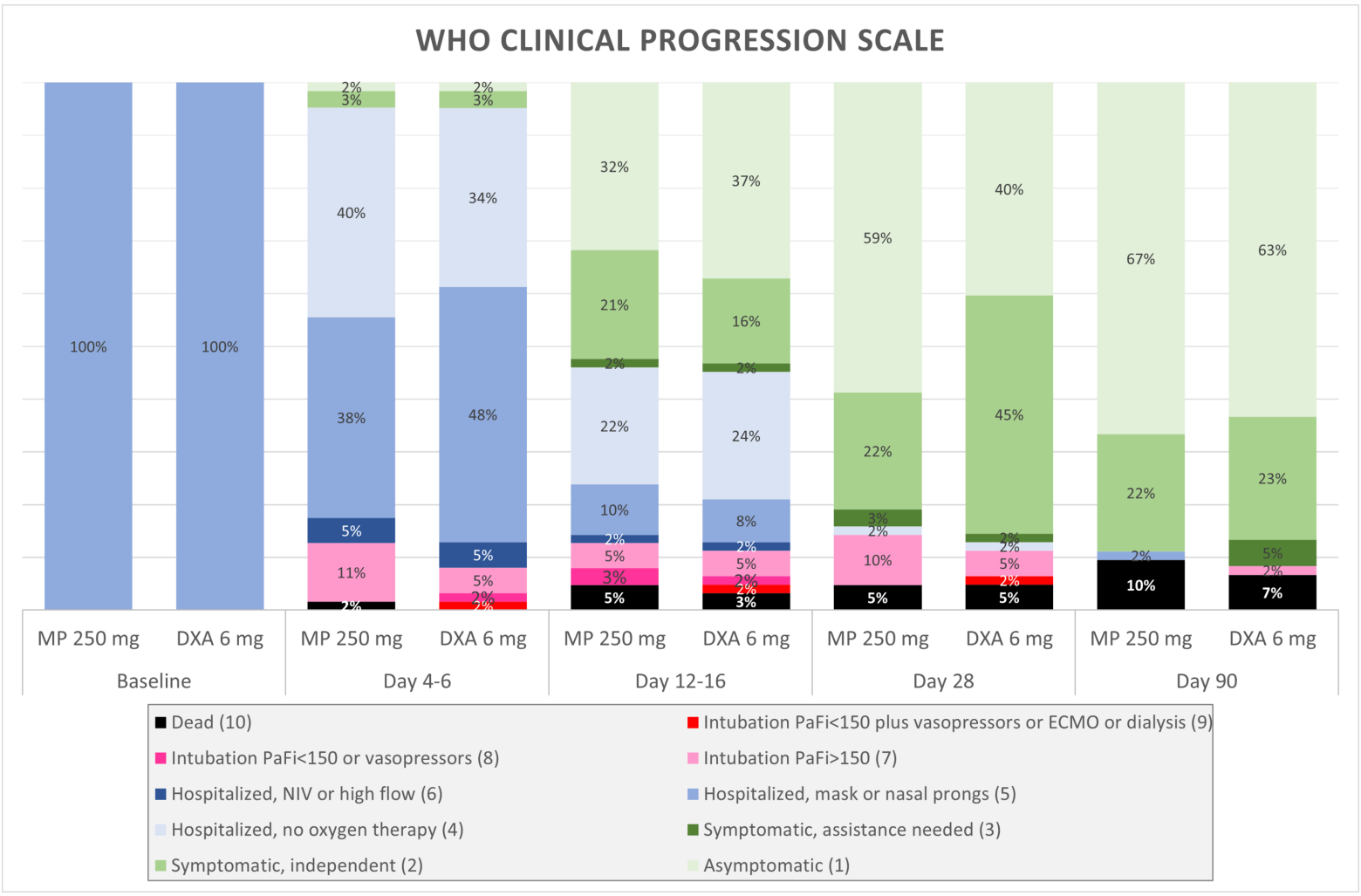

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