Supplementary file

Review protocol
The review protocol was registered on the PROSPERO database with ID CRD42020190183 (1).

Literature search and study selection
A systematic literature review was conducted on May 14th and again on November 7th 2020, ending on the same days, independently by two authors (GD and GC) using 5 databases: PubMed, Web of Science, Scopus, Latin American and Caribbean health Sciences Literature (LILACS) and Cochrane Central. The research strategies were ((glucocorticoid* OR corticosteroid* OR steroid*) AND (SARS* OR MERS* OR COVID*) AND (puls* OR bol*)) in word, title and abstract sections; where possible they were also searched in all fields and "registro de ensayos clinicos" sections. Detailed research strategies and results are described in Table S1. References from review articles and meta-analyses focusing on SARS-CoV, MERS-CoV and SARS-CoV2 were examined to identify additional studies.

Duplicated studies were first excluded, and then titles and abstracts were carefully scanned by two authors (GD and GC). Studies were included if they met all of the following criteria (Table S2): 1) Patients with SARS-CoV, MERS-CoV or SARS-CoV2 infection; 2) Treatment with methylprednisolone 500mg/day or more or other corticosteroids equivalent doses; 3) Any study design. If the dose of steroids was not determinable from title nor abstract, articles were not excluded and they were then evaluated using the full text. After the evaluation of the full text, reviews were excluded and relevant cited papers checked for eligibility. If full text was not available, the publishing Journal or the authors were contacted by email or if available through ResearchGate to request a copy. If data from full text were not clear, authors were contacted by email or if available through ResearchGate to ask for further details.

For the primary outcomes concerning treatment efficacy, only studies that directly compared pulse-therapy and any other treatment were considered. For the secondary outcomes, concerning treatment safety (apart from oro-tracheal intubation), both comparative and non-comparative studies were included. If the number of patients receiving pulse-therapy was not available, the study was excluded.

No language restriction was considered. One full-text in Chinese was available after contacting authors and journals and it did not meet the criteria for inclusion in the primary outcome analysis. One full-text in Russian was available (2): it was evaluated and data were extracted by only one author J.M. No years of publication restriction was applied and only published articles were considered. This study was done in accordance with PRISMA recommendations.

The primary outcomes of this systematic review were:

- Any cause death
- ICU admission

Secondary outcomes were:
- Oro-tracheal intubation
- Osteonecrosis
- Hyperglycaemia
- Psychosis
- Super-infections

Data extraction and management
Data regarding the papers were managed using Mendeley (Elsevier)®.
Data for every included study were collected in an Excel (Microsoft)® sheet including all main article characteristics and study outcomes.

Statistical analysis
We synthesised results in tables for primary outcomes and secondary outcomes, divided for disease (one for SARS, one for MERS and one for

Table S1. Research strategies and research results.

Database	Research strategy	Papers found
PubMed	(((glucocordicoid* OR steroid* OR corticosteroid*)) AND (pulse* OR "high dose")) AND (COVID19 OR COVID-19 OR SARS-CoV2 OR SARS OR MERS OR Coronavirus)	115
Web of Science	TOPIC: (glucocorticoid* OR corticosteroid* OR steroid*) AND TOPIC: (COVID* OR SARS-CoV2 OR SARS* OR MERS* OR Coronavir*) AND TOPIC: (pulse* OR high dose) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.	128
Scopus	(TITLE-ABS-KEY (glucocorticoid* OR steroid* OR corticosteroid*) AND TITLE-ABS-KEY (puls* OR bol*) AND TITLE-ABS-KEY (sars* OR covid* OR mers*))	88
LILACS	glucocorticoi* OR steroid* OR corticosteroid* [Titulo, resumen, asunto] and COVID* OR SARS* OR MERS* [Titulo, resumen, asunto] and puls* OR bol* [Titulo, resumen, asunto]	70
Cochrane Central	glucocorticoid* OR corticosteroid* OR steroid* in Title Abstract Keyword AND COVID* OR SARS* OR MERS* OR Coronavir* in Title Abstract Keyword AND puls* OR bol* in Title Abstract Keyword - (Word variations have been searched)	23

Table S2. Systematic literature review's P.I.C.O.S.

Parameter	Inclusion criteria	Exclusion criteria
Population	Patients with SARS, MERS or SARS-CoV2 infection	
Intervention	Methylprednisolone 500mg/day or more or equivalent dose of other glucocorticoids	Treatment defined as "pulse therapy" but <500mg/day of Methylprednisolone or equivalent
Comparator	Any other treatment	
Outcomes	Death, ICU admission, intubation	
Study design	Randomised and non-randomised controlled trial, single arm trial, prospective and retrospective cohort studies, case series	Reviews

Table S3a. Characteristics and primary outcomes of the 15 included articles describing patients that underwent glucocorticoids pulse-therapy in SARS-CoV infection during the acute phase.

First author	Year	Patients - whole study	Patients - pulse-therapy group	Deaths - whole study	Deaths - pulse-therapy group	Lethality - pulse-therapy group (%)	ICU - whole study	ICU - pulse-therapy group	ICU - pulse-therapy group (%)
Chan[6]	2003	1521 pts, 676M, 845F, mean age 42.5 years (SD 19.5years)	737	215	NA	NA	NA	NA	NA
Yam[4]	2007	1287 pts, 737F, 550M, age range 29-81 years	220	230	66	30	247	48	22
Tsui[7]	2003	323 pts, 127M, 196F, mean age of 41±14 (range 18–83)	220	26	26	12	67	67	31
Booth[8]	2003	144 pts, 88F, 56M, mean age 45 years (34-57)	1	8	NA	NA	29	N.A.	N.A.
Sung[9]	2004	138 pts	107	15	9	8	37	37	35
Lau[10]	2004	88pts, 33M, 55F, median age 40.5 years (13-74)	30	1	NA	NA	21	NA	NA
Ho[3]	2003	72 pts, 42F, 30M	61	4	NA	NA	12	NA	NA
Li[11]	2003	43 pts	9	1	0	0	NA	NA	NA
Soo[12]	2004	40 pts, mean age 43.5 years	40	5	5	12	NA	NA	NA
So[13]	2003	31 pts, 11M, 20F, mean age 39.6 years (SD 13.3)	11	1	0	0	0	NA	NA
Jang[14]	2004	29pts, 9M, 20F, median age 39 years (range 22-82)	17	4	3	18	NA	NA	NA
Lee[15]	2003	17 pts, mean age 35 years (22-57)	11	1	1	9	1	1	9
Jones[16]	2004	12 pts	3	N.A.	N.A.	NA	NA	NA	NA
Joynt[17]	2004	8pts, 6M, 2F, age 33-73 (median 53)	8	3	3	37,5	8	8	100
Wong[18]	2003	4 pts, 4F, 0M, age 44-73	4	4	4	100	4	4	100

Table S3b. Secondary outcomes in the papers patients that underwent glucocorticoids pulse-therapy in SARS-CoV infection.

First author	Year	Patients - whole study	Patients - pulse-therapy group	Considered outcome - whole study, n (%)	Considered outcome - pulse-therapy group, n (%)
Oro-tracheal intubation					
Wong[18]	2003	4	4	4 (100%)	4 (100%)
Joynt[17]	2004	8	8	6 (75%)	6 (75%)
Yam[19]	2007	1287	220	165 (12%)	32 (15%)
Sung[9]	2004	138	107	21 (15%)	21 (20%)
Lee[20]	2003	17	11	1 (6%)	1 (9%)
Hyperglicaemia					
Li[21]	2003	43	9	2	0 (0%)
Sung[9]	2004	138	107	23	23 (17%)
Super-infections					
Yam[19]	2007	1287	220	52 (4%, 42 fungal, 10 tuberculosis)	8 (3%, 7 fungal infections, 1 tuberculosis)
Sung[9]	2004	138	107	17 (12%)	17 (15%, in 6 patients before the administration of pulse therapy)

COVID19). We decided not to perform quantitative synthesis due to the low quality of included comparative studies focusing on steroids pulse therapy compared to other therapies.

Data synthesis
We directly extracted the total number of deaths and ICU admission from the included papers. This was a discrepancy from the study protocol and it has been done because of the inclusion of only six studies in the primary end-points analysis, with high risk of bias and heterogeneity.

Results
Twenty-two papers describing patients that received glucocorticoids pulse-therapy in COVID-19 were found, but eleven were excluded because the number of patients that received pulse-therapy was not available or the pulse-therapy dose was lower than 500mg/day of methylprednisolone.

No paper was found for MERS, while 32 papers regarding SARS, 21 describ-

Risk of bias domains

Table S4. Risk of bias evaluation using ROBINS-I tool for the two papers on SARS and the four papers on COVID-19 included in the primary outcomes analysis.

ing the acute phase of the disease and 11 describing the sequelae of the considered patients (Table S3a and Table S3b). The number of patients that received pulse-steroids therapy was reported in 18 out of 32 papers and these 18 were included in the systematic review. Of these 18 papers, 10 reported the number of patients died and 6 the number of patients admitted to ICU among the ones that received pulse-therapy.

Two papers directly focusing on pulse-therapy compared to non-pulse therapies were found (3, 4) for SARS and four were found for COVID-19 and they were considered for efficacy outcomes (Table S1) and assessed for risk of bias.

The secondary outcomes of this systematic review were available as follow: 5 for oro-tracheal intubation; 0 for osteonecrosis; 2 for hyperglycaemia; 0 for psychosis; 2 for super-infections (Table S3b).

Risk of bias assessment
The quality of the evidence was very

low for both outcomes and both included studies had an high overall risk of bias using ROBINS-I tool (5) (Table S4).

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