

Effect of glucocorticoids on the development of COVID-19-associated pulmonary aspergillosis: a meta-analysis of 21 studies and 5174 patients

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Supplementary Appendix

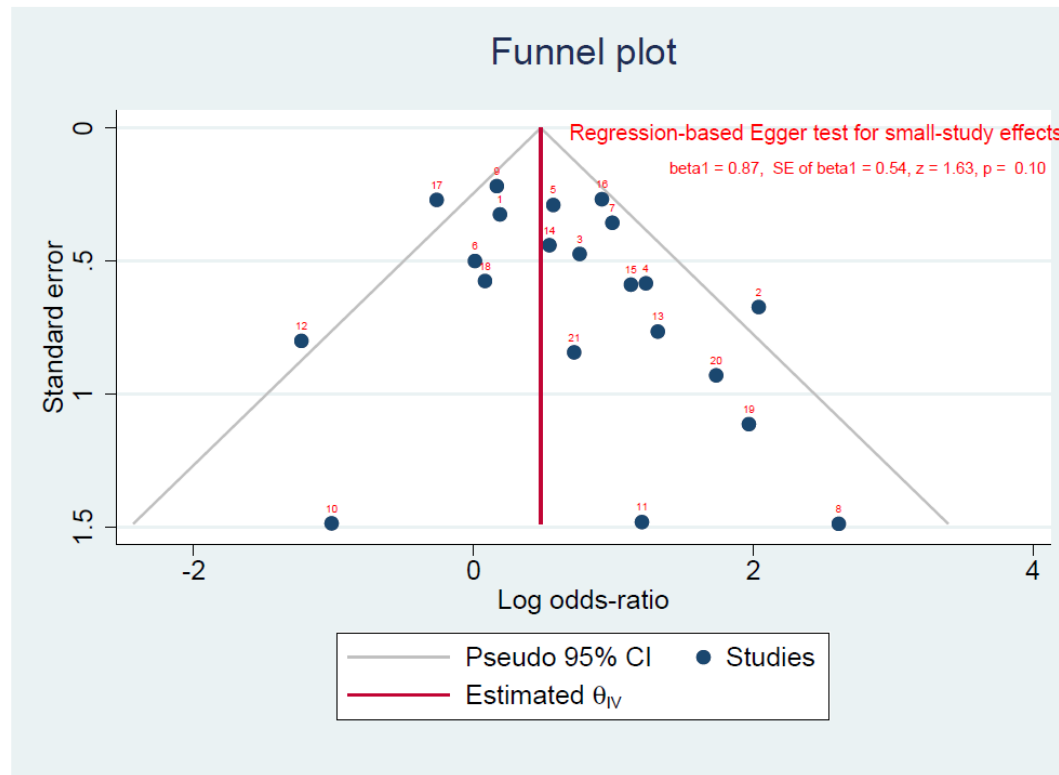


Fig. S1: Funnel plot showing significant bias between glucocorticoids (GC) and no-glucocorticoids (No-GC) treatment groups. Seven imputed studies were required to nullify the bias. The numbering of studies in the plot corresponds to forest plot of the analysis.

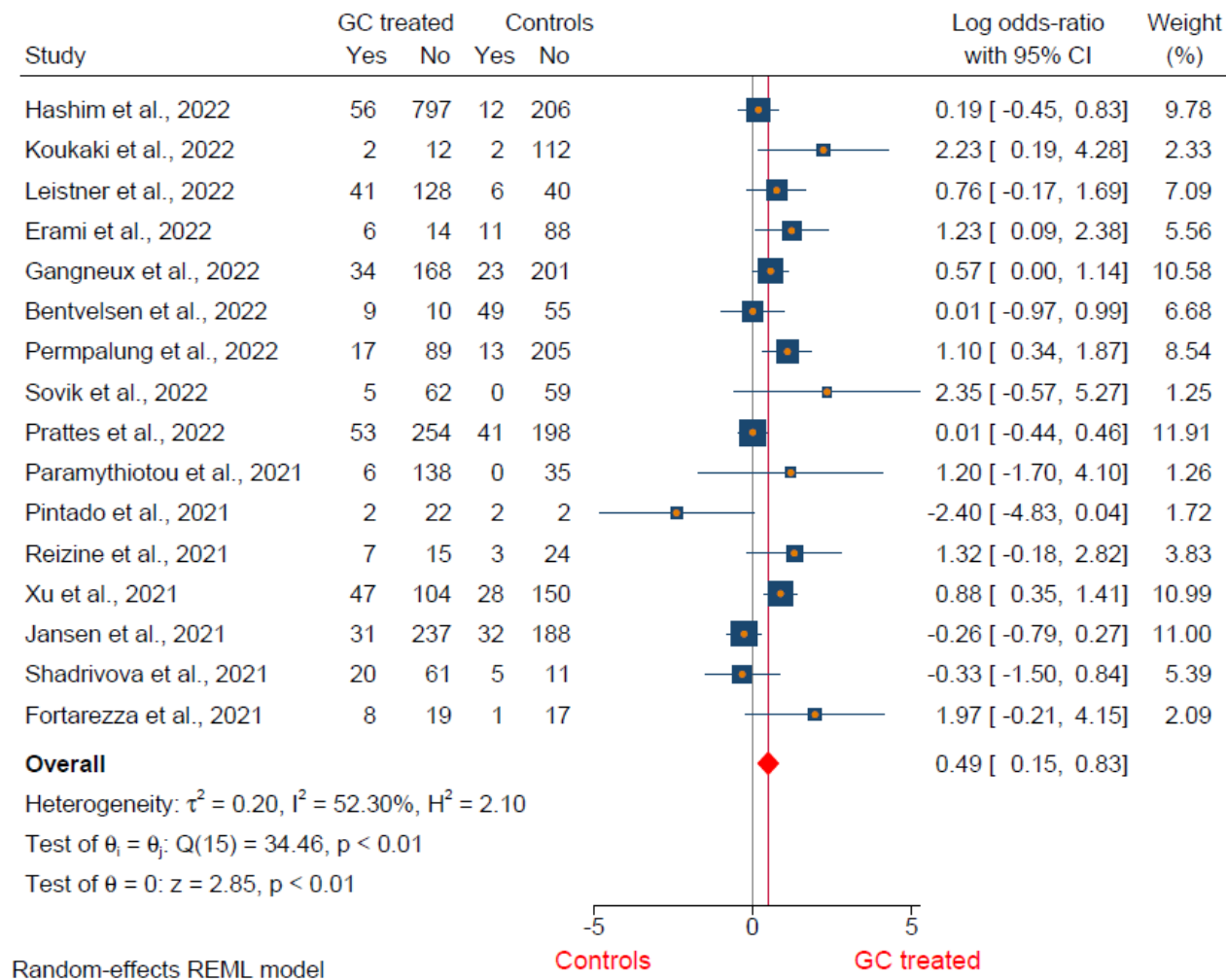


Fig. S2: Pooled log odds ratio (LOR) of CAPA development in studies with ECMM/ISHAM definition of CAPA.

Table-S1: Number of Studies identified through different databases and manual search	
Source	Number of Studies
PubMed	105
Embase	445
Scopus	731
Google Schola	970
Manual Search of citations	05
Total	2256

Table-S2: NOS Scale for Quality Assessment of Studies					
Study	Selection	Comparability	Outcome	Overall Score (Stars)	Overall Score (Numbers)
Hashim et al., 2022 (3)	★★★★	★★	★★★	★★★★★★★★★	9
Koukaki et al.2022 (27)	★★★★	★	★★★	★★★★★★★★★	8
Leistner et al, 2022 (28)	★★★★	★★	★★★	★★★★★★★★★	9
Erami et al; 2022 (29)	★★★★	★★	★★	★★★★★★★★★	8
Gangunuex et al. 2022 (30)	★★★★	★	★★★	★★★★★★★★★	8
Bentvelsen et al; 2022 (31)	★★★★	★	★★	★★★★★★★	7
Perampalung et al; 2022(32)	★★★★	★	★★	★★★★★★★	7
Sovik et al. 2022 (33)	★★★★	★★	★★	★★★★★★★★★	8
Prattes et al. 2022 (34)	★★★★	★	★★★	★★★★★★★★★	8
Fekkar et al, 2021(4)	★★★★	★	★★	★★★★★★★	7
Paramythiotou et al 2021 (35)	★★★★	★	★★★	★★★★★★★★★	8
Pintado et al, 2021(36)	★★★★	★	★★	★★★★★★★	7
Reizine et al, 2021(37)	★★★★	★	★★★	★★★★★★★★★	8
Bartoletti et al, 2021 (38)	★★★★	★	★★	★★★★★★★	7
Delliere et al, 2021 (39)	★★★★	★	★★★	★★★★★★★★★	8
Xu et al, 2021 (40)	★★★★	★	★★★	★★★★★★★★★	8
Jansen et al. (41)	★★★★	★	★★	★★★★★★★	7
Shadrivova et al, 2021 (42)	★★★★	★★	★★	★★★★★★★★★	8
Fortarezza et al, 2021 (43)	★★★★	★★	★★★	★★★★★★★★★	9
Chauvet et al; 2020 (44)	★★★★	★★	★★	★★★★★★★★★	8
Wang et al, 2020 (45)	★★★★	★	★★	★★★★★★★	7

Table-S3: Exclusion of IM treated patients from studies with GC and IM treatment

Studies (Reference)	Total Patients (CAPA+ noCAPA)	GC+*IM treated CAPA + noCAPA)	No GC or IM treated CAPA + noCAPA) (Controls)	IM Treated (CAPA + noCAPA)	GC treated (CAPA+ noCAPA)	CAPA in GC	CAPA in controls
1. Hashim et al., 2022 (3)	1161 (74+1087)	943 (62+ 881)	218 (12+206)	90 (6+84)	853 (56+797)	56/853	12/218
2. Koukaki et al; 2022 (27)	178 (14+164)	64 (12+52)	114 (2+112)	50 (10+40)	14 (2+12)	2/14	2/114
3. Permpalung et al; 2022 (32)	396 (39+357)	178 (26+152)	218 (13+205)	72 (9+63)	106 (17+89)	17/106	13/218
4. Sovik et al; 2022 (33)	155 (5+150)	72 (5+67)	59 (0+59)	5 (0+5)	67 (5+62)	5/67	0/59
5. Prattes et al; 2022 (34)	585 (109+476)	346 (68+278)	239 (41+198)	39 (15+24)	307 (53+254)	53/307	41/239
6. Fekkar et al; 2021 (4)	145 (6+139))	24 (0+24)	121 (6+115)	10 (0+10)	14 (0+14)	0/14	6/121
7. Pintado et al; 2021 (36)	83 (16+67)	79 (14+65)	4 (2+2)	55 (12+43)	24 (2+22)	2/24	2/4
8. Bartoletti et al; 2021 (38)	103 (30+73)	79 (22+57)	24 (8+16)	79 (22 +57)	0/0	0/0	8/24
9. Delliere et al; 2021 (39)	108 ((21+87)	16 (6+10)	92 (15+77)	11 (4+7)	5 (2+3)	2/5	15/92
10. Xu et al; 2021 (40)	335 (78+257)	157 (50+107)	178 (28+150)	6 (3+3)	151 (47+104)	47/151	28/178
11. Shadrivova et al; 2021 (42)	131 (43+88)	115 (38+77)	16 (5+11)	34 (18+16)	81 (20+61)	20/81	5/16

Abbreviations:

CAPA: COVID-19-associated pulmonary aspergillosis, GC: Glucocorticoids, IM: Immunomodulator

***IM Treatment:** IM includes various non-GC immunomodulatory agents such as Tocilizumab (anti-IL6 receptor monoclonal antibody); Sarilumab (IL6 receptor antagonist) Anti-IL1 monoclonal antibody; Anakinra (IL1-recptor antagonist) etc. The patients not responding to GC are usually given IM. Thus GC treated patients were considered to represent GC+IM treated patients unless otherwise indicated in the study.

Table-S4: GC dose and type based subgroups of included studies

Study (Reference)	Low dose GC treatment	CAPA in Low-dose-GC	CAPA in controls
1. Hashim et al., 2022 (3)	Dexamethasone : 6mg/equivalent MP daily up to 10 days.	36/603	12/218
2. Leistner et al; 2022 (28)	Dexamethasone : 6mg daily up to 10 days.	41/169	6/46
3. Sovik et al; 2022 (33)	Dexamethasone : 6mg daily for 11 days	5/67	0/59
4. Paramythiotou et al; 2021 (35)	Dexamethasone : 6mg daily for 10 days.	6/144	0/35
5. Pintado et al; 2021 (36)	Prednisolone : 1.3mg/kg daily; duration not defined	2/24	2/4
6. Reizine et al; 2021 (37)	Dexamethasone : 6mg daily x 10 days.	7/22	3/27
7. Xu et al; 2021 (40)	Methylprednisolone : $\geq$ 20-40mg daily for seven days.	47/151	28/178
8.. Jansen et al; 2021 (41)	Prednisolone : cumulative dose 5.36 mg/kg.	31/268	32/220
9.. Shadrivova et al; 2021 (42)	Prednisolone : >60mg daily; duration not defined.	20/81	5/16
10. Fortarezza et al; 2021 (43)	Dexamethasone : 6mg daily up to 10 days.	8/27	1/18
11. Wang et al; 2020 (45)	Methylprednisolone : 40-80 mg daily; duration not defined.	6/63	2/41
Study (Reference)	High dose GC treatment	CAPA in High-dose-GC	CAPA in control
1. Hashim et al., 2022 (3)	Methylprednisolone: 125 mg daily for three days.	17/291	12/218
2. Koukaki et al; 2022 (27)	Dexamethasone : 20mg daily for >10 days.	2/14	2/114
3. Fekkar et al; 2021 (4)	Dexamethasone : 20mg daily for 10 days.	0/14	6/121
4. Permpalung et al; 2022 (32)	Prednisolone :120-160mg, Methylprednisolone: 160-245mg; Hydrocortisone: 425-500mg; or Dexamethasone::36-50mg (total in 3-6 days). Patients received two/more GC type in overlap.	17/106	13/218
5. Delliery et al, 2021 (39)	Dexamethasone : cumulative dose of >1000mg.	2/5	15/92
6. Chauvet et al; 2020 (44)	Dexamethasone : 20mg daily; duration not defined.	3/09	03/37
Study (Reference)	Dexa-GC treatment	CAPA in Dexa-GC	CAPA in control
1. Hashim et al; 2022 (3)	Dexamethasone: 6mg up to 10 days.	36/603	12/218
2. Koukaki et al; 2022 (27)	Dexamethasone: 20mg daily for >10 days.	2/14	2/114
3. Leistner et al; 2022 (28)	Dexamethasone: 6mg daily up to 10 days.	41/169	6/46
4. Gangneux et al; 2022 (30)	Dexamethasone: dose not defined.	34/202	23/224
5. Permpalung et al; 2022 (32)	Dexamethasone: 36-50mg (total in 3-6 days).	9/84	13/218
6. Sovik et al; 2022 (33)	Dexamethasone: 6mg daily for 11 days.	5/67	0/59
7. Fekkar et al; 2021 (4)	Dexamethasone: 20mg daily for 10 days.	0/14	6/121
8. Paramythiotou et al; 2021 (35)	Dexamethasone: 6mg daily for 10 days.	6/144	0/35
9. Reizine et al; 2021 (37)	Dexamethasone: 6mg daily x 10 days.	7/22	3/27
10. Delliery et al, 2021 (39)	Dexamethasone: cumulative dose of >1000mg.	2/5	15/92
11. Fortarezza et al; 2021 (43)	Dexamethasone: 6mg daily up to 10 days.	8/27	1/18
12. Chauvet et al; 2020 (44)	Dexamethasone: 20mg daily; duration not defined.	3/9	3/37
Study (Reference)	Non-Dexa-GC treatment	CAPA in Non-Dexa-GC	CAPA in control
1. Hashim et al; 2022 (3)	Methylprednisolone: (=6mg Dexa) or 125mg daily x 10 days.	37/703	12/218
2. Permpalung et al; 2022 (32)	Prednisolone :120-160mg, Methylprednisolone :160-245mg; HC:425-500 mg (days:3-6)	17/106	13/218
3. Pintado et al; 2021 (36)	Prednisolone : 1.3mg/kg daily; duration not defined.	2/24	2/4
4. Xu et al; 2021 (40)	Methylprednisolone: $\geq$ 20-40mg daily for seven days.	47/151	28/178
5. Jansen et al; 2021 (41)	Prednisolone : cumulative dose 5.36 mg/kg.	31/268	32/220
6. Shadrivova et al; 2021 (42)	Prednisolone : >60mg daily; duration not defined.	20/81	5/16
7. Wang et al; 2020 (45)	Methylprednisolone: 40-80 mg daily; duration not defined.	6/63	2/41

Table-S5: CAPA in GC and control groups of studies with ECMM/ISHAM definition of CAPA

Study (Reference)	Total CAPA in Patients	CAPA in GC group	CAPA in controls
1. Hashim et al; 2022 (3)	74/1161	56/853	12/218
2. Koukaki et al; 2022 (27)	14/178	2/14	2/114
3. Leistner et al; 2022 (28)	47/215	41/169	6/46
4. Erami et al; 2022 (29)	17/119	6/20	11/99
5. Gangneux et al; 2022 (30)	57/426	34/202	23/224
6. Bentvelsen et al; 2022 (31)	58/123	9/19	49/104
7. Permpalung et al; 2022 (32)	39/396	17/106	13/218
8. Sovik et al; 2022 (33)	5/155	5/67	0/59
9. Prattes et al; 2022 (34)	109/585	53/307	41/239
10. Paramythiotou et al; 2021 (35)	6/179	6/144	0/35
11. Pintado et al; 2021 (36)	16/83	2/24	2/4
12. Reizine et al; 2021 (37)	10/49	7/22	3/27
13. Xu et al; 2021 (40)	78/335	47/151	28/178
14. Jansen et al; 2021 (41)	63/488	31/268	32/220
15. Shadrivova et al; 2021 (42)	43/131	20/81	5/16
16. Fortarezza et al; 2021 (43)	9/45	8/27	1/18
Abbreviations: CAPA: COVID-19-associated pulmonary aspergillosis, GC: Glucocorticoids.			

Table-S6: Summary of the analysed studies

Study Groups	Studies (n)	CAPA in GC (%)	CAPA in No-GC (%)	τ^2	I^2	H^2	Q	$\beta 1$	LOR (95% Confidence Interval)
GC-treated vs controls	20	355/2565	254/2110	0.19, p=0.01	46.61, p=0.01	1.87, p=0.01	37.76, p=0.01	0.76, p=0.13	0.54 (0.22, 0.86), z=3.29, p<0.01
Low-dose GC vs controls	11	212/1578	91/862	0.25, p=0.01	49.55, p=0.01	1.98, p=0.01	22.59, p=0.01	-	0.41 (-0.07, 0.89), z=1.69, p=0.09
high-doseGC vs controls	6	41/439	51/800	0.29, p=0.15	39.66, p=0.15	1.66, p=0.15	8.03, p=0.15	-	0.90 (0.17, 1.62), z=2.43, p=0.01
Dexa vs controls	12	156/1447	84/1209	0.03, p=0.44	8.38, p=0.44	1.09, p=0.44	11.04, p=0.44	-	0.71 (0.35, 1.07), z=3.89, p<0.01
Non-Dexa-GC vs controls	7	160/1396	94/895	0.36, p<0.01	68.75, p<0.01	3.20, p<0.01	20.33, p<0.01	-	0.21 (-0.36, 0.79), z=0.72, p=0.47
GC-treated vs controls (ISHAM group)	16	344/2474	228/1819	0.20, p<0.01	52.30, p<0.01	2.10, p<0.01	34.46, p<0.01		0.49 (0.15, 0.83), z=2.85, p<0.01

τ^2 : Measure of heterogeneity; I^2 : Measure of heterogeneity; H^2 : Measure of heterogeneity; Q: Cochran's Q Test for heterogeneity; β_1 : Regression based Egger's test for quantification of publication bias; LOR: Measure of effect size; Z-value: Measure of standard deviations below or above the population mean.