Supplementary Figures and Tables

Supplementary Table 1 Search Strategy for Medline (Ovid) 1946-present

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 (influenza* or flu).tw.
5 (h1n1 or h5n1 or h3n2).tw.
6 or/1-5
7 exp Adrenal Cortex Hormones/
8 corticosteroid*.tw,nm.
9 adrenal cortex hormon*.tw.
10 (adren* cortic* adj1 (hormone* or steroid*)).tw.
11 adrenocorticosteroid*.tw,nm.
12 adrenocorticoid*.tw,nm.
13 corticoid*.tw,nm.
14 glucocorticoid*.tw,nm.
15 hydroxycorticosteroid*.tw,nm.
16 exp Steroids/
17 steroid*.tw,nm.
18 (hydrocortisone* or prednisolone* or prednisone* or dexamethasone* or methylprednisolone*).tw,nm.
19 or/7-18
20 6 and 19

SUPPLEMENTARY TABLE 2 Characteristics of included studies

Study/year (country) (reference)	Design	Setting/inclusion criteria	CS given (n)	CS not given (n)	Patient characteristics	Disease severity scores	Corticosteroid therapy dose/timing/duration	Outcomes reported
Al-Busaidi 2016 (Oman)(45)	Single centre, retrospective cohort	In-hospital	11	57	Median age (years): 23 (range 25 days to 67 years)	Not reported	Not reported	Length of stay
Balaganesakumar 2013 (India)(25)	Multicentre, prospective cohort study	In-hospital/admissions with influenza	70	210	Median age (years): 26 (1 to 82)	Not reported	Not reported	Mortality
Boudreault 2011 (USA)(47)	Single-centre, retrospective cohort	Non-ICU/HCT recipients with RTI	80 (low-dose 43 and high-dose 37)	63	Median age (years): no CS 42 (32 to 51); low-dose CS 42 (28 to 53); high-dose CS 40 (32 to 54)	Not reported	Highest dose in 2/52 preceding influenza Low-dose (pred/methylpred < 1 mg/kg/day); high-dose (pred/methylpred >= 1 mg/kg/day)	MV, time to death, PVS
Brun-Buisson 2011 (France)(15)	Multicentre, retrospective analysis of prospectively collected data	ICU/severe respiratory failure (ARDS or MV)	83 (early CS 50 and late CS 33)	125	Median age (years): no CS 45 (35 to 55); CS 49 (34 to 56) Immunosuppression: no CS 18.4%; CS 21.7%	Median SAPSIII cohort 52.0 (44.0 to 64.0); no CS 53.0 (46.0 to 66.0); CS group 51.0 (44.0 to 61.0); P = 0.25	Median daily dose: 270 (200 to 400) mg of hydrocortisone equivalent Timing: within median 1 day (0 to 6) of MV Duration: median 11 days (6 to 20)	Hospital mortality, length of ICU stay, adverse events
Cao 2016 (China)(26)	Multicentre, retrospectiv	In-hospital ≥ 14 years with pneumonia	204	84	Median age (years): 58 (IQR 45 to 68)	Moderate to severe	Low-moderate dose: 168 (82.4), high dose 36 (17.6). Median dose	Mortality, adverse

	e cohort study					ARDS 207 (71.9)	(mg/day of methylprednisolone equivalent) 80 (IQR 40 to 120)	events, viral shedding
Chawla 2013 (India)(27)	Single-centre, retrospective cohort study	ICU/admissions with influenza	38	39	Mean age (years): 40.9 (± 13.4)	Not reported	Duration of therapy: mean (days) 10.6 (± 7.8)	Mortality
Delaney 2016 (Canada)(28)	Multicentre, prospective cohort study	ICU/age ≥ 18 years; critically ill with confirmed, probable or highly suspected influenza	280	327	Mean age (years): no CS 46.2 (± 15.2); CS 48.8 (± 15.3) Asthma: CS 29.3%; no CS 12.8%; P = < 0.001 COPD: CS 25.0%; no CS 9.2%; P = < 0.001 Immunosuppressed: CS 8.9%; no CS 3.1%; P = 0.002	Mean APACHE II score: CS 21.2 (± 10.3); no CS 20.1 (± 9.7); P = 0.22 Mean SOFA score: CS 11.4 (±3.8); no CS 11.3 (± 3.6); P = 0.70	Median daily dose: 227 (154 to 443) mg of hydrocortisone equivalent Timing: median 0 days (0 to 3) of critical illness onset; median 2 days (1 to 8) from hospital admission Duration: median 7 days (4 to 13)	Mortality, hospital-acquired infections
Delgado-Rodriguez 2012 (Spain)(46)	Multicentre, prospective cohort	In-hospital/ILI, RTI, septic shock, multi-organ failure	31	782	Cohort median age (years): 41 (19 to 55)	Not reported	Corticosteroid use 90 days prior to admission	Poor outcome (ICU admission and in-hospital death), LOS
Han 2011 (China - Shenyang City)(49)	Multicentre, retrospective cohort	In-hospital/age > 3 years	46 (early CS 17 and late CS 29)	37	Median age (years): no CS 38 (5 to 75); CS 43 (3 to 70)	Median PMEWS: no CS group 2 (0 to 5); CS group 2 (0 to 5)	Methylpred and dexamethasone	Critical illness

Huang 2017 (Taiwan)(29)	Single-centre, retrospective cohort study	In-hospital/ age > 18 years	29	19	Cohort mean age (years): 65.9 (± 19.2) Chronic pulmonary disease: respiratory distress cohort 27.1%	Respiratory distress	Dose and type: not reported ("Medium to high dose" defined as ≥ 0.5 to 2 mg/kg/day) Timing: early (before/within 72 hours of NAIs) 58.6% Duration: short (≤ 3 days) 13.8%; 4 to 13 days 48.3%); ≥ 14 days 34.5%)	Mortality
Jain 2009 (USA) (48)	Multicentre, retrospective cohort	In-hospital/ILI with hospital admission ≥ 24 hours	86	153	Cohort median age: 21 years (21 days to 86 years) Asthma: 28%; COPD: 8% Immunosuppression: 15%	Not reported	Not reported	Death/ICU admission versus survival/no ICU admission
Kim 2011 (South Korea)(30)	Multicentre, retrospective cohort/case-control	ICU/age ≥ 15 years; presence of critical illness	107	138	Mean age (years): no CS 54.1 (± 19.3); CS 56.9 (± 17.2) Asthma: CS 9%; no CS 7% COPD: CS 13%; no CS 4%	Mean (SD) APACHE II: no CS group 17.5 (± 8.5); CS group 21.2 (± 7.7); P value = 0.001	Dose: median pred equivalent 75 (50 to 81) mg/day Duration: median days 6 (3 to 14)	Mortality (14-day, 30-day and 90-day), LOS, acquired infections
Kinikar 2012 (India)(31)	Single centre, retrospective cohort study	ICU/admissions with influenza < 12 years	21	71	Cohort median age (years): 2.5 (1.3 to 6) Asthma: 4.3%	Not reported	Dose: not reported Timing: not reported Duration: described as "short course"	In-hospital mortality

					Congenital heart disease: 6.5%			
Kudo 2012 (Japan)(51)	Single-centre, retrospective cohort	In-hospital/hospitalised patients with respiratory disorders	46	12	Cohort median age (years): 8 (0 to 71) Asthma: 29.2%	Not reported	Dose: methylpred 1 to 1.5 mg/kg, 2 to 4 times/day Duration: median 5.1 days Timing: median 2.1 days following symptom onset	LOS
Lee 2015 (China)(32)	Multicentre, retrospective analysis of prospectively collected data	In-hospital/age > 17 years	610	2039	Cohort median age (years): 63 (42 to 79)	Ventilatory support and/or ICU 305 (11.5)	Not reported	Mortality, bacterial superinfection, LOS
Li 2012 (China - Anhui province)(33)	Multicentre, retrospective cohort study	In-hospital/pregnant, severe disease	27	19	Median age (years): adults who died 21 (18 to 31) and survivors 21 (18 to 27)	Not reported	Not reported	Mortality
Li 2017(34)	Multicentre, retrospective analysis of prospectively collected data	In-hospital with viral pneumonia > 14 years	1055	1086	Median age (years): no CS 33.7 (24.6 to 48.7); CS 35.0 (23.8 to 52.4) Asthma: no CS 1.5%; CS 2.1% COPD: no CS 4.3%; CS 5.6%	PaO_2/FiO_2 (mmHg): no CS 286.2 (191.7 to 388.2); CS 173.3 (100 to 272.4)	Dose: median methylprednisolone equivalent 80 (53.3 to 160) mg/day; Mean methylprednisolone equivalent 141.3 (± 142) Duration: median (days) 7 (4 to 8); Mean (days) 7.7 (± 6.8)	Mortality, ICU admission, hospital-acquired infection, MV

					Immunosuppression: no CS 1.4%; CS 3.2%		Timing: median (days) 6 (4 to 8); mean (days) 6.7 (± 4)	
Liem 2009 (Vietnam)(35)	Multicentre, retrospective cohort	In-hospital/hospitalised patients with influenza	29	38	Cohort median age (years): 25 (16 to 42)	Not reported	Dose: methylpred 1 to 3 mg/kg/day for 7 days	In-hospital mortality
Linko 2011 (Finland)(36)	Multicentre, prospective cohort study	ICU/admissions with influenza	72	60	Median age (years): no CS 44 (25 to 57); CS 51 (40 to 56) COPD: no CS 5%; CS 8% Other obstructive pulmonary disease: no CS 23%; CS 21%	Median SAPSII: no CS 22 (15 to 30); CS 31 (24 to 36); P = 0.001	Methylpred and/or hydrocortisone Dose: mean (SD) of highest methylpred dose 94 (± 43) mg and hydrocortisone 214 (± 66) mg Timing: median (IQR) days after symptom onset 5.0 (2.8 to 8.3)	In-hospital mortality, MV, LOS
Mady 2012 (Saudi Arabia)(37)	Single-centre, retrospective cohort study	ICU/influenza with respiratory failure	43	43	Cohort mean age (years): 40.8 Asthma or COPD: 38.3%	Mean APACHEIV: 110.5 versus 100.6 (P > 0.05), not specified for which treatment group	Methylpred Dose: 1 mg/kg per day for 7 days	Mortality
Moreno 2018 (Spain)(38)	Multicentre, prospective cohort study	ICU/viral pneumonia	604	1242	Median age (years): CS 53 (41 to 62); no CS 51 (39 to 61)	Median APACHE II score: CS group 15 (10 to 20); No CS group 14 (10 to 19)	Median daily dose methylprednisolone equivalent 80 (60 to 120) mg. Median duration (days) 7 (5 to 10). Administered within 24	ICU mortality

						(P value 0.0001)	hours of ICU admission.	
Ono 2016(50)	Multicentre retrospective cohort study	Medical insurance database, < 65 years, first episode of hospitalisation with confirmed influenza	804	87250	All < 65 years. Asthma: hospitalised 39.5%; non-hospitalised 23.5% COPD: hospitalised 2.9%; non-hospitalised 0.5% Immunosuppression: hospitalised 0.36%; non-hospitalised 0.13%	Not reported	Dose not reported. Timing: > 30 days steroid use in 6 month baseline prior to influenza diagnosis	Rate of hospitalisation
Patel 2013 (India - Gujarat)(39)	Single-centre, retrospective cohort study	In-hospital/admissions with influenza	39	24	Cohort median age (years): 34 (3 to 69)	Not reported	Dose: methylprednisolone 40 mg 3 times a day, twice a day and once a day, for week 1, 2 and 3 respectively	Mortality
Sertogullarindan 2011 (Turkey)(40)	Single-centre, prospective cohort study	ICU/severe community-acquired pneumonia and influenza	7	13	Cohort median age (years): 36 (15 to 72) COPD: 10%	Not reported	Not reported	Mortality
Sheu 2017 (Taiwan)(41)	Multicentre, retrospective cohort study	ICU admissions with confirmed influenza	101	91	Cohort mean age (years): 58.3	ARDS: Mild 8.3%; moderate 29.2%; severe 62.5%	Not reported	Mortality

Viasus 2011 (Spain)(42)	Multicentre, prospective cohort study	In-hospital/ non-immunosuppressed, admitted > 24 hours	37	129	Median age (years): no CS 35 (28 to 47); CS 44 (36 to 53) Chronic pulmonary disease: no CS 17.1%; CS 45.9%	Number in high-risk PSI classes: CS 8 (21.6); no CS 8 (6.4); P < 0.05	Duration: median days 9 (5 to 13.5)	Severe disease (composite outcome of ICU admission/death), acquired infection
Wirz 2016 (Switzerland)(52)	Multicentre RCT of adjunct prednisone therapy versus placebo in community-acquired pneumonia	Non-ICU with community-acquired pneumonia (influenza subgroup n = 24)	11	13	All trial participants: mean age (years): CS arm 70.3 (± 17.5); placebo arm 69.0 (± 17) COPD: CS arm 19.3%; placebo 15.4%	PSI mean score: CS 92.5 (± 38.2); placebo 89.2 (± 35.5)	Dose: oral prednisone 50 mg/day Duration: 7 days Timing: early	Any-cause mortality at 30 d, hospital readmission at 30 days post discharge, time to effective hospital discharge, time to clinical stability
Wu 2012 (Taiwan)(53)	Single-centre, prospective cohort	Mixed cohort of out-patients and in-patients	17	189	Age >= 65 years in cohort: 12.6% Chronic lung disease: 9.7% Malignancy: 8.7%	Not reported	Dose/duration: not reported Unclear if CS commenced prior to or following diagnosis	Complicated influenza (requiring hospitalisation)
Xi 2010 (China - Beijing)(43)	Multicentre, retrospective cohort study	In-hospital/age ≥ 18 years	52	103	Cohort mean age (years): 43 (±18.6) COPD: 6.5%	Not reported	Dose: daily median dose equivalent to methylpred 80 mg (IQR 80 to 160 mg)	In-hospital mortality Subgroup analysis of mortality by CS dose
Yu 2011 (China - Zhengzhou)(44)	Multicentre, retrospectiv	Not defined	54	74	Cohort mean age (years): females	Not reported	Dose: not reported	Mortality

	e cohort study				28.5 (± 16.4); males 28.5 (± 20.4) Range 8 months to 79 years		Duration: mean (days); died 8.3 (± 8.0); survived 2.6 (± 4.2) Timing: 'Early'	

SUPPLEMENTARY TABLE 3 Risk of bias in observational studies using the Newcastle-Ottawa Scale

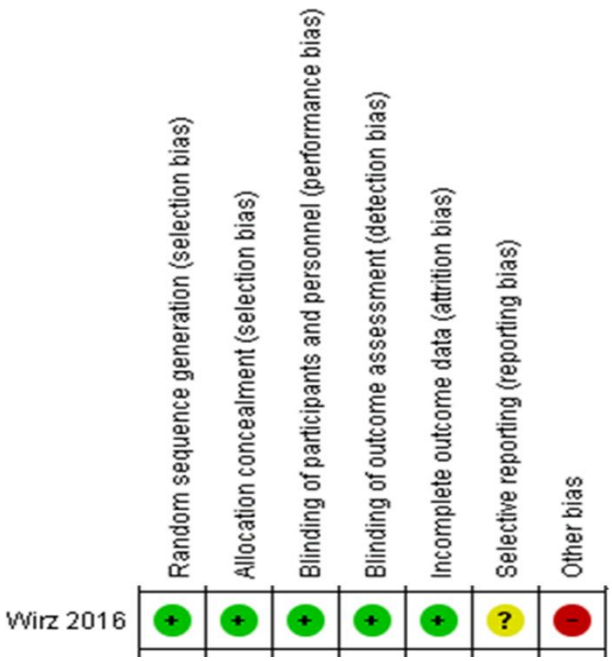
Study (reference number)	Outcome	Selection domain (maximum 4 stars)	Comparability domain (maximum 2 stars)	Outcome domain (maximum 3 stars)
Al-Busaidi 2016 (45)	Length of stay	3	1	2
Balaganesakumar 2013 (25)	Mortality	2	1	2
Boudreault 2011 (47)	Time to death	2	1	2
Brun-Buisson 2011(15)	In-hospital mortality	3	2	3
Brun-Buisson 2011(15)	Length of ICU stay	3	0	3
Brun-Buisson 2011(15)	ICU-acquired infection	3	0	3
Cao 2016(26)	Mortality	4	2	3
Cao 2016(26)	Hospital-acquired infection	4	2	2
Cao 2016(26)	Viral shedding	4	2	2
Chawla 2013(27)	Mortality	3	0	3
Delaney 2016(28)	Mortality	4	2	3
Delaney 2016(28)	ICU-acquired infection	4	0	3
Delgado-Rodriguez 2012 (46)	Composite outcome of ICU admission and mortality	3	2	3
Han 2011 (49)	Critical illness	3	2	3
Jain 2009 (48)	ICU admission death versus survival/no ICU admission	4	0	3
Huang 2017(29)	Mortality	2	0	2
Kim 2011 (30)	Mortality	4	2	3
Kim 2011(30)	Mechanical Ventilation	4	0	3
Kim 2011(30)	Length of Stay	4	0	3
Kim 2011(30)	Hospital-acquired infection	4	0	3
Kinikar 2012(31)	In-hospital mortality	3	0	3
Kudo 2012 (51)	Length of Stay	4	0	2
Lee 2015(32)	Mortality	4	2	3
Lee 2015(32)	Hospital-acquired infection	4	0	3
Lee 2015(32)	Length of Stay	4	2	3
Li 2012(33)	Mortality	2	0	3
Li 2017(34)	Mortality	4	2	3
Li 2017(34)	ICU admission	4	0	3

Li 2017(34)	Hospital-acquired infection	4	0	2
Li 2017(34)	Mechanical Ventilation	4	0	3
Liem 2009(35)	In-hospital mortality	4	1	3
Linko 2011(36)	In-hospital mortality	4	2	3
Linko 2011(36)	Mechanical Ventilation	4	0	3
Linko 2011(36)	Length of Stay	4	0	3
Mady 2012 (37)	Mortality	3	0	3
Moreno 2018(38)	ICU mortality	4	2	3
Moreno 2018(38)	ICU Length of Stay	4	0	2
Moreno 2018(38)	Mechanical Ventilation	4	1	3
Ono 2016 (50)	Hospitalisation	2	2	3
Patel 2013(39)	Mortality	2	0	3
Sertogullarindan 2011(40)	Mortality	3	0	3
Viasus 2011(42)	In-hospital mortality	4	0	3
Viasus 2011(42)	Hospital-acquired infection	4	0	3
Wu 2012 (53)	Influenza requiring hospitalisation	4	1	3
Xi 2010(43)	In-hospital mortality	3	1	3
Yu 2011(44)	Mortality	2	1	1

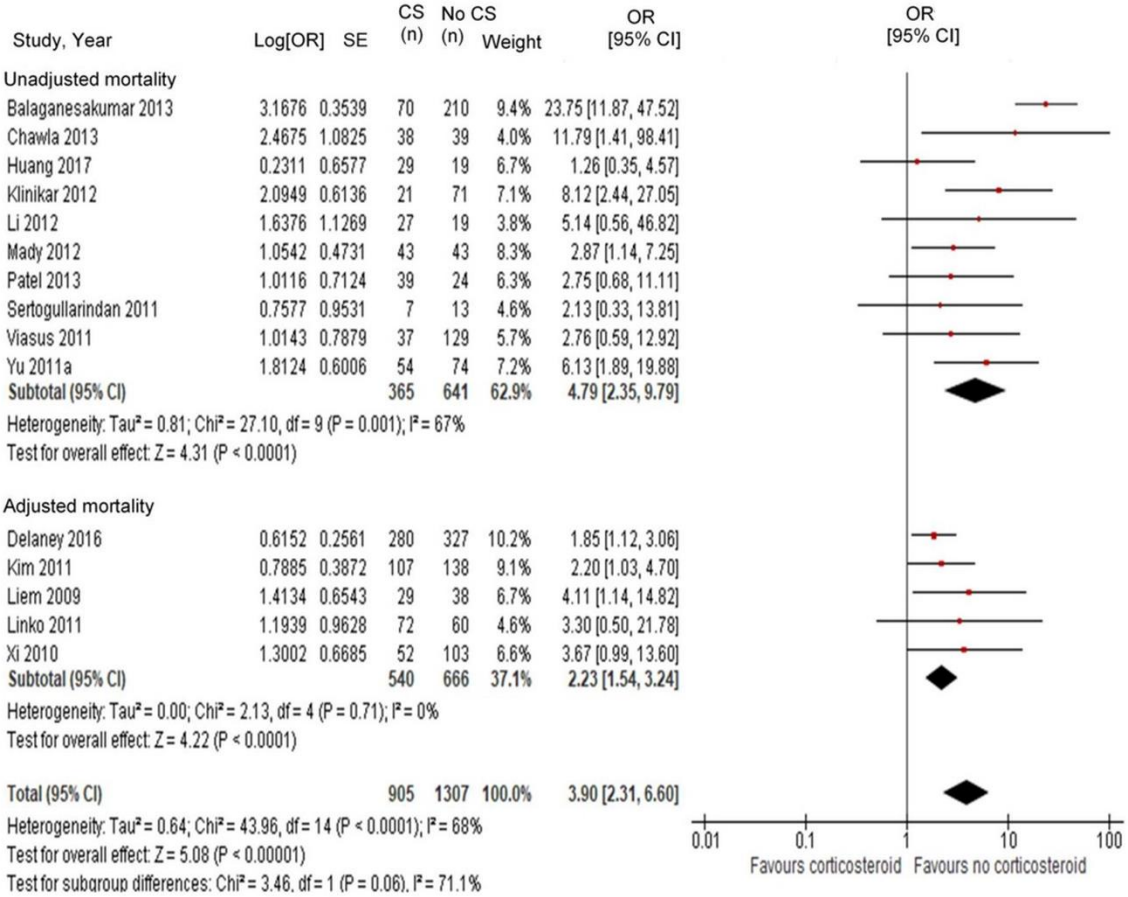
Supplementary Table 4: GRADE assessment of outcomes: corticosteroid therapy compared to no corticosteroid therapy in the treatment of influenza

Outcomes	**Anticipated absolute effects** (95% CI) *		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no CS therapy	Risk with CS therapy				
Mortality	70 per 1,000	**209 per 1,000** (160 to 267)	**OR 3.90** (2.31 to 6.60)	9536 (21 observational studies)	⨁◯◯◯ VERY LOW [a]	We downgraded the certainty of the evidence from low (observational data) to very low due to high risk of indication bias (sicker patients with influenza were more likely to receive corticosteroids) and clinical/statistical heterogeneity (unadjusted estimates of odds ratios for mortality were presented in some studies and the definition of mortality varied across studies)
Rate of admission of ICUs	260 per 1,000	**643 per 1000 (599 to 684)**	**OR 5.13 (4.26 6.17)**	2141 (1 observational study)	⨁◯◯◯ VERY LOW [a]	
Hospital-acquired infection	72 per 1000	**175 per 1000 (105 to 277)**	**OR 2.74 (1.51 to 4.95)**	6114 (7 observational studies)	⨁◯◯◯ VERY LOW [a]	
Mechanical ventilation	418 per 1000	**Ranged from 561 to 890 per 1000**	**OR ranged from 1.78 (1.35 to 2.35) to 11.29 (8.25 to 15.44)**	4364 (4 observational studies)	⨁◯◯◯ VERY LOW [a]	

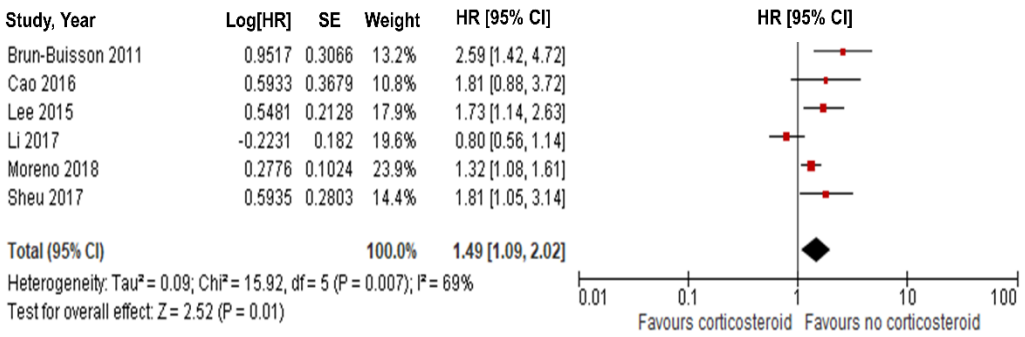
Supplementary figure 1



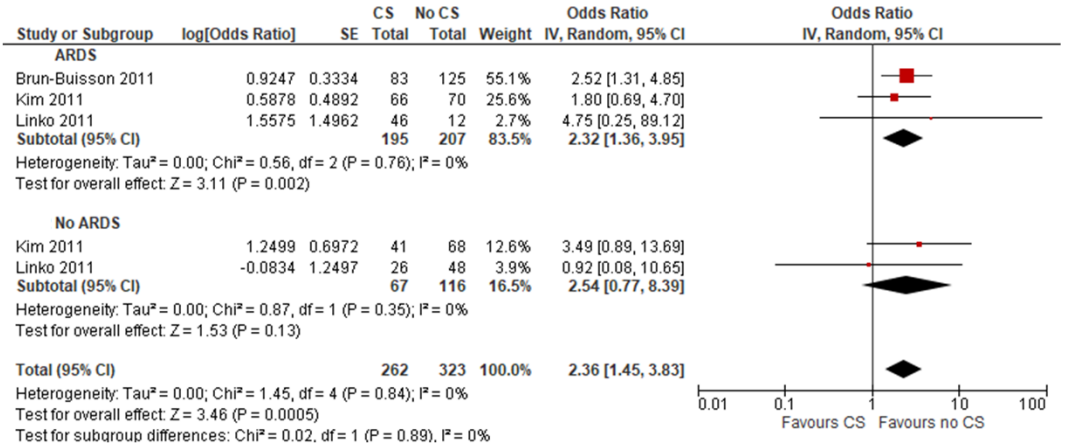
Supplementary figure 2



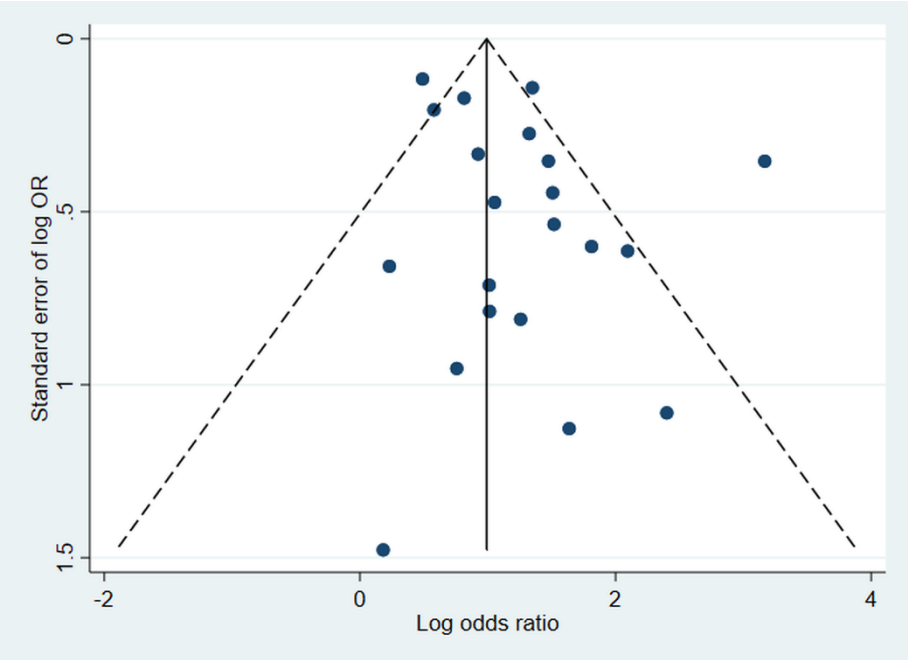
Supplementary figure 3: Meta-analysis -HRs



Supplementary figure 4: Subgroup analysis - ARDS versus no ARDS



Supplementary figure 5: Funnel plot



Supplementary figure 6: Meta-analysis HAI