

Table S1: Details of search strategy

Search strategy for PubMed database (from its inception to May, 2021)		
No.	Search strategy	Items found
#1	((((((((("hypertone"[All Fields] OR "hypertonic"[All Fields]) OR "hypertonic"[All Fields]) OR "muscle hypertonia"[MeSH Terms]) OR ("muscle"[All Fields] AND "hypertonia"[All Fields]) OR "muscle hypertonia"[All Fields]) OR "hypertonicity"[All Fields]) OR ("high"[All Fields] AND (((("osmosis"[MeSH Terms] OR "osmosis"[All Fields]) OR "osmotic"[All Fields]) OR "osmotical"[All Fields]) OR "osmotically"[All Fields]) OR "osmotics"[All Fields]))) OR 3[UID]) OR 5[UID]) OR 7[UID]	48123
#2	(((("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields]) OR "saline"[All Fields]) OR "salines"[All Fields]) OR (((((((("pharmaceutical solutions"[Pharmacological Action] OR "solutions"[MeSH Terms]) OR "solutions"[All Fields]) OR "solution"[All Fields]) OR "pharmaceutical solutions"[MeSH Terms]) OR ("pharmaceutical"[All Fields] AND "solutions"[All Fields]) OR "pharmaceutical solutions"[All Fields]) OR "solutal"[All Fields]) OR "solute"[All Fields]) OR "solute s"[All Fields]) OR "soluted"[All Fields]) OR "solutes"[All Fields]) OR "solution s"[All Fields])) OR ("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields])	1074253
#3	(((("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields]) OR "bronchiolitides"[All Fields]) OR (((("bronchopneumonia"[MeSH Terms] OR "bronchopneumonia"[All Fields]) OR "bronchopneumonias"[All Fields]) OR "bronchopneumoniae"[All Fields])) OR (((("respiratory syncytial viruses"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields]) AND "viruses"[All Fields])) OR "respiratory syncytial viruses"[All Fields]) OR ((("respiratory"[All Fields] AND "syncytial"[All Fields]) AND "virus"[All Fields])) OR "respiratory syncytial virus"[All Fields])) OR ((("respiratory syncytial viruses"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields]) AND "viruses"[All Fields])) OR "respiratory syncytial viruses"[All Fields])) OR "RSV"[All Fields]	37957
#4	#1 AND #2 AND #3	202
Search strategy for EMBASE database (from its inception to May, 2021)		
No.	Search strategy	Items found
#1	hypertonic OR high osmotic OR 3% OR 5% OR 7%	37608
#2	saline OR Sodium Chloride OR solution	1076968
#3	bronchiolitis OR bronchopneumonia OR respiratory syncytial virus OR respiratory syncytial viruses OR RSV	61574
#4	#1 AND #2 AND #3	335
Search strategy for CENTRAL database (from its inception to May, 2021)		
No.	Search strategy	Items found
#1	hypertonic OR high osmotic OR 3% OR 5% OR 7%	1318529
#2	saline OR solution OR Sodium Chloride	76096
#3	bronchiolitis OR bronchopneumonia OR respiratory syncytial virus OR respiratory syncytial viruses OR RSV	2598
#4	#1 AND #2 AND #3	383

Table S2: relevant ongoing studies in the international trial registers

ClinicalTrials.gov	
NCT02029040	bronchiolitis
NCT01238848	bronchiolitis
NCT04140214	bronchiolitis
NCT03880903	bronchiolitis
NCT03143231	bronchiolitis

ISRCTN Registry	
None	

Table S3: Characteristic of included studies

Study	Location	Study design	Age (months)	Sample size	Intervention	Control	Method	Outcomes
Al-Ansari 2010	Qatar (2007-2008)	RCT	Con 3.30±2.43, 3%HS 3.84±2.84, 5%HS 4.02±2.56	171	HS(5%)+ Epi, HS(3%)+ Epi	NS(0.9%)+ Epi	Every 4h until discharge	LOS, CSS (Wang et al), AE
Angoulvant 2017	France (2012-2014)	RCT	Con 3 (2-5), 3%HS 3 (2-5)*	772	HS(3%)	NS(0.9%)	20 minutes per time for twice	ROH, AE
Anil 2010	Turkey (2005-2006)	RCT	NS+Epi 10.4±5.7, 3%HS+Epi 9.4±5.0, NS+Sal 9.0±6.2, 3%HS+Sal 9.7±6.2, NS 9.1±4.4	186	HS(3%)+ Epi/Sal	NS(0.9%)+ Epi/Sal or NS alone	Twice at 30-min interval	ROH, AE
Bashir 2018	India (2014-2015)	RCT	Con 4.0 (2.0-7.0), 3%HS 4.0 (2.63-8.0)#	189	HS(3%)	NS(0.9%)	2h for 3 doses, followed by 4h for 6 doses, followed by 6h until discharge.	LOS, CSS (Wang et al), AE

Everard 2014	UK (2011-2013)	RCT	Con 3.4±2.8, 3%HS 3.3±2.6	291	HS(3%)	supportive care without inhalations	Every 6h once the primary outcome had been achieved.	LOS, AE
Flores 2016	Portugal (2012-2014)	RCT	Con 3.8±2.5, 3%HS 3.3±2.4	68	HS(3%)+ Sal	NS(0.9%)+ Sal	Every 6 h until discharge	LOS, CSS (Wang et al), AE
Florin 2014	US (2010-2011)	RCT	Con 6.1±3.6, 3%HS 7.2±5.1	62	HS(3%)+Epi	NS(0.9%)+ Epi	Once	ROH, AE
Grewal 2009	Canada (2004-2005)	RCT	Con 4.4±3.4, 3%HS 5.6±4.0	46	HS(3%)+Epi	NS(0.9%)+ Epi	Four times in 120 minutes	ROH, AE
Ipek 2011	Turkey (2009-2010)	RCT	NS+Sal 8.13±4.75, NS 7.40±3.08, 3%HS+Sal 7.90±3.57, 3%HS 8.40±4.19	120	HS(3%) with/withou t Sal	NS(0.9%) with/without Sal	Every 20 min until 3 doses had been administere d (0, 20 and 40th min).	ROH, CSS (Wang et al), AE
Jacobs 2013	US (2010-2012)	RCT	Con 5.6±3.3, 3%HS 6.0±3.9	101	HS(7%)+ Epi	NS(0.9%)+ Epi	Every 6h until discharge from ED	ROH, CSS (modifie d from Wang et al), AE
Khanal 2015	Nepal(2014)	RCT	Con 9.51 ±4.28, 3% HS 9.82±5.06	100	HS(3%)+ L-Epi	NS(0.9%)+ L-Epi	Twice	CSS (Wang et al), AE
Köse 2016	Turkey (2014)	RCT	Con 7.6 (1-18), 3%HS 7.6 (2-23), 7%HS 7.7 (1-24)#	104	HS(7%)+ Sal, HS(3%)+ Sal	NS(0.9%)+ Sal	Every 6h until discharge	LOS, CSS (Wang et al), AE
Kuzik 2007	Canada (2003-2006)	RCT	Con 9.51 ±4.28 4.6±4.7, 3%HS 4.4±3.7	96	HS(3%)+ Sal	NS(0.9%)+ Sal	Every 2h for 3 doses, followed by every 4h for 5 doses, followed by every 6h	LOS, AE

							until discharge	
Kuzik 2010	Canada (2008-2009)	RCT	Con 9.2±5.2, 3%HS 8.6±5.6	81	HS(3%)+Sal	NS(0.9%)+Sal	Three times in 1h	ROH, CSS (RDAI), AE
Li 2014	China (2012-2013)	RCT	Con 7.6±3.9, 3%HS 6.7±3.1, 5%HS 6.7±3.6	124	HS(5%), HS(3%)	NS(0.9%)	Twice per day for 3 days	CSS (Wang et al), AE
Luo 2010	China (2007-2008)	RCT	Con 5.6±4.5, 3%HS 6.0±4.3	93	HS(3%)+Sal	NS(0.9%)+Sal	Every 8h until discharge	LOS, CSS (Wang et al), AE
Luo 2011	China (2008-2009)	RCT	Con 5.8±4.3, 3%HS 5.9±4.1	112	HS(3%)	NS(0.9%)	Every 2 h for 3 doses, followed by every 4 h for 5 doses, followed by every 6 h until discharge	LOS, CSS (Wang et al), AE
Mahesh Kumar 2013	India (2007-2009)	RCT	5.93±3.83	40	HS(3%)+Sal	NS(0.9%)+Sal	Every 6h until discharge	LOS, CSS (Wang et al)
Mandelberg 2003	Israel (2000-2001)	RCT	Con 2.6±1.9, 3% HS 3±1.2	53	HS(3%)+Epi	NS(0.9%)+Epi	Every 8h until discharge	LOS, CSS (Wang et al), AE
Miraglia2012	Italy (2008-2010)	RCT	Con 4.2±1.6, 3%HS 4.8±1.3	106	HS(3%)+Epi	NS(0.9%)+Epi	Every 6h until discharge	LOS, CSS (Wang et al)
Morikawa 2018	Japan (2008-2013)	RCT	Con 4.2±3.0, HS 4.4±3.1	128	HS(3%)+Sal	NS(0.9%)+Sal	Four times daily until discharge	LOS, CSS (Wang et al), AE
Ojha 2014	Nepal (2012-2013)	RCT	Con 8.51±4.24, 3%HS	59	HS(3%)	NS(0.9%)	Every 8h until discharge	LOS, CSS

			8.61±5.74 2					(Wang et al), AE
Pandit 2013	India (2009-2011)	RCT	Con 4.08 ± 1.90, 3%HS 3.92 ± 1.72	100	HS(3%)+A dr	NS(0.9%)+A dr	Three times with an interval of one hour	LOS, CSS (RDAI), AE
Park 2015	korea (2003-2004)	RCT	Con 6.1 ± 3.2, 3%HS 5.6±2.7	80	HS(3%)+fenoterol	NS(0.9%)+fenoterol	Every 6h until discharge	LOS, CSS (Wang et al), AE
Ratajczyk-Pekrul 2016	Poland (2011-2013)	RCT	Con 4.43, 3%HS 5.34	78	HS(3%)+Sa 1	NS(0.9%)+Sa 1	Every 4h until discharge	LOS, CSS (Wang et al), AE
Sarrell 2002	Israel (2000-2001)	RCT	Con 12.3± 1.1, 3%HS 12.1±0.9	65	HS(3%)+terbutaline	NS(0.9%)+terbutaline	Every 8h for 5 days	ROH, CSS (Wang et al), AE
Sharma 2013	India (2009-2010)	RCT	Con 4.18±4.24, 3%HS 4.93±4.31	248	HS(3%)+Sa 1	NS(0.9%)+Sa 1	Every 4h until discharge	LOS, CSS (Wang et al), AE
Silver 2015	US (2011-2014)	RCT	Con 4.4±3.0, 3%HS 3.9±3.0	227	HS(3%)	NS(0.9%)	Every 4h until discharge	LOS, CSS (RDAI), AE
Tal 2006	Israel (2001-2002)	RCT	Con 2.3±0.7, 3%HS 2.8±1.2	41	HS(3%)+Epi	NS(0.9%)+Epi	Every 8h until discharge	LOS, CSS (Wang et al), AE
Teunissen 2014	Netherlands (2009-2011)	RCT	Con 3.6±5.0, 3% HS 3.6±5.2, 6% HS 3.4±3.8	247	HS(6%)+Sal, HS(3%)+Sal	NS(0.9%)+Sal	Every 8h until discharge	LOS, CSS (Wang et al), AE
Tinsa 2014	Tunis (2012)	RCT	Con 3.06±2.47, 5%HS 3.76±2.8	94	HS(5%)	NS(0.9%)	Every 4h until ready for discharge	LOS, CSS (Wang et al), AE
Uysalol 2017	Turkey (2011-2012)	RCT	Con 7 (4-10), 3%HS 7 (4-10)*	156	HS(3%)	NS(0.9%)	Every 4h until discharge	LOS, AE

Wu 2014	US (2008-2011)	RCT	Con 6.40±5.33, 3% HS 6.57±5.17	408	HS(3%)+ Sal	NS(0.9%)+ Sal	Every 20 minutes to 3 doses in ED, admitted patients continued receiving every 8h until discharge	ROH, LOS, CSS (RDAI), AE
Hmar 2021	India (2016-2018)	RCT	Con 10.02±5.4 5, 3% HS 8.45±4.88	158	HS(3%)+ Sal	NS(0.9%)+ Sal	Every 6h until discharge	LOS, CSS (Wang et al)
Raphaelle 2019	Switzerland (2013-2016)	RCT	Con 7.7±5.48, 3% HS 7.7±5.07	120	HS(3%)	supportive care without inhalations	Every 6h until discharge	LOS, CSS (Wang et al)

HS: hypertonic saline, NS: normal saline, RCT: Randomized controlled study, LOS: length of stay in hospital, ROH: rate of hospitalization, CSS: clinical severity scores, AE: adverse event, ED: emergency department, *: median (25th, 75th), #: median (range), &: median (IQR).

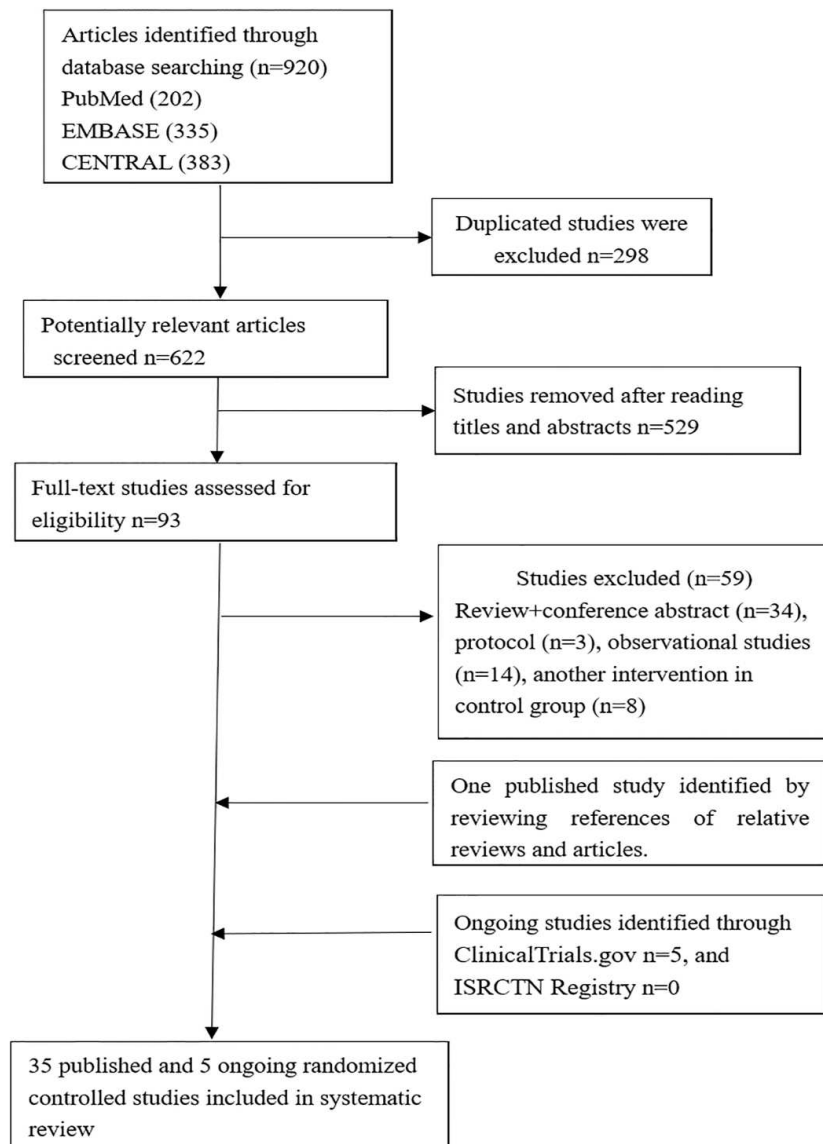


Figure S1: The flow diagram of identifying relevant studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Al-Ansari 2010	+	+	+	?	?	+	+
Angoulvant 2017	+	+	+	+	+	+	+
Anil 2010	+	?	+	+	+	?	?
BaShir 2018	+	?	+	+	+	?	+
Everard 2014	+	?	?	?	+	+	?
Flores 2016	+	+	+	+	+	?	+
Florin 2014	+	+	+	+	+	+	+
Grewal 2009	+	+	+	+	+	+	+
Hmar 2021	+	?	?	?	+	+	?
Ipek2011	-	?	+	+	+	?	?
Jacobs 2013	+	+	+	+	+	+	+
Khanal 2015	+	+	+	+	+	?	+
Kose 2016	+	?	+	?	+	?	?
Kuzik 2007	+	?	+	+	+	?	?
Kuzik 2010	+	?	+	+	+	+	+
Li 2014	+	?	?	?	+	?	?
Luo 2010	+	?	+	+	+	?	?
Luo 2011	+	+	+	+	?	?	+
Mahesh Kumar2013	+	?	?	?	+	?	?
Mandelberg 2003	+	?	+	+	+	?	?
Miraglia 2012	+	?	+	+	+	+	+
Morikawa 2018	+	+	-	+	+	?	?
Nenna2013	+	+	+	?	+	?	?
Ojha 2014	+	+	+	+	+	?	+
Pandit 2013	+	+	-	-	+	?	?
Raphaelle 2019	+	?	?	?	+	+	?
Ratajczyk-Pekrul 2016	+	+	+	+	+	?	+
Sarrell 2002	+	?	+	+	+	?	?
Sharma 2013	+	+	+	+	+	?	+
silver2015	+	+	+	+	+	+	+
Tal 2006	+	?	+	+	+	?	+
Teunissen 2014	+	?	+	+	+	?	+
Tinsa 2014	+	?	+	+	+	?	+
Uysalol 2017	+	?	+	?	+	?	?
Wu 2014	+	?	+	+	+	-	?

Figure S2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

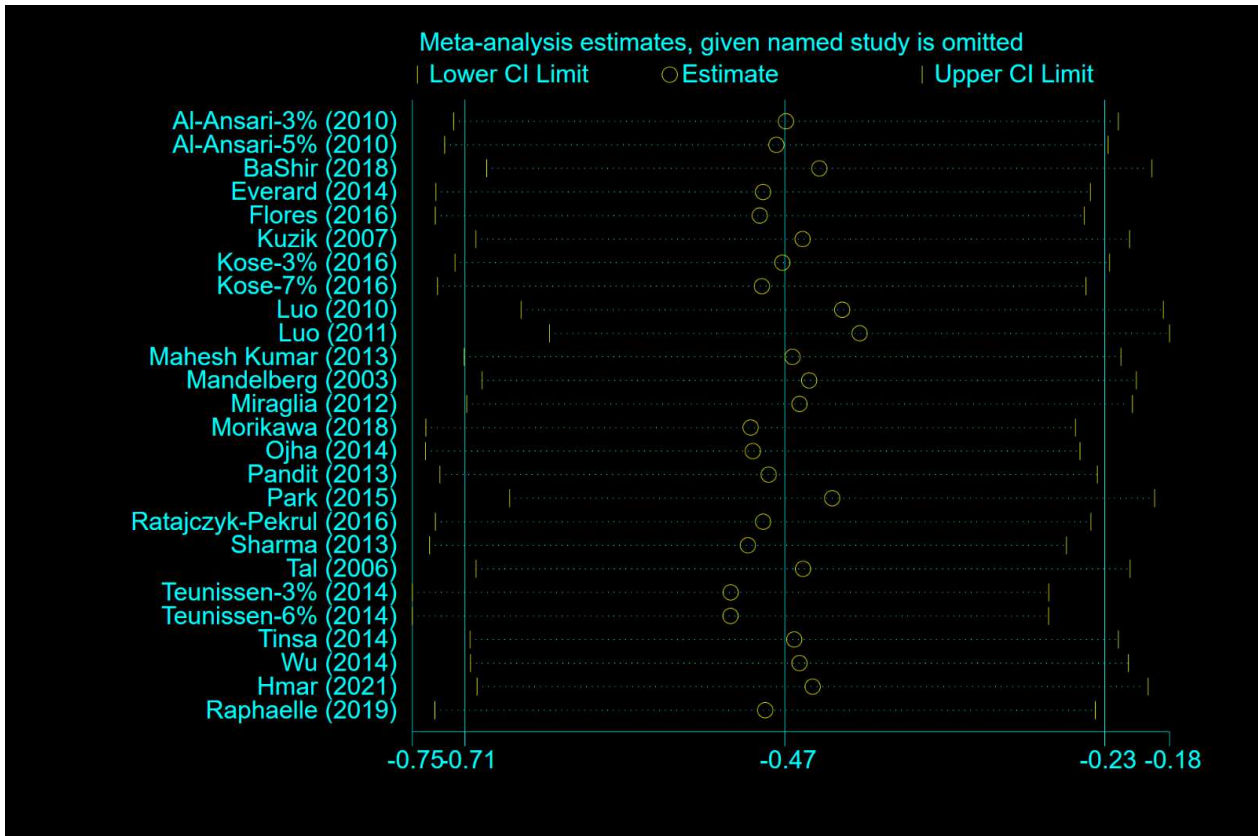


Figure S3: Sensitivity analysis for LOS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

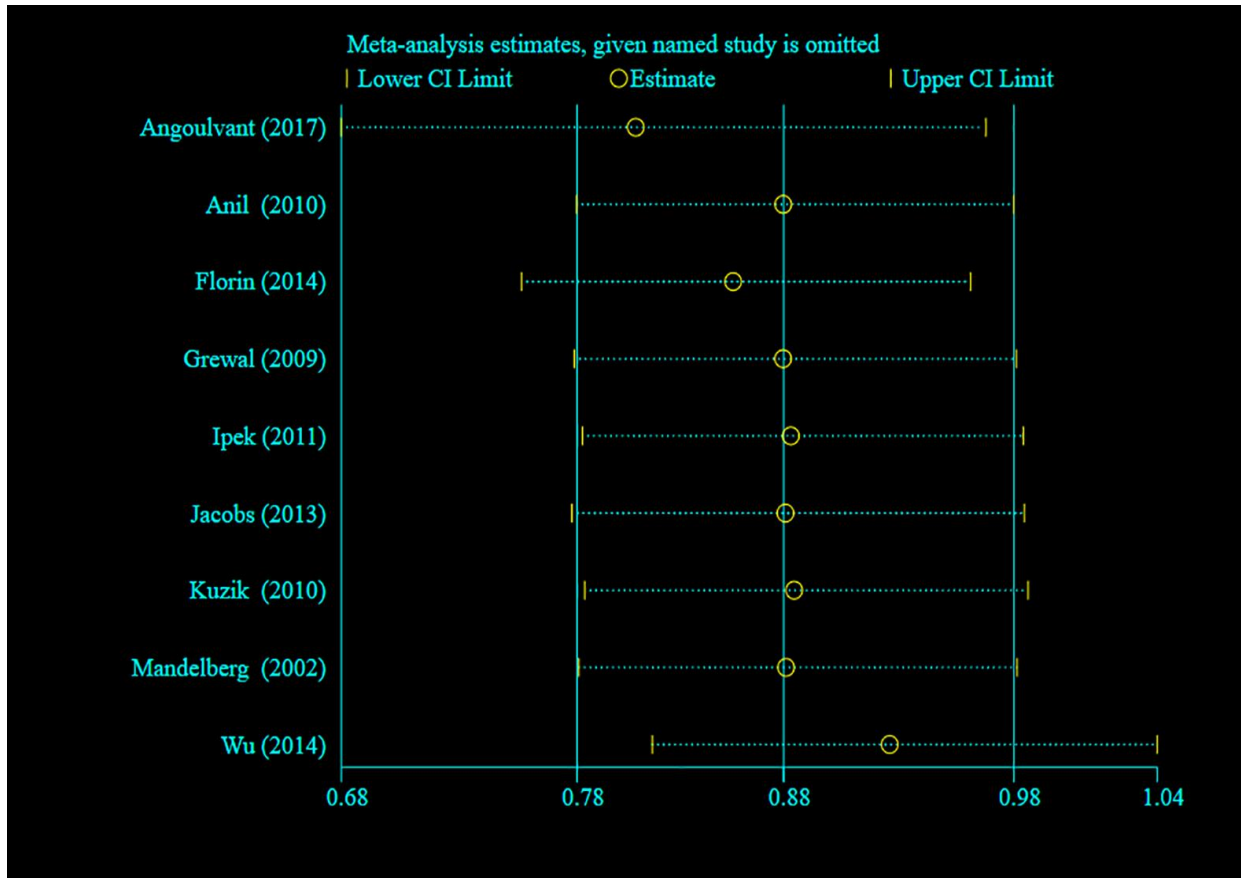


Figure S4: Sensitivity analysis for ROH in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

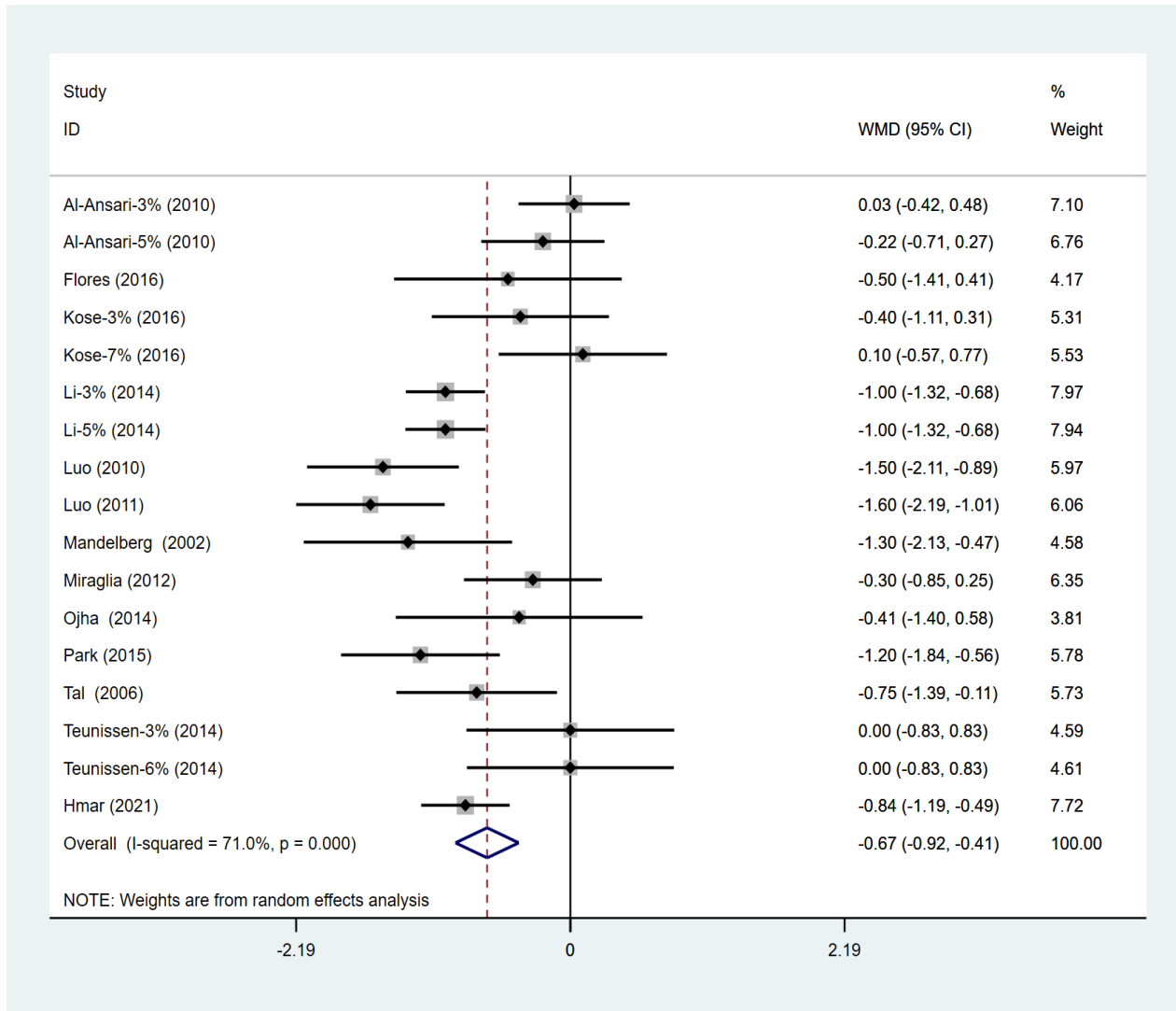


Figure S5: The effects of nebulized hypertonic saline treatment on the 24h-CSS in bronchiolitis.

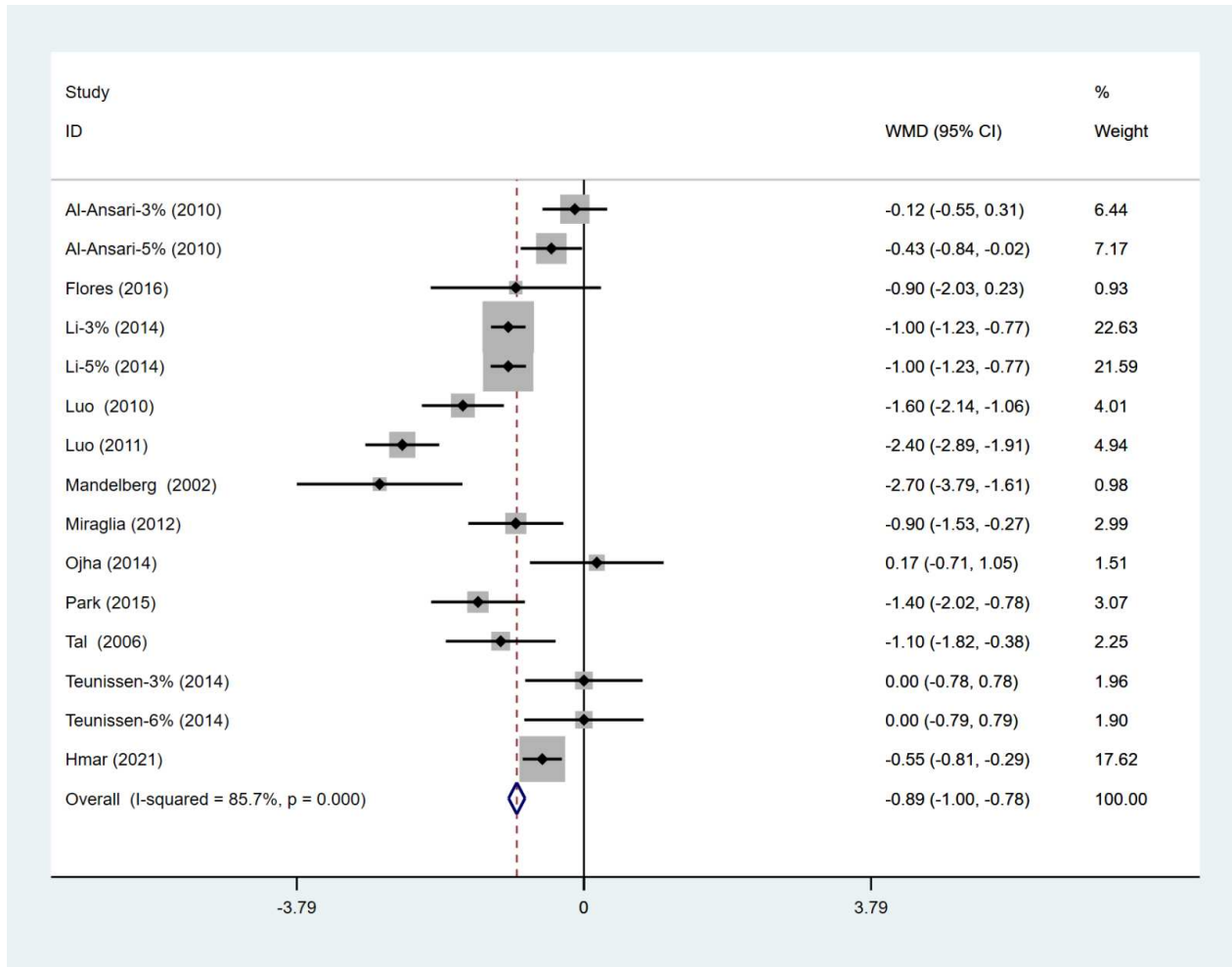


Figure S6: The effects of nebulized hypertonic saline treatment on the 48h-CSS in bronchiolitis.

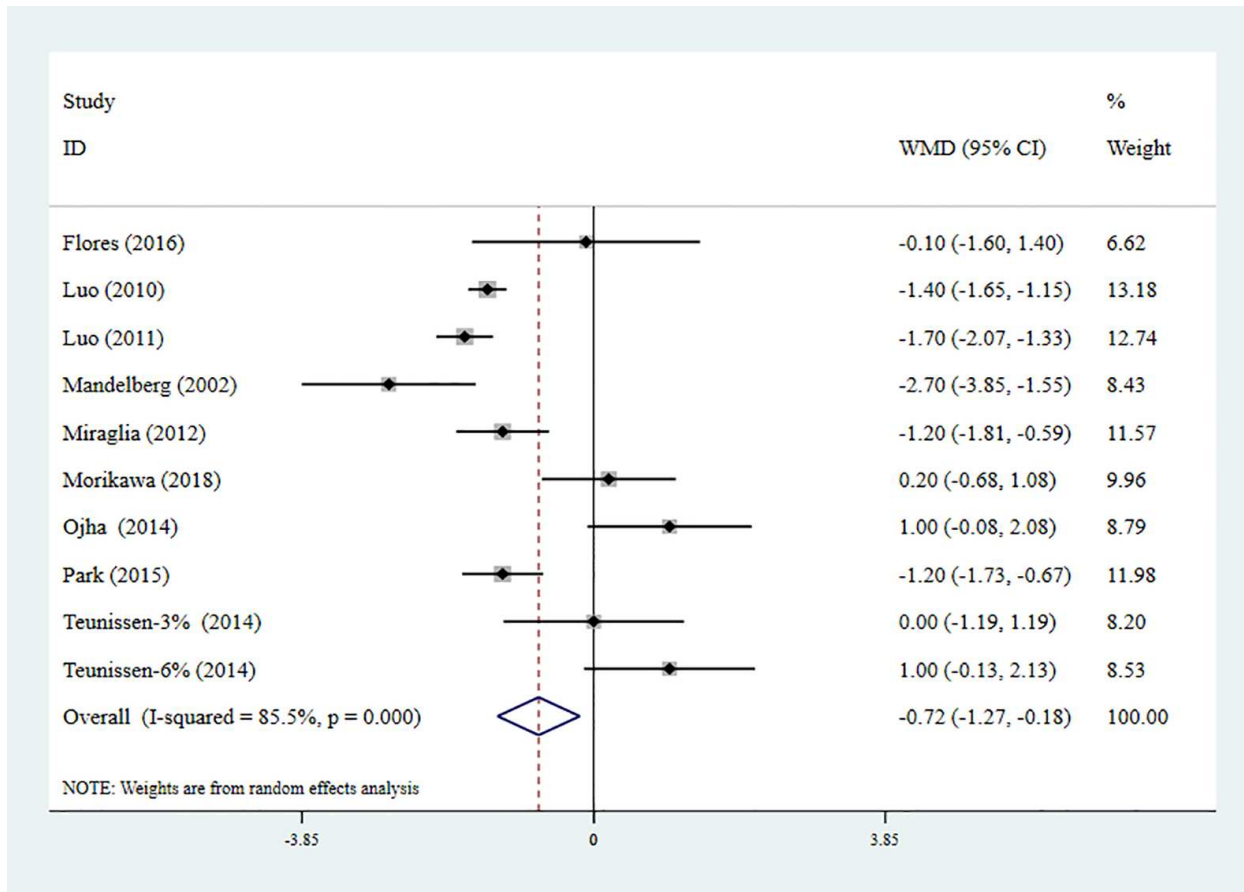


Figure S7: The effects of nebulized hypertonic saline treatment on the 72h-CSS in bronchiolitis.

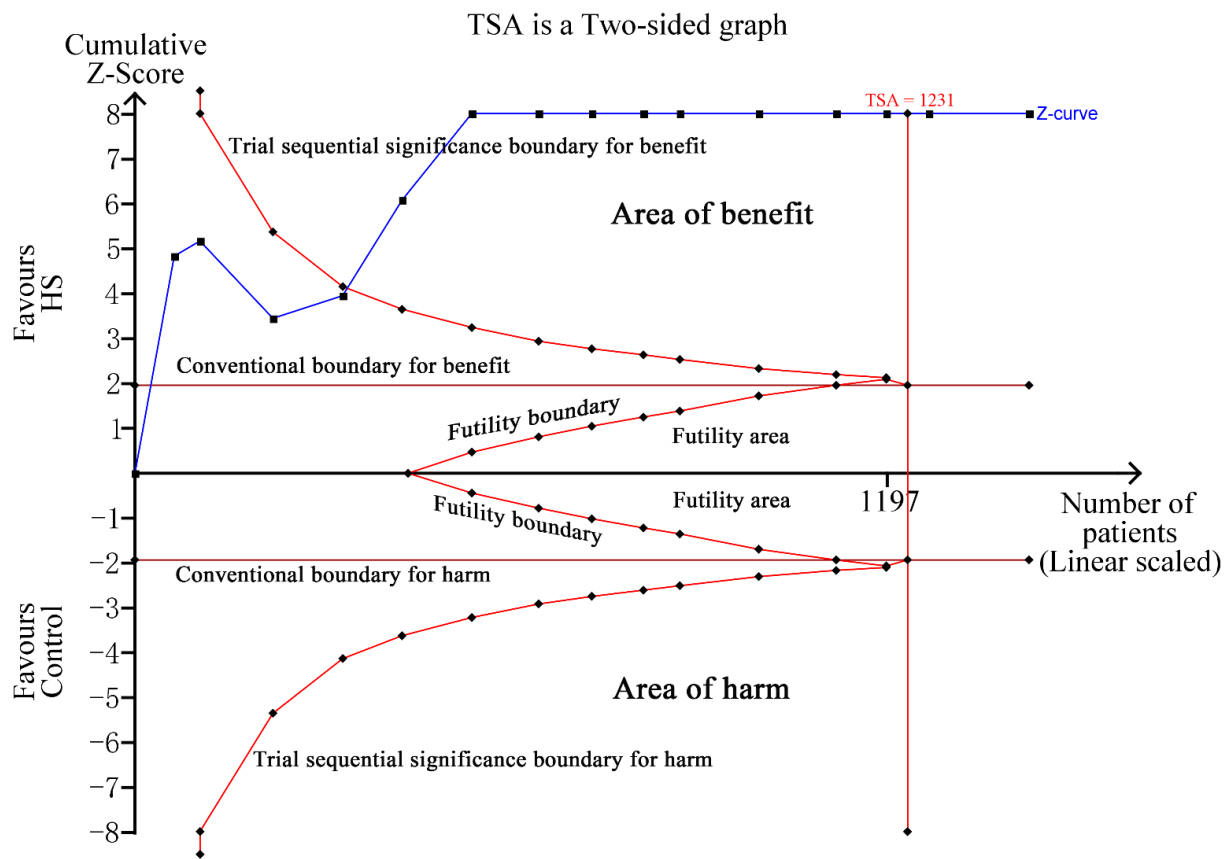


Figure S8: Trial sequential analysis for 24h-CSS in bronchiolitis, α of 5 % (two sided), β of 20 %.

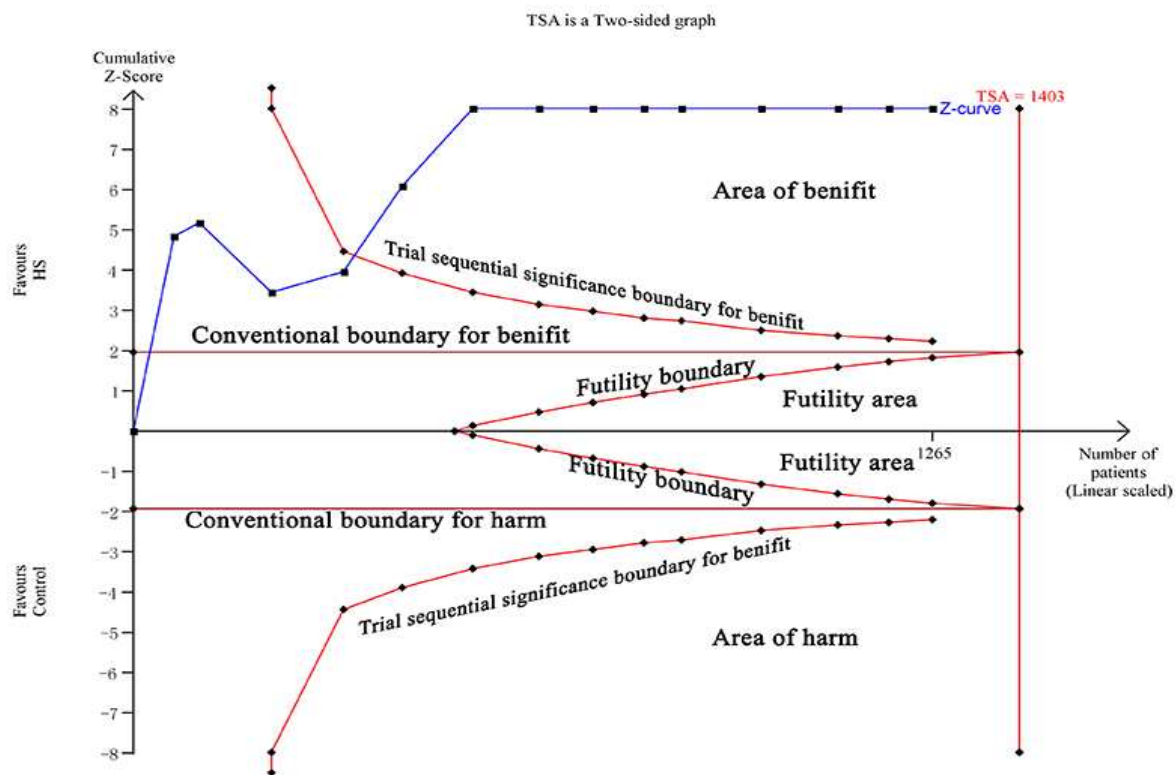


Figure S9: Trial sequential analysis for 48h-CSS in bronchiolitis, α of 5 % (two sided), β of 20 %.

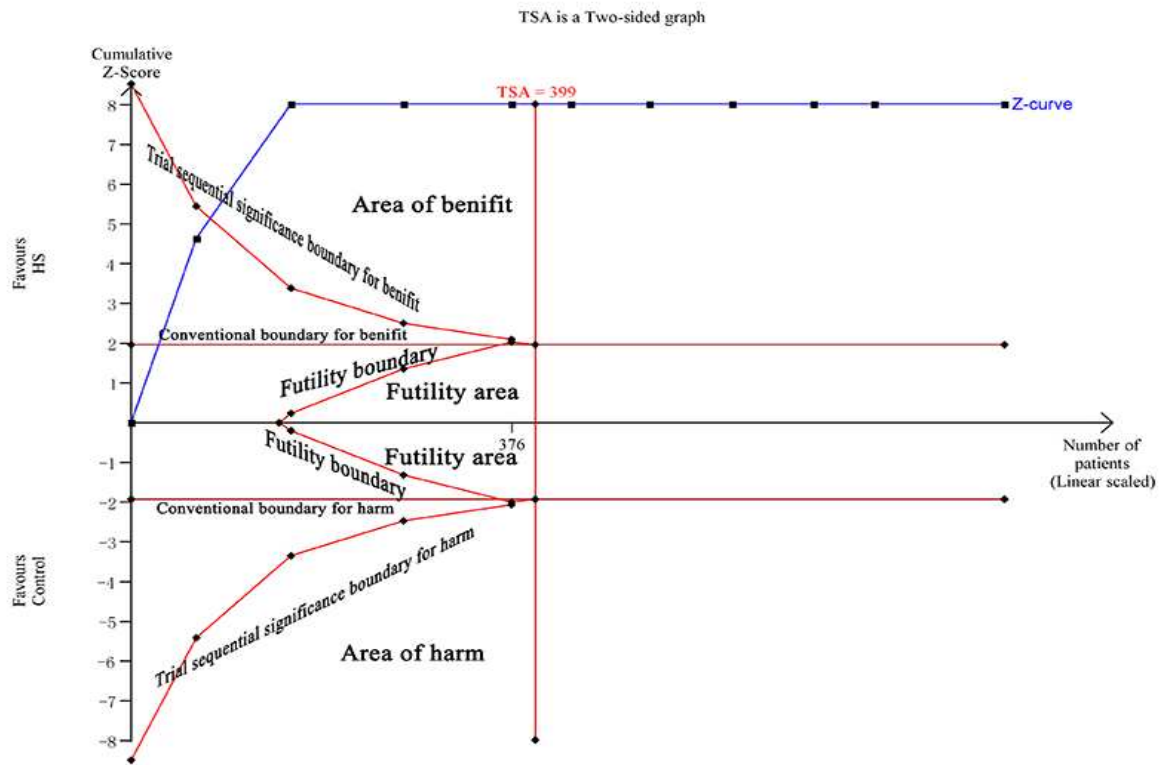


Figure S10: Trial sequential analysis for 72h-CSS in bronchiolitis, α of 5 % (two sided), β of 20 %.

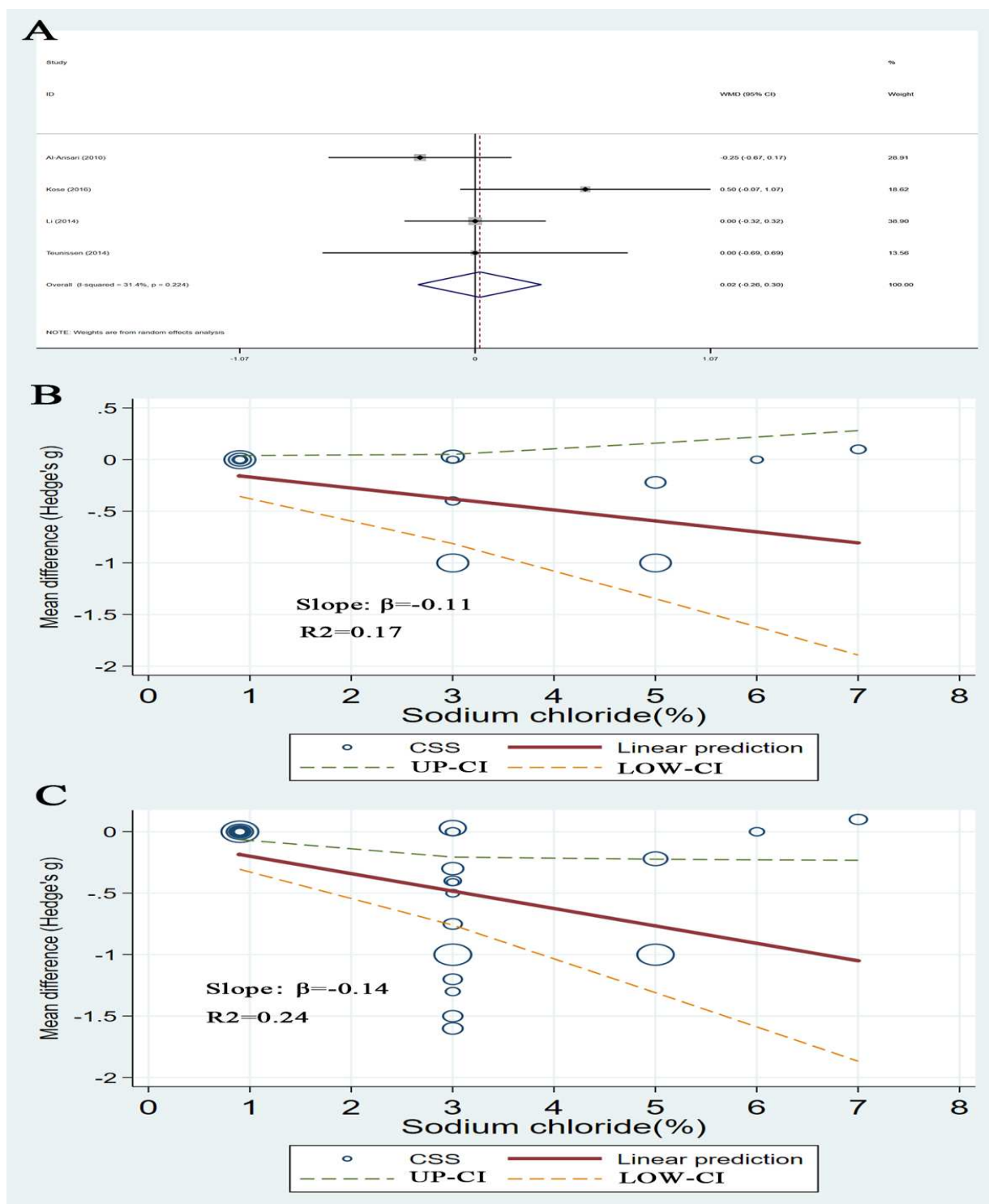


Figure S11: Exploring the appropriate dose of nebulized hypertonic saline for bronchiolitis in 24h-CSS. (A): there was no significant difference between 3% HS and the higher dose (>3%) of HS; (B): The random-effects dose-response meta-regression model with REMR approach of studies containing more than 2 doses of HS. (C): The random-effects dose-response meta-regression model with REMR approach of all studies.

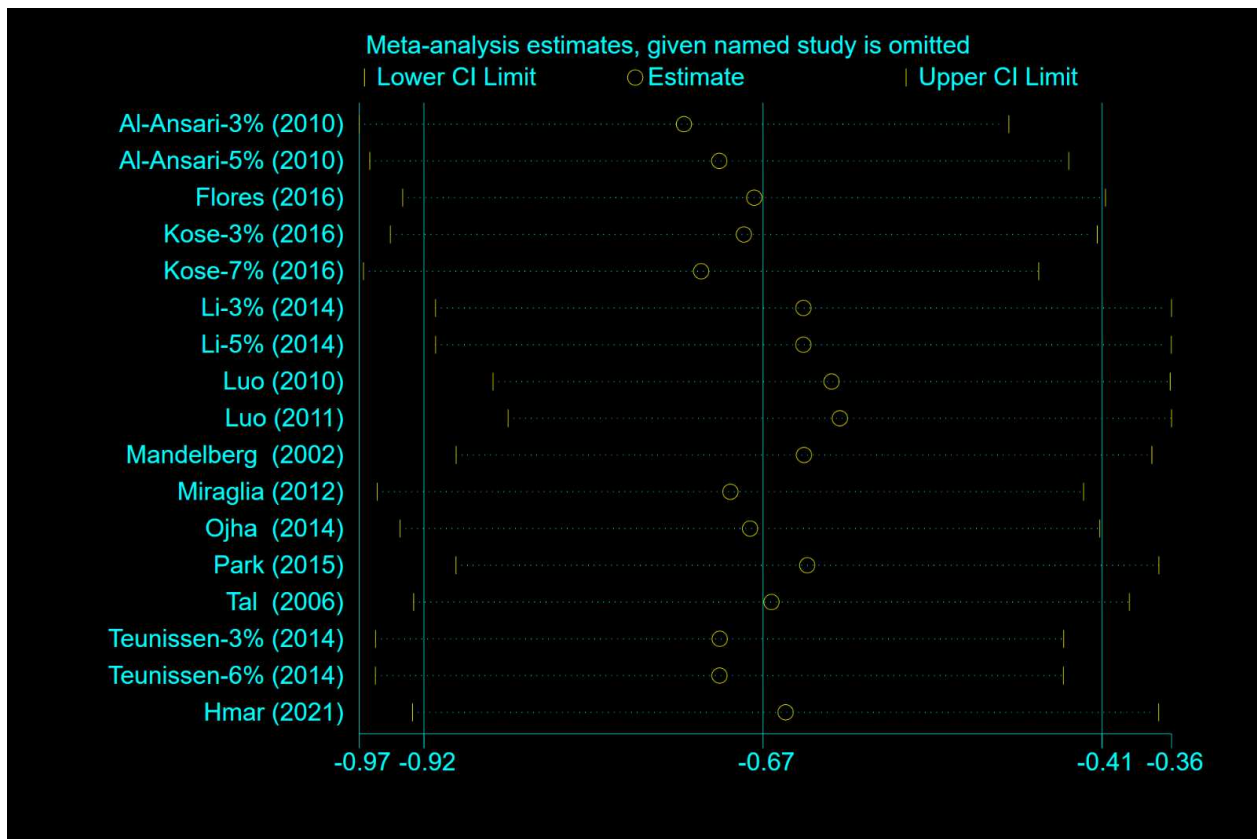


Figure S12: Sensitivity analysis for 24h-CSS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

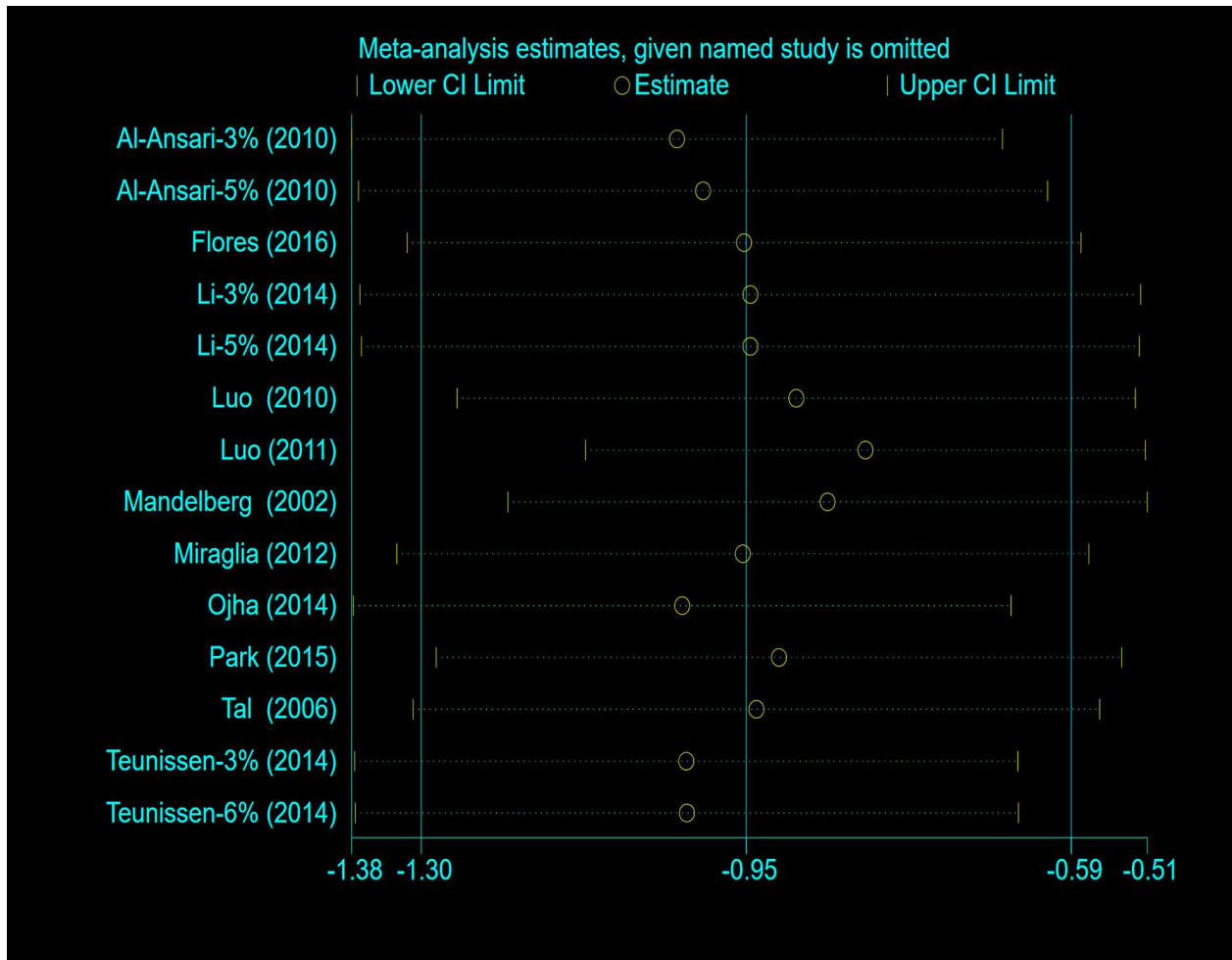


Figure S13: Sensitivity analysis for 48h-CSS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

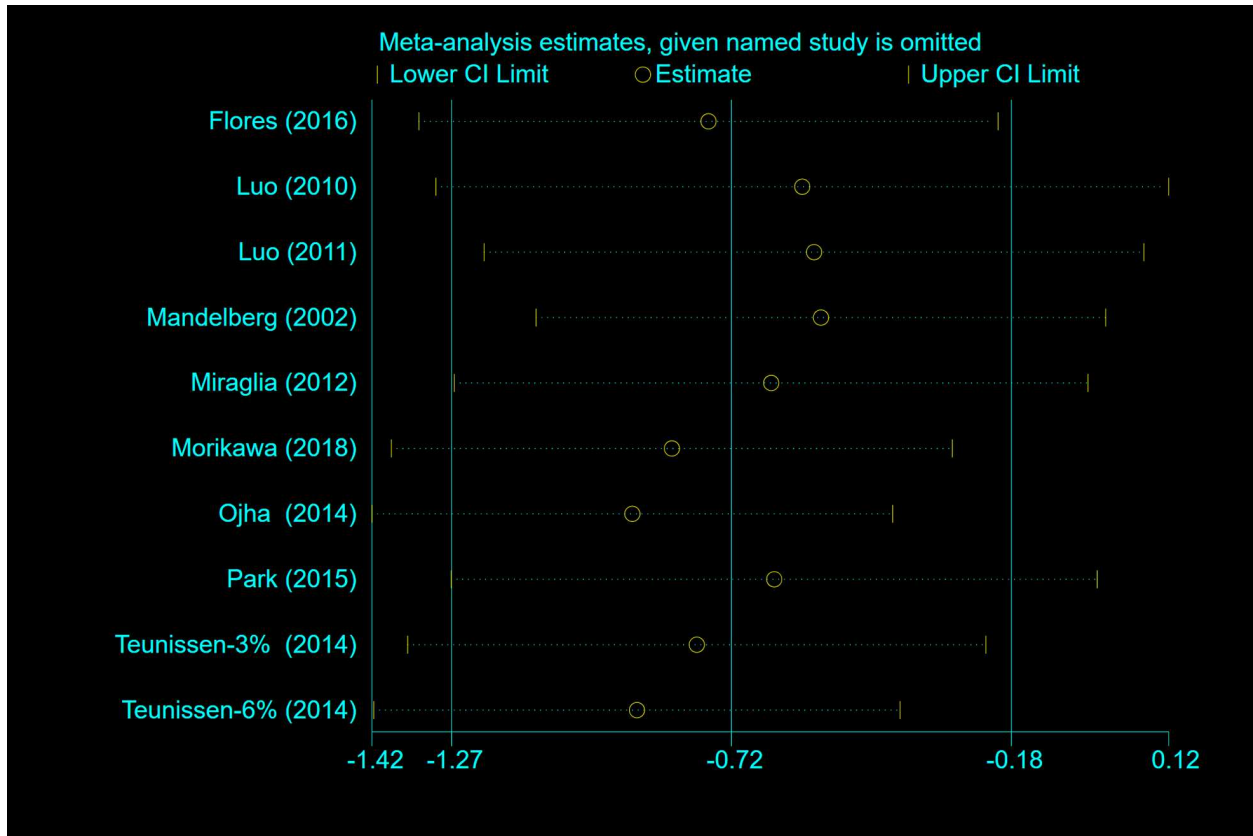


Figure S14: Sensitivity analysis for 72h-CSS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.