Supplementary appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Carlo Salvarani, Marco Massari, Massimo Costantini, et al. Intravenous methylprednisolone pulses in hospitalized patients with severe COVID-19 pneumonia

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1. THE RCT-MP-COVID-19 STUDY GROUP

(The list was ordered by number of patients enrolled)

The following institutions were involved in this study. For each institution the study group members involved with the design and implementation of the study are reported.

Azienda USL -IRCCS di Reggio Emilia:

- Malattie Infettive: Marco Massari, Fabio Sampaolesi, Romina Corsini
- Pneumologia: Nicola Facciolongo, Chiara Barbieri; Francesco Menzella; Matteo Fontana, Silvia Capobelli.
- Reumatologia: Carlo Salvarani, Maria Grazia Catanoso, Gianluigi Bajocchi
- Direzione Scientifica: Massimo Costantini, Franco Merlo, Gabriella Mariani, Luisa Savoldi, Francesca Franzoni, Silvio Cavuto.
- Unità per il coinvolgimento dei pazienti nei processi di ricerca: Chiara Barbieri
- Farmacia: Caterina Turrà, Anna Maria Valcavi.
- Alta Intensità di Cure: Emanuele Alberto Negri
- Direzione Sanitaria: Giorgio Mazzi

Regione Emilia Romagna: Anna Maria Marata

IRCCS Policlinico S. Orsola-Malpighi, Alma Mater Studiorum Università di Bologna

- Malattie Infettive: Pierluigi Viale, Fabio Trapani, Giacomo Fornaro
- Pneumologia e Terapia Intensiva Respiratoria: Stefano Nava, Ilaria Bassi, Federico Tagariello

Azienda Ospedaliera Universitaria di Careggi, Firenze

- Malattie Infettive e Tropicali: Alessandro Bartoloni, Lorenzo Zammarchi, Beatrice Borchi, Lucia Graziani, Michele Spinicci, Jessica Mencarini, Marta Tilli, Iacopo Vellere
- Farmacia: Michele Cecchi, Manuela Angileri.

IRCCS Ospedale Policlinico San Martino Genova

- Pneumologia interventistica: Emanuela Barisione, Teresita Aloè
- Area Medica Critica: Eleonora Arboscello, Paola Pitto, Caterina Passalia
- Medicina e Chirurgia di accettazione e di urgenza: Paolo Barbera.
- Farmacia: Sabrina Beltramini, Federica Mina
- Epidemiologia Clinica: Luca Boni, Paolo Bruzzi

ASST di Cremona

- Malattie Infettive: Angelo Pan

Azienda Ospedaliera Universitaria, Policlinico di Modena

- Malattie Infettive: Giovanni Guaraldi, Giovanni Dolci, Giulia Jole Burastero, Giacomo Ciusa, Jovana Milic, Marianna Ravasi

Ospedale di Treviso

- Malattie Infettive: Walter Inojosa, Piergiorgio Scotton

Ospedale San Donato Arezzo

- Pneumologia: Raffaele Scala, Luca Guidelli, Marco Ferri, Marusca Mazzetti
- Farmacia ospedaliera: Daniela Morisciano, Romina Castellani

Ospedale Guglielmo da Saliceto di Piacenza

- Pneumologia: Cecilia Burattini, Franco Cosimo, Ielpo Antonella
- Malattie Infettive: Mauro Codeluppi, Maria Cristina Leoni, Laura Gerna, Alberto Catania, Annalisa Mancini.

Ospedale San Gerardo, Monza

- Pneumologia: Fabrizio Luppi, Francesco Ammatuna, Sara Busnelli.
- Terapia Intensiva: Giuseppe Foti, Beatrice Vergnano, Emanuele Rezoagli, Annalisa Benini, Roberto Rona, Ilaria Mariani
- Farmacia: Dario Cerri, Cristina Zanini.

ASL1 Imperiese, Sanremo

- Malattie Infettive: Giovanni Cenderello, Tita Farinella Sara, Sciolè Katiusha, Nicola Forni
- Laboratorio Analisi: Domenico Marra
- Farmacia: Silvia Di Francesco, Roberta Mazzocchi

Azienda Socio-Sanitaria 5, La Spezia

- Malattie Infettive: Kamal Eldin Tarek, Stefania Artioli, Meazza Massimiliano

Azienda Ospedaliera S. Antonio e Biagio e C. Arrigo di Alessandria

- Pneumologia: Mario Salio, Giulia Salomoni, Federica Arcadipane
- Infrastruttura ricerca, formazione e innovazione: Serena Penpa, Antonio Maconi
- Farmacia: Francesca Cammalleri

Ospedale di Bolzano

- Malattie Infettive: Greta Spoladore, Raffaella Binazzi
- Servizio Farmaceutico: Marta Mazzer, Paola Cristina Cappelletto.

2. ADDITIONAL DETAILS ON METHODS

The trial was designed between September and October 2021, by a multidisciplinary group at the Azienda USL-IRCCS of Reggio Emilia. The group included clinical specialists in Infectious Diseases (Marco Massari), Rheumatology (Carlo Salvarani), Respiratory Disease (Nicola Facciolongo), Pharmacology (Caterina Turrà), a group of statisticians (Silvio Cavuto, Luisa Savoldi) and clinical epidemiologists (Domenico Franco Merlo, Paolo Bruzzi and Massimo Costantini).

No funding was obtained for this study. The coordinator centre and all participating centres are using local resources to conduct the trial.

CS, MC, FM, PB, GM drafted the first version of the manuscript. A second revision of the manuscript was performed by PV, SN, GD. PB, LB, MC, FM contributed to the statistical section of the manuscript. CT revised the pharmacological section. The manuscript was revised and approved by all the authors, who agreed the submission for publication.

3. POPULATIONS IN STUDY

3.1. Randomised patients: 304

3.2. Population for Intention To Treat (ITT) analysis: 301
Three patients withdrew consent to the study during the first day after randomisation:

ID-code	Arm	comments
017-123	Standard	withdrew consent 1 day after randomization
016-150	Standard	withdrew consent 1 day after randomization
001-300	Experimental	withdrew consent 1 day after randomization

3.3. Population for safety analyses: 298

ID-code	Arm	comments
003-036	Standard	No experimental treatment
008-101	Experimental	No experimental treatment
016-150	Standard	Withdrew consent
012-206	Standard	No experimental treatment
017-251	Experimental	No experimental treatment
001-300	Experimental	Withdrew consent

Note: 1 patient (code 017-123) withdrew consent after one bolus and was included in the safety analysis until this date.

4. ADDITIONAL DETAILS ON RESULTS

Other data about safety

Table S1. Adverse Events by MedDRA system organ class in the Safety Population (no.=298)

	Adverse Events (no.)							
	Placebo + Standard				MTP pulses + Standard			
	*Grades **				*Grades **			
MedDRA system organ class	***1 -2***	***3 -4***	***5***	***Total***	***1 -2***	***3 -4***	***5***	***Total***
Accidents and injuries (SMQ)	1	0	0	1	0	0	0	0
Blood and lymphatic system disorders	0	0	0	0	1	1	0	2
Breast disorders	0	0	0	0	1	0	0	1
Cardiac disorders	2	1	0	3	2	3	0	5
Endocrine disorders	0	0	0	0	1	0	0	1
Gastrointestinal disorders	2	1	0	3	3	1	1	5
Gastrointestinal haemorrhage	0	1	0	1	0	0	0	0
General disorders and administration site conditions	7	1	0	8	2	6	0	8
General system disorders NEC	1	0	0	1	0	0	0	0
Infections and infestations	5	3	4	12	6	5	0	11
Investigations	2	3	0	5	1	0	0	1
Metabolism and nutrition disorders	17	6	0	23	22	8	1	31
Musculoskeletal and connective tissue disorders	3	0	0	3	1	0	0	1
Psychiatric disorders	2	2	0	4	2	2	0	4
Renal and urinary disorders	4	2	0	6	1	3	0	4
Respiratory, thoracic, and mediastinal disorders	2	5	1	8	4	5	0	9
Skin and subcutaneous tissue disorders	1	0	0	1	1	0	0	1
Surgical and medical procedures	0	1	1	2	0	0	1	1
Vascular disorders	2	2	1	5	4	1	0	5
Total	51	28	7	86	52	35	3	90

* Grade AEs: 1 = Mild; 2 = Moderate, 3 = Severe; 4 = Life-Threatening; 5 = Death

Table S2. Summary of Serious Adverse Events (SAEs)

ID - Centre	MedDRA SOC term	MedDRA SOC code	MedDRA PT term	MedDRA PT code	Seriousness	Grade *	Related	Interval onset /outcome (days)	Outcome
Placebo + standard									
271-011	**Gastrointestinal haemorrhage**	10017955	Gastrointestinal disorders	10017947	Important event	4	Yes		Unknown
063-004	**General disorders and administration site conditions**	10018065	Pyrexia	10037660	Important event	2	No	1	Resolved
021-003	**Infections and infestations**	10021881	Septic shock	10040070	Life threatening	5	No	6	Fatal
035-004			Lung abscess	10025028	Hospitalisation	4	Yes		Unknown
049-001			Enterococcal infection	10061124	Important event	3	No	20	Resolved
286-017			Staphylococcal infection	10058080	Death	5	Yes	12	Fatal
286-017			Pneumonia klebsiella	10035717	Death	5	No	12	Fatal
286-017			Candida infection	10074170	Death	5	No	6	Fatal
042-004	**Renal and urinary disorders**	10038359	Renal failure	10038435	Important event	3	No		Unknown
035-004	**Respiratory, thoracic and mediastinal disorders**	10038738	Pneumothorax	10035759	Important event	3	No	3	Resolved
042-004			Pneumothorax	10035759	Hospitalisation	3	No	5	Resolved
071-006			Pneumonia aspiration	10035669	Life threatening	5	No	21	Fatal
130-008	**Surgical and medical procedures**	10042613	Endotracheal intubation	10067450	Life threatening	4	No		Unknown
293-008			Endotracheal intubation	10067450	Death	5	No	9	Fatal
105-013	**Vascular disorders**	10047065	Cerebral haemorrhage	10008111	Life threatening	5	No	1	Fatal
166-001			Cerebral haemorrhage	10008111	Hospitalisation	3	No	16	Resolved
MTP pulses + Standard									
209-013	**Cardiac disorders**	10007541	Cardiac failure	10007554	Important event	3	No		Improved
085-001	**Gastrointestinal disorders**	10017947	Haemorrhagic necrotic pancreatitis	10076058	Life threatening	5	No	7	Fatal
024-001	**Infections and infestations**	10021881	Pseudomonas infection	10061471	Important event	3	No	10	Resolved
245-001			Escherichia sepsis	10015296	Important event	3	No	13	Resolved
250-020			Septic shock	10040070	Important event	3	Yes		Improved
012-003	**Respiratory, thoracic and mediastinal disorders**	10038738	Pneumonia bacterial	10060946	Life threatening	4	No		Improved
250-020			Pneumonia bacterial	10060946	Important event	3	Yes		Improved
278-008	**Surgical and medical procedures**	10042613	Endotracheal intubation	10067450	Life threatening	5	No	9	Fatal
077-005	**Vascular disorders**	10047065	Cerebral ischaemia	10008120	Disability	4	No		Ong./Worsen.

* Grade: 1 = Lightweight; 2 = Moderate, 3 = Severe; 4 = Very Severe; 5 = Death

5. Subgroup analyses

In these subgroup analyses Hazard ratios (HRs) estimates obtained in the Cox model were reported within each subgroup, while the presence of a significant variation of the HRs across strata of each factor was assessed by means of the appropriate treatment-by-factor interaction tests. The P values of the interaction tests are reported, but should be considered with caution, due to the lack of correction for multiplicity.

Table S3: Clinical outcomes at 30 days according to PaO_2/FiO_2 at randomisation

Strata:

- PaO_2/FiO_2, between 100 and 200 (no.=143)
- PaO_2/FiO_2, between 201 and 300 (no.=158)

	Placebo + Standard no. (% at 30 dd)	**MTP pulses + Standard no. (% at 30 dd)**	**Rate Ratio (95% CI)**
PaO_2/FiO_2, between 100 and 200			
Discharge without oxygen	51/73 (70.7)	45/70 (66.7)	0.71 (0.48-1.08)
Admission to ICU or death	17/73 (23.4)	18/70 (25.7)	1.14 (0.59-2.21)
Deaths	12/73 (16.5)	9/70 (12.9)	0.77 (0.32-1.83)
PaO_2/FiO_2, between 201 and 300			
Discharge without oxygen	60/77 (79.5)	67/81 (82.9)	1.16 (0.82-1.65)
Admission to ICU or death	7/77 (9.1)	11/81 (13.7)	1.50 (0.58-3.88)
Deaths	6/77 (8.1)	5/81 (6.3)	0.79 (0.24-2.59)

Tests for interaction for discharge without oxygen (P=0.083), admission to ICU or death (P=0.522), deaths (P=0.758).

Table S4: Clinical outcomes at 30 days according to the modality of oxygen administration at randomisation

Strata:

- Supplemental standard oxygen (no. 205)
- NIV or high-flow oxygen (no.=96)

	Placebo + Standard no. (% at 30 dd)	**MTP pulses + Standard no. (% at 30 dd)**	**Rate Ratio (95% CI)**
Standard oxygen			
Discharge without oxygen	79/101 (79.6)	84/104 (81.1)	0.93 (0.68-1.26)
Admission to ICU or death	12/101 (12.0)	14/104 (13.5)	1.15 (0.53-2.48)
Deaths	9/101 (9.1)	7/104 (6.9)	0.75 (0.28-2.01)
NIV or high-flow oxygen			
Discharge without oxygen	32/49 (66.3)	28/47 (62.0)	0.86 (0.52-1.43)
Admission to ICU or death	12/49 (24.6)	15/47 (31.9)	1.33 (0.62-2.85)
Deaths	9/49 (18.6)	7/47 (14.9)	0.82 (0.31-2.20)

Tests for interaction for discharge without oxygen (P=0.822), admission to ICU or death (P=0.885), deaths (P=0.932).

Table S5: Clinical outcomes at 30 days according to C-reactive protein (CPR) at randomisation

Strata:

- CPR greater than 5 and less or equal 10 (no. 137)
- CPR greater than 10 and less or equal 15 (no. 93)
- CPR greater than 15 (no.=71)

	Placebo + Standard no. (% at 30 dd)	**MTP pulses + Standard no. (% at 30 dd)**	**Rate Ratio (95% CI)**
CPR > 5 and ≤ 10			
Discharge without oxygen	55/68 (82.2)	52/69 (75.4)	0.73 (0.50-1.07)
Admission to ICU or death	6/68 (8.9)	13/69 (19.0)	2.29 (0.87-6.03)
Deaths	5/68 (7.5)	8/69 (11.8)	1.61 (0.53-4.93)
CPR > 10 and ≤ 15			
Discharge without oxygen	31/46 (67.8)	34/47 (75.0)	1.14 (0.70-1.86)
Admission to ICU or death	11/46 (23.9)	8/47 (17.1)	0.68 (0.27-1.70)
Deaths	8/46 (17.4)	1/47 (2.3)	0.12 (0.01-0.93)
CPR > 15			
Discharge without oxygen	25/36 (71.2)	26/35 (75.9)	1.07 (0.62-1.85)
Admission to ICU or death	7/36 (19.8)	8/35 (22.9)	1.22 (0.44-3.36)
Deaths	5/36 (14.5)	5/35 (14.3)	1.04 (0.30-3.60)

Tests for interaction for discharge without oxygen (P=0.276), admission to ICU or death (P=0.145), deaths (P=0.021).

Table S6: Clinical outcomes at 30 days according to the age at randomisation

Strata:

- Age (years) ≤ 60 (no. 120)
- Age (years) > 60 (no. 181)

	Placebo + Standard no. (% at 30 dd)	**MTP pulses + Standard no. (% at 30 dd)**	**Rate Ratio (95% CI)**
Age (years) ≤ 60			
Discharge without oxygen	57/59 (96.6)	57/61 (93.4)	0.78 (0.54-1.13)
Admission to ICU or death	2/59 (3.4)	3/61 (4.9)	1.46 (0.24-8.77)
Deaths	2/59 (3.4)	0/61 (-)	0.19 (0.01-4.28)
Age (years) > 60			
Discharge without oxygen	54/91 (59.3)	55/90 (61.1)	0.97 (0.66-1.41)
Admission to ICU or death	22/91 (24.2)	27/90 (30.0)	1.27 (0.73-2.24)
Deaths	16/91 (17.6)	15/90 (16.7)	0.97 (0.47-1.97)

Tests for interaction for discharge without oxygen (P=0.435), admission to ICU or death (P=0.884), deaths (P=0.054).

Table S7: Clinical outcomes at 30 days according to Body Mass Index at randomisation

Strata:

- BMI 1st quartile, ≤ 24,6 (no.=58)
- BMI 2nd quartile, 24,7-27.6 (no.=59)
- BMI 3rd quartile, 27.7- 30.9 (no.=58)
- BMI 4th quartile, ≥ 31.0 (no.=58)

	Placebo + Standard no. (% at 30 dd)	**MTP pulses + Standard no. (% at 30 dd)**	**Rate Ratio (95% CI)**
BMI 1st quartile			
Discharge without oxygen	17/31 (54.8)	19/27 (70.4)	1.36 (0.71-2.62)
Admission to ICU or death	8/31 (25.8)	7/27 (25.9)	0.98 (0.36-2.71)
Deaths	7/31 (22.6)	2/27 (7.4)	0.37 (0.08-1.72)
BMI 2nd quartile			
Discharge without oxygen	15/23 (65.2)	26/36 (72.2)	1.01 (0.53-1.90)
Admission to ICU or death	6/23 (26.1)	7/36 (19.4)	0.74 (0.25-2.22)
Deaths	5/23 (21.7)	4/36 (11.1)	0.50 (0.13-1.91)
BMI 3rd quartile			
Discharge without oxygen	22/29 (75.9)	22/29 (75.9)	0.88 (0.49-1.59)
Admission to ICU or death	5/29 (17.2)	4/29 (13.8)	0.78 (0.21-2.91)
Deaths	3/29 (10.3)	2/29 (6.9)	0.68 (0.12-3.94)
BMI 4th quartile			
Discharge without oxygen	25/29 (86.2)	22/29 (75.9)	0.76 (0.43-1.35)
Admission to ICU or death	2/29 (6.9)	5/29 (17.2)	2.68 (0.52-13.8)
Deaths	0/29 (-)	2/29 (6.9)	5.19 (0.20-136)

Tests for interaction for discharge without oxygen (P=0.6071), admission to ICU or death (P=0.581), deaths (P=0.046).