Table S1: Details of search strategy

No.	Search strategy for PubMed database (from its inception to May, 2021)	Items found
	Search strategy	
#1	((((((((("hypertone"[All Fields] OR "hypertonic"[All Fields]) OR "hypertonics"[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

No.	Search strategy for EMBASE database (from its inception to May, 2021)	Items found
	Search strategy	
#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

No.	Search strategy for CENTRAL database (from its inception to May, 2021)	Items found
	Search strategy	
#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

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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/without Sal	NS(0.9%) with/without Sal	Every 20 min until 3 doses had been administered (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 (modified 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

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							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 untill 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

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			8.61±5.742					(Wang et al), AE
Pandit 2013	India (2009-2011)	RCT	Con 4.08 ± 1.90, 3%HS 3.92 ± 1.72	100	HS(3%)+Adr	NS(0.9%)+Adr	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%)+Sal	NS(0.9%)+Sal	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%)+Sal	NS(0.9%)+Sal	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±5.45, 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).
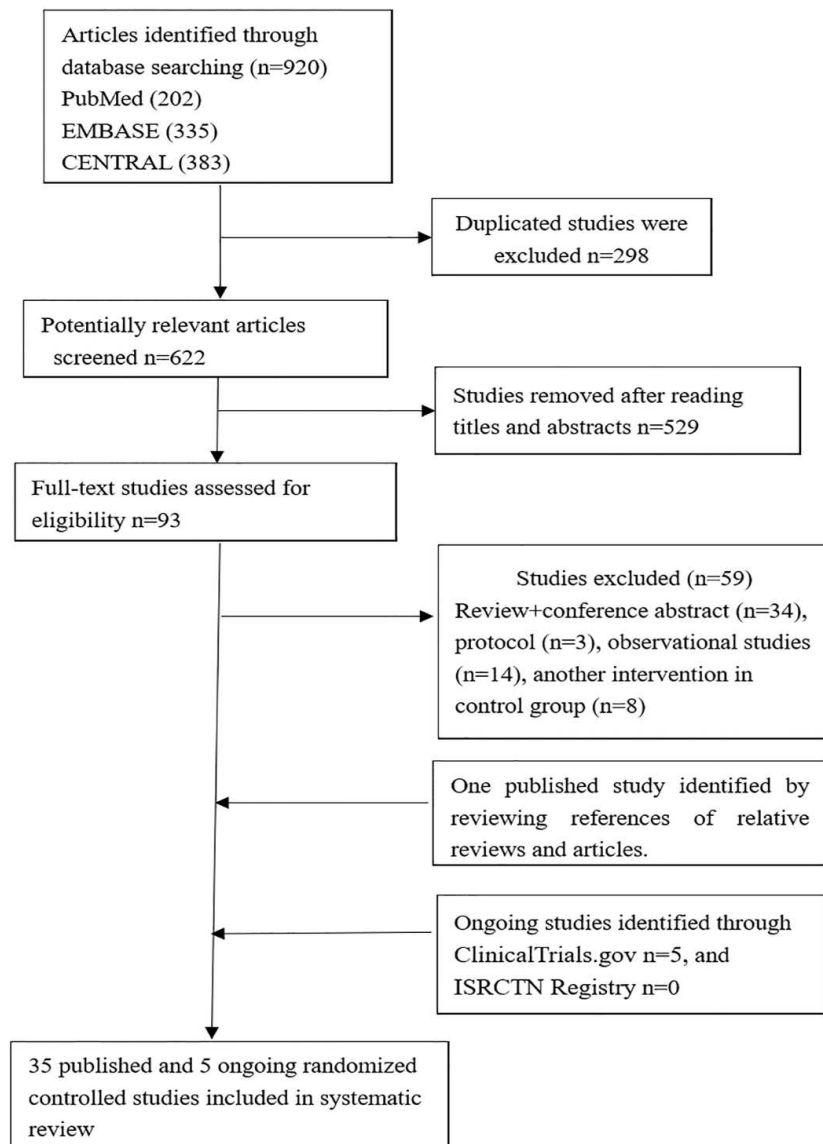
Figure S1: The flow diagram of identifying relevant studies.

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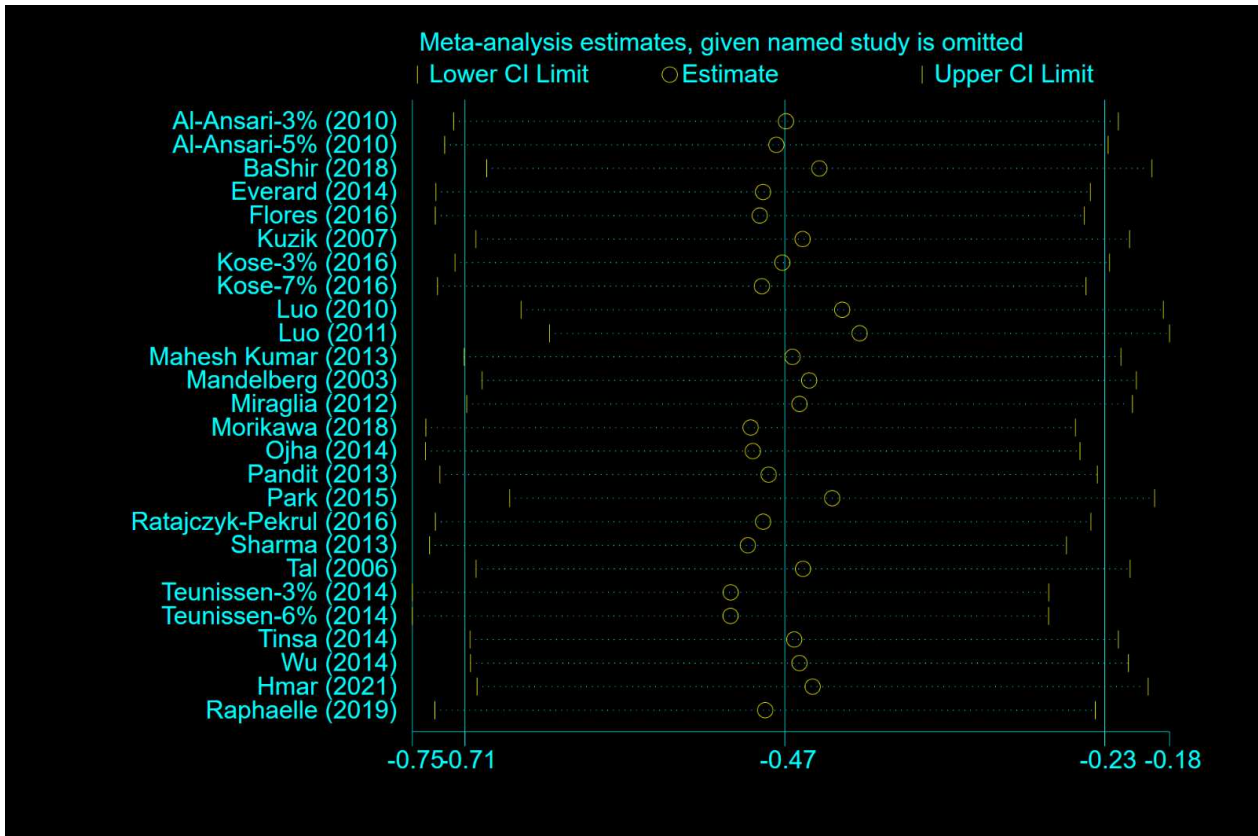Figure S2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

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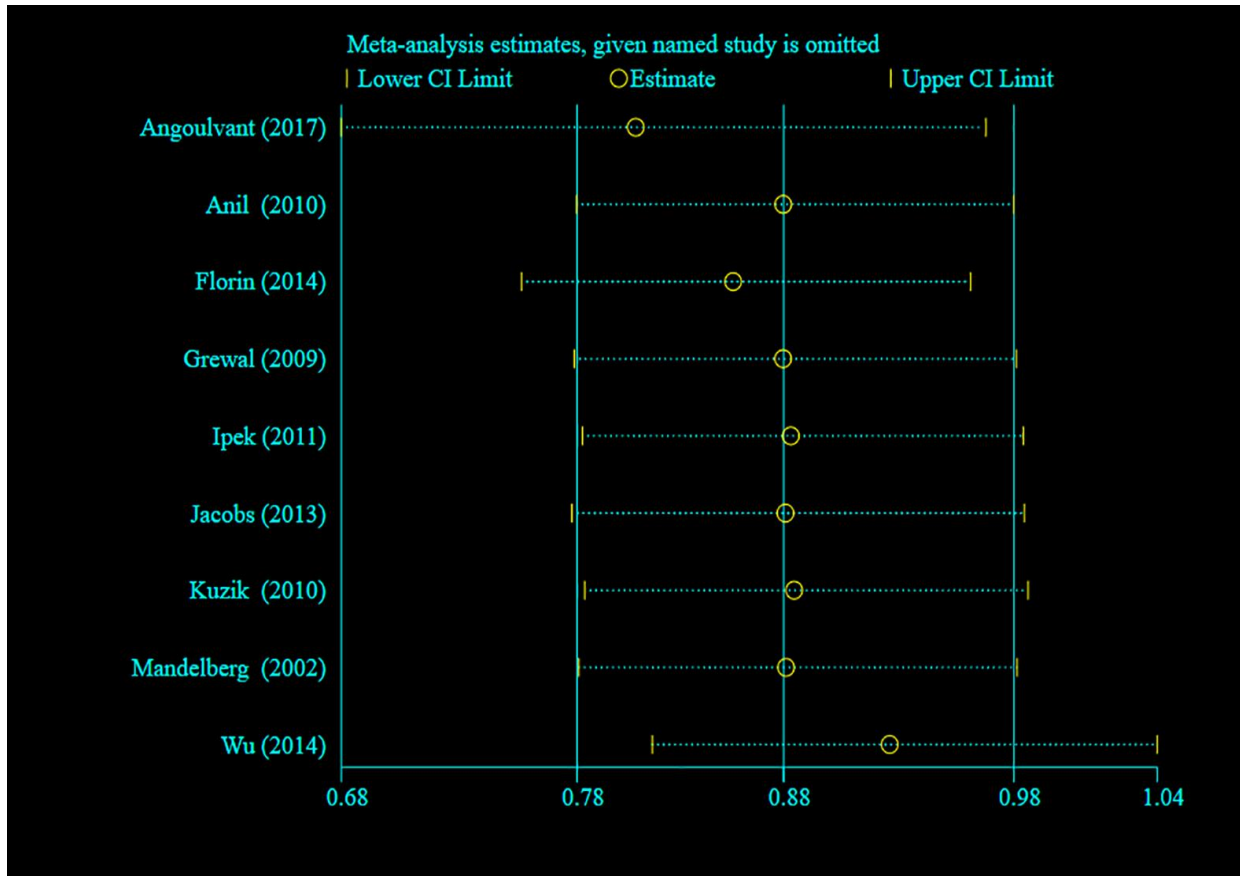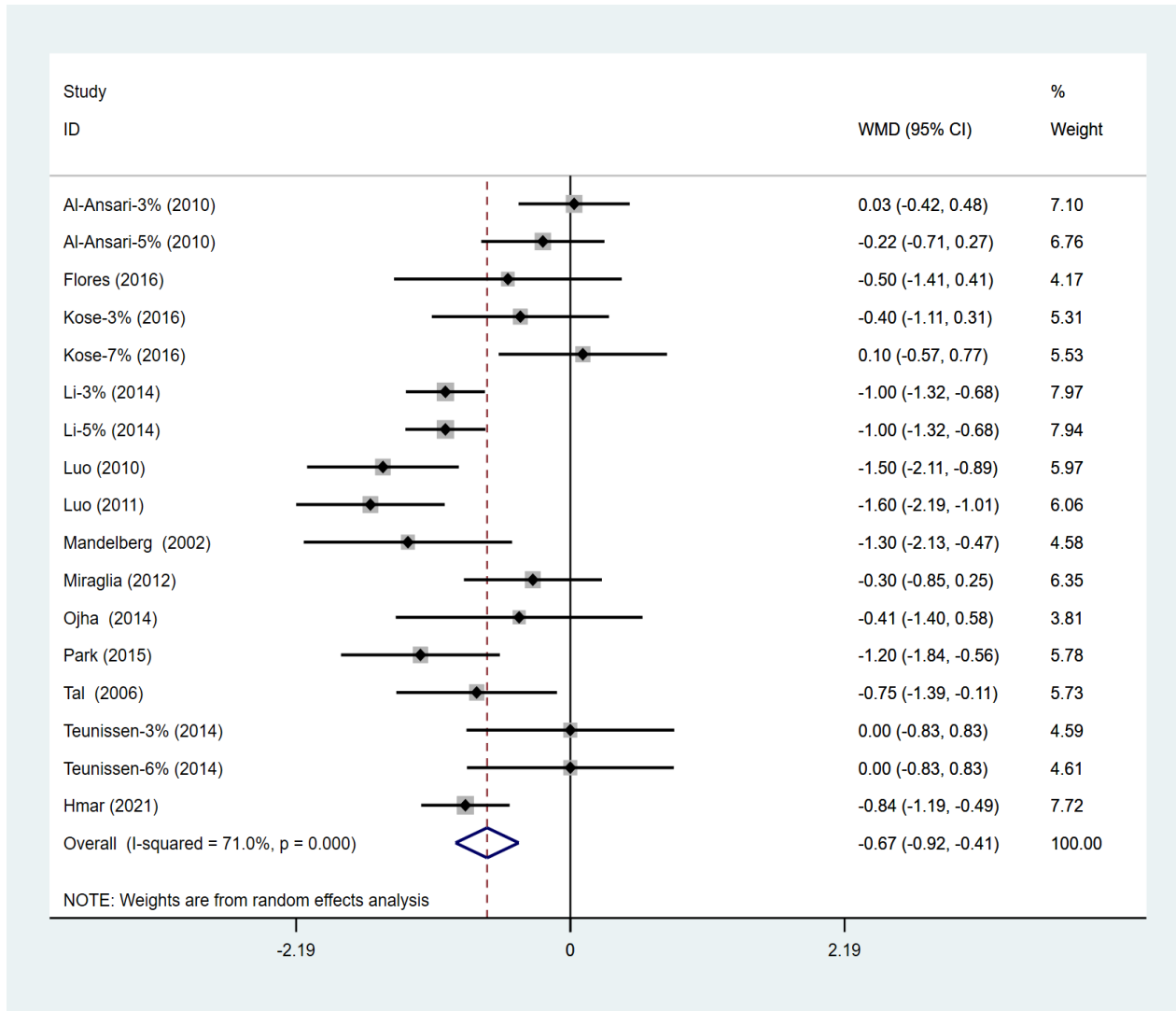
Figure S4: Sensitivity analysis for ROH in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

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

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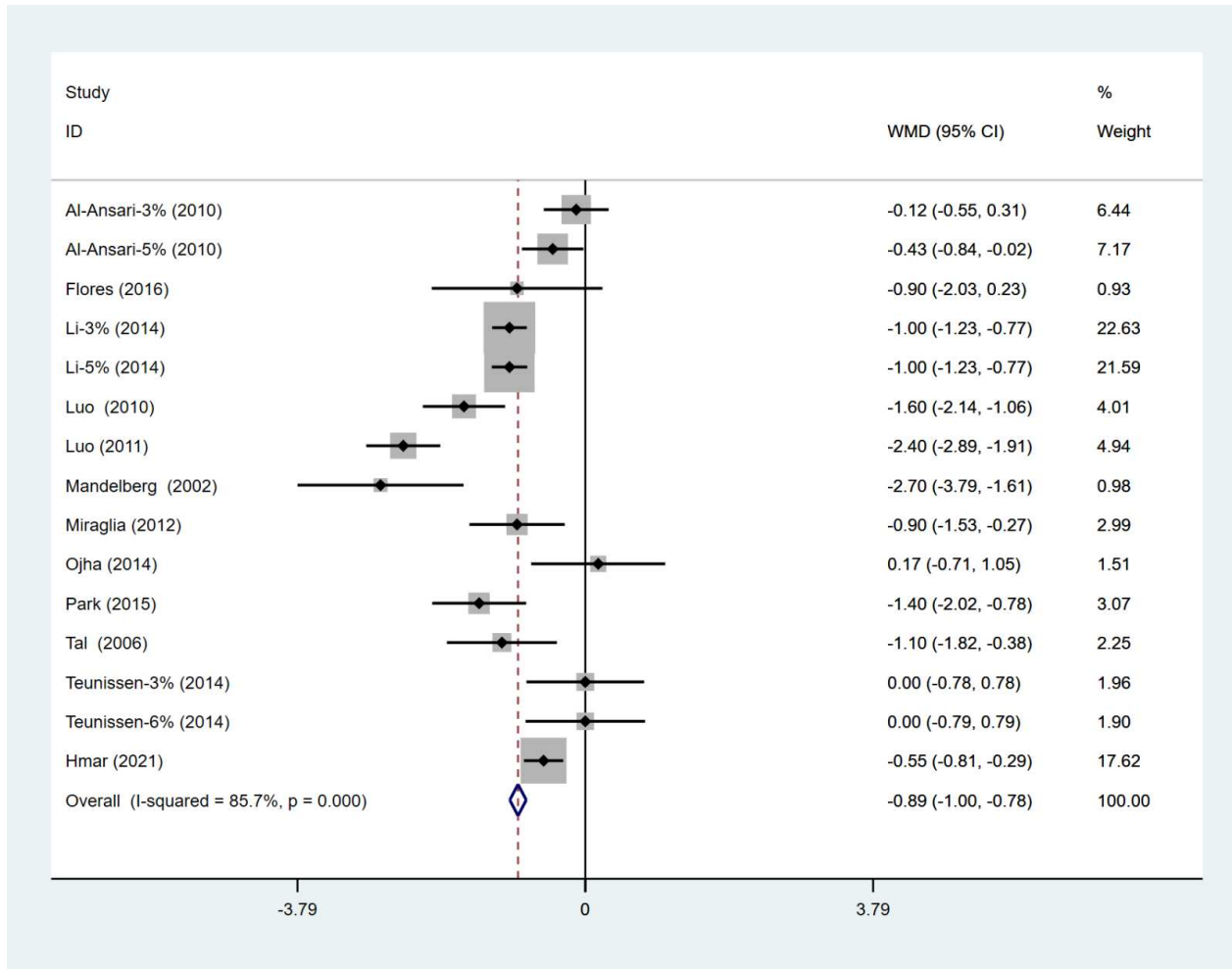
Figure S6: The effects of nebulized hypertonic saline treatment on the 48h-CSS in bronchiolitis.

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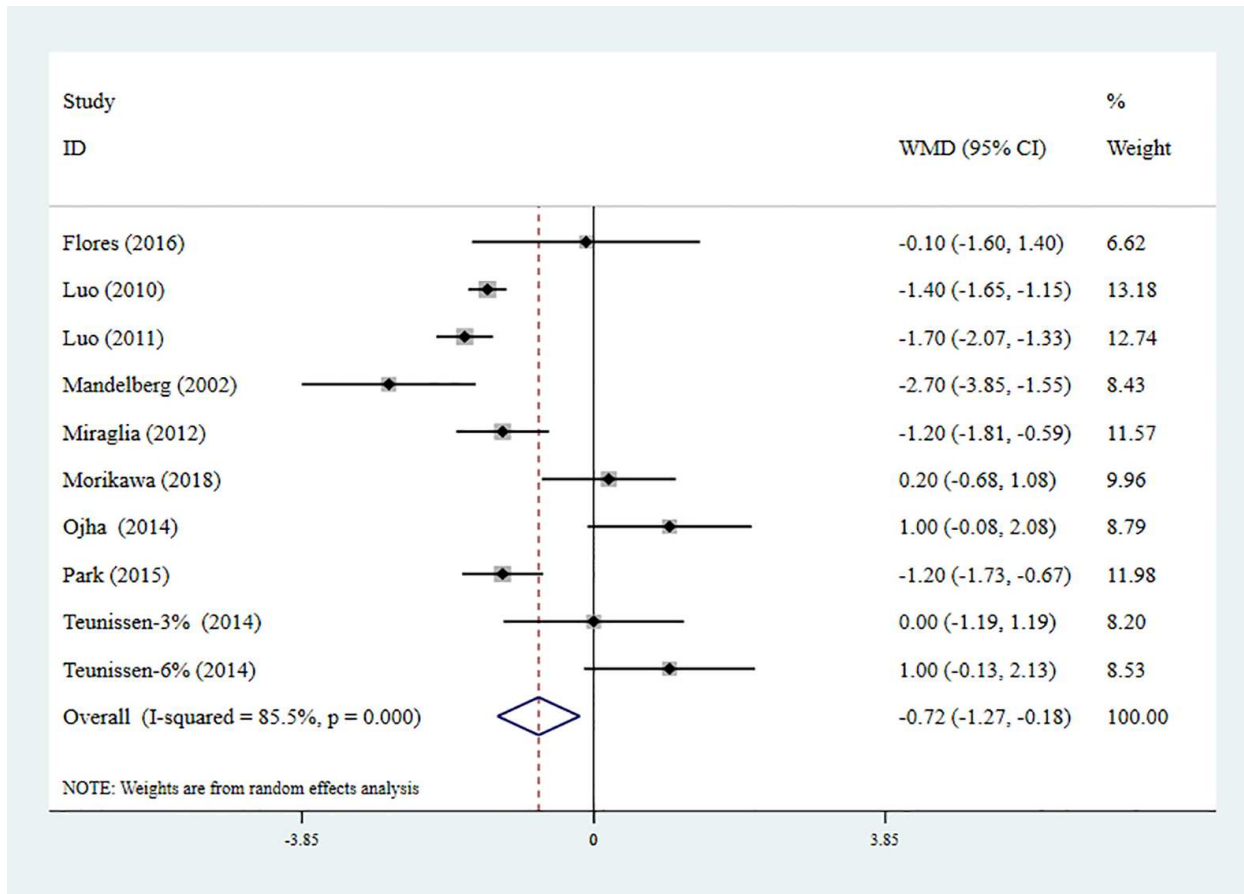
Figure S7: The effects of nebulized hypertonic saline treatment on the 72h-CSS in bronchiolitis.
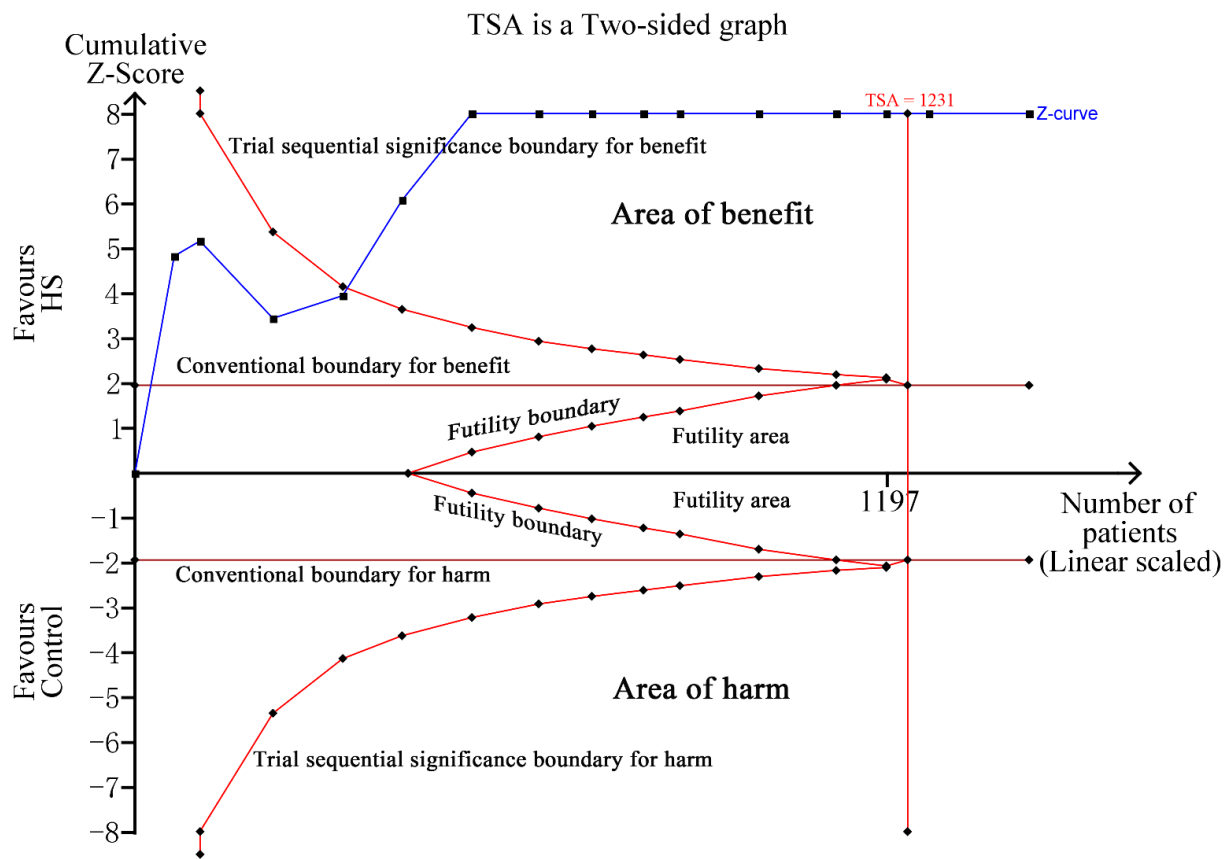
Figure S8: Trial sequential analysis for 24h-CSS in bronchiolitis, α of 5 % (two sided), β of 20 %.
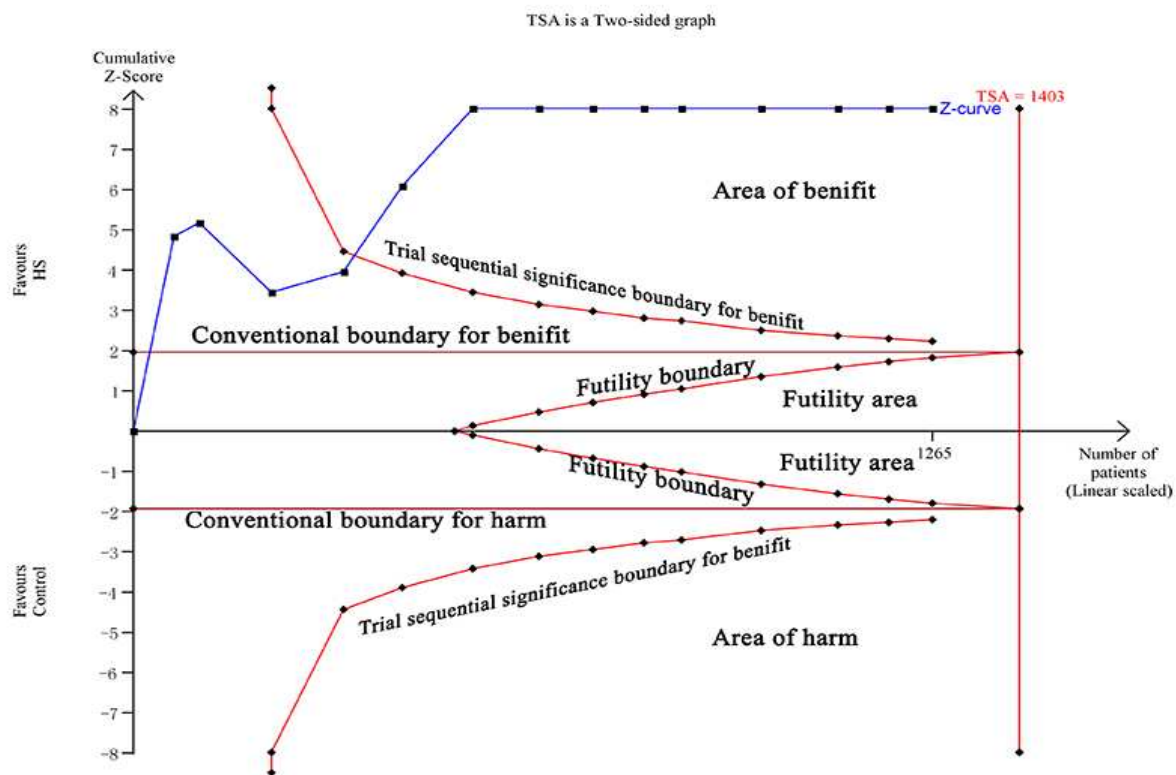
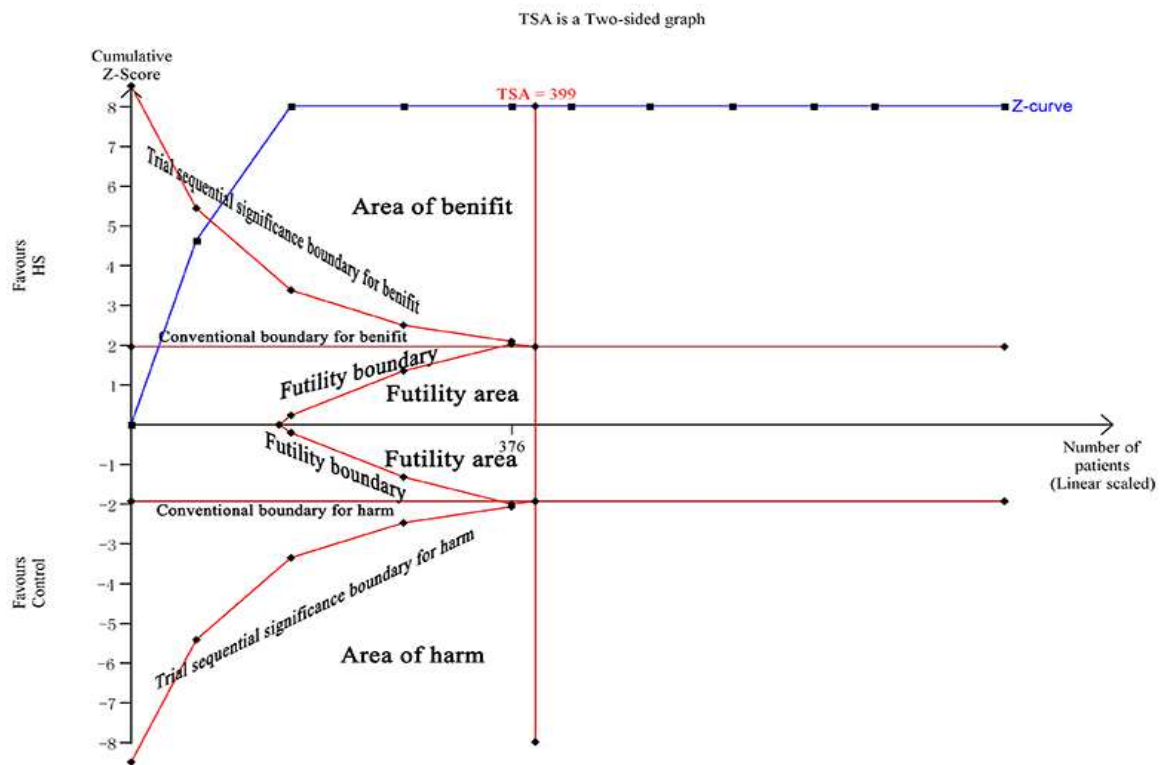Figure S9: Trial sequential analysis for 48h-CSS in bronchiolitis, α of 5 % (two sided), β of 20 %.

Figure S10: Trial sequential analysis for 72h-CSS in bronchiolitis, α of 5 % (two sided), β of 20 %.
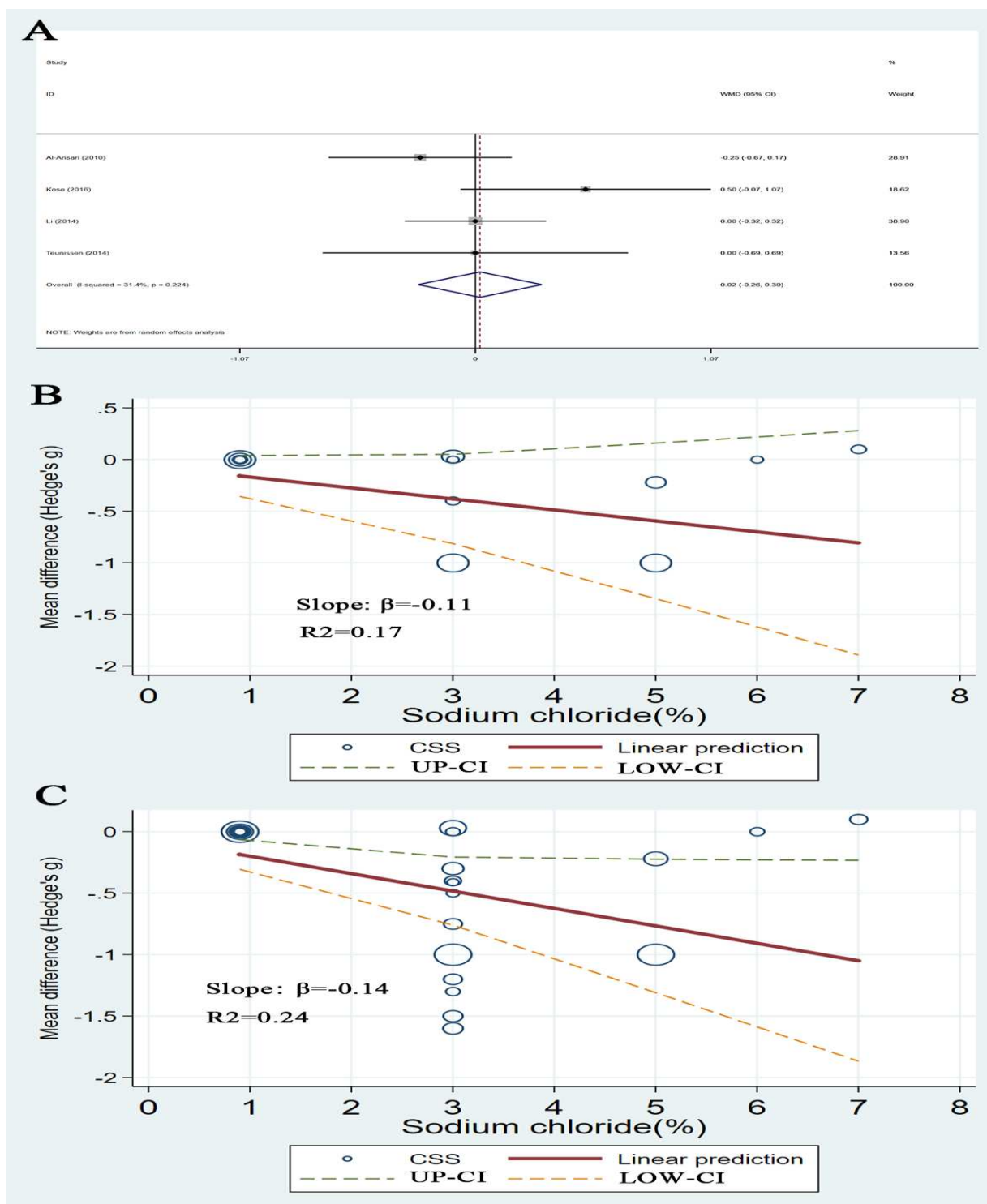
Figure S11: Exploring the appropriate dose of nebulized hypertonic saline for bronchiolitis in 24h-CSS. (A): there was no significant difference between 3% HS and the higher dose(>3%) of HS; (B): The random-effects dose–response meta-regression model with REMR approach of studies containing more than 2 doses of HS. (C): The random-effects dose–response meta-regression model with REMR approach of all studies.
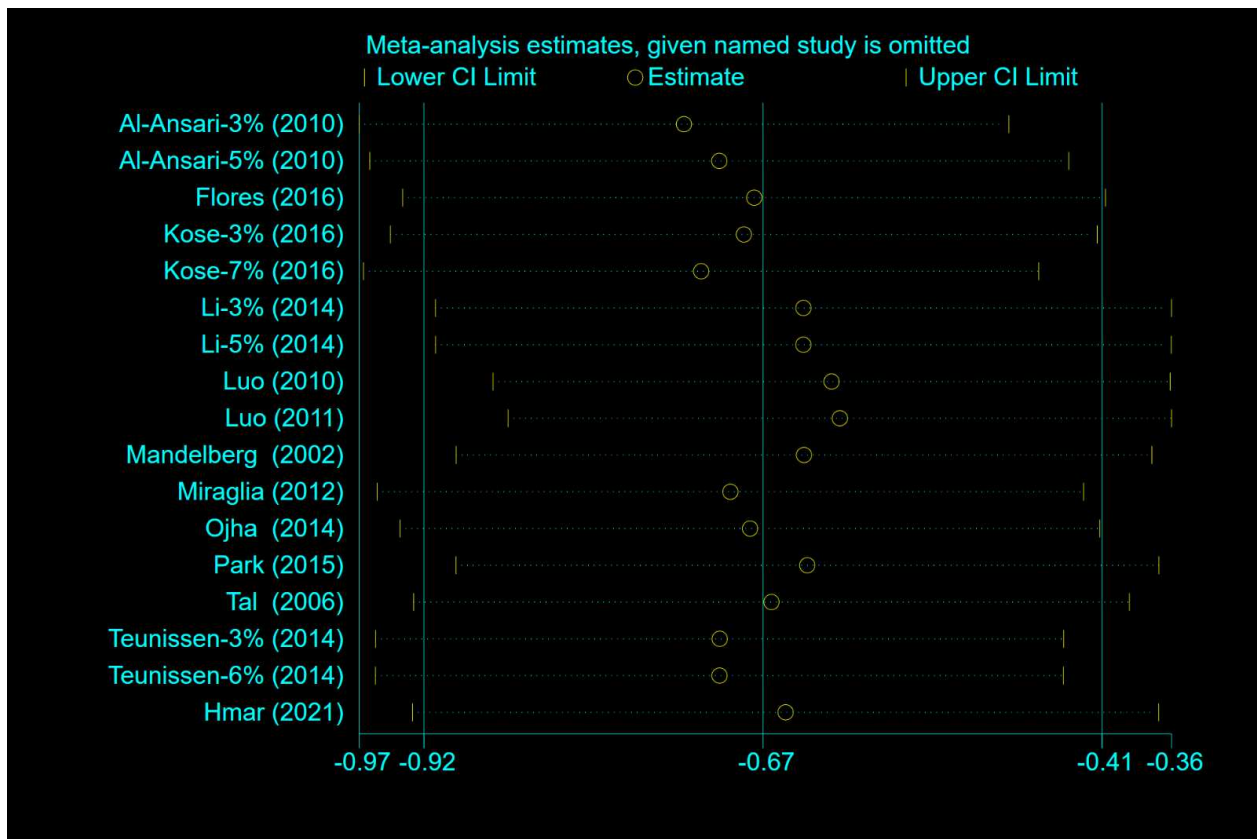
Figure S12: Sensitivity analysis for 24h-CSS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

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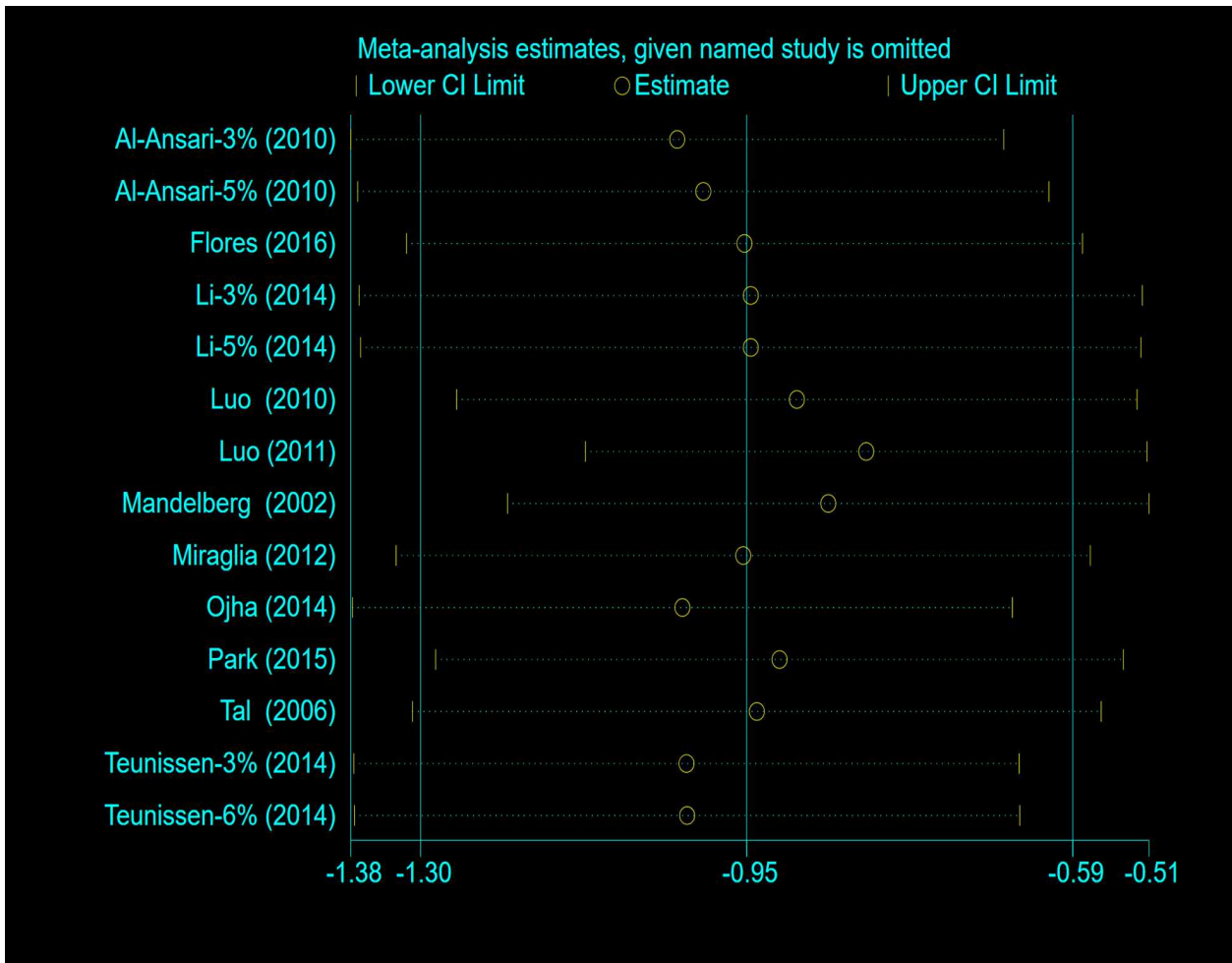
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Figure S13: Sensitivity analysis for 48h-CSS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.

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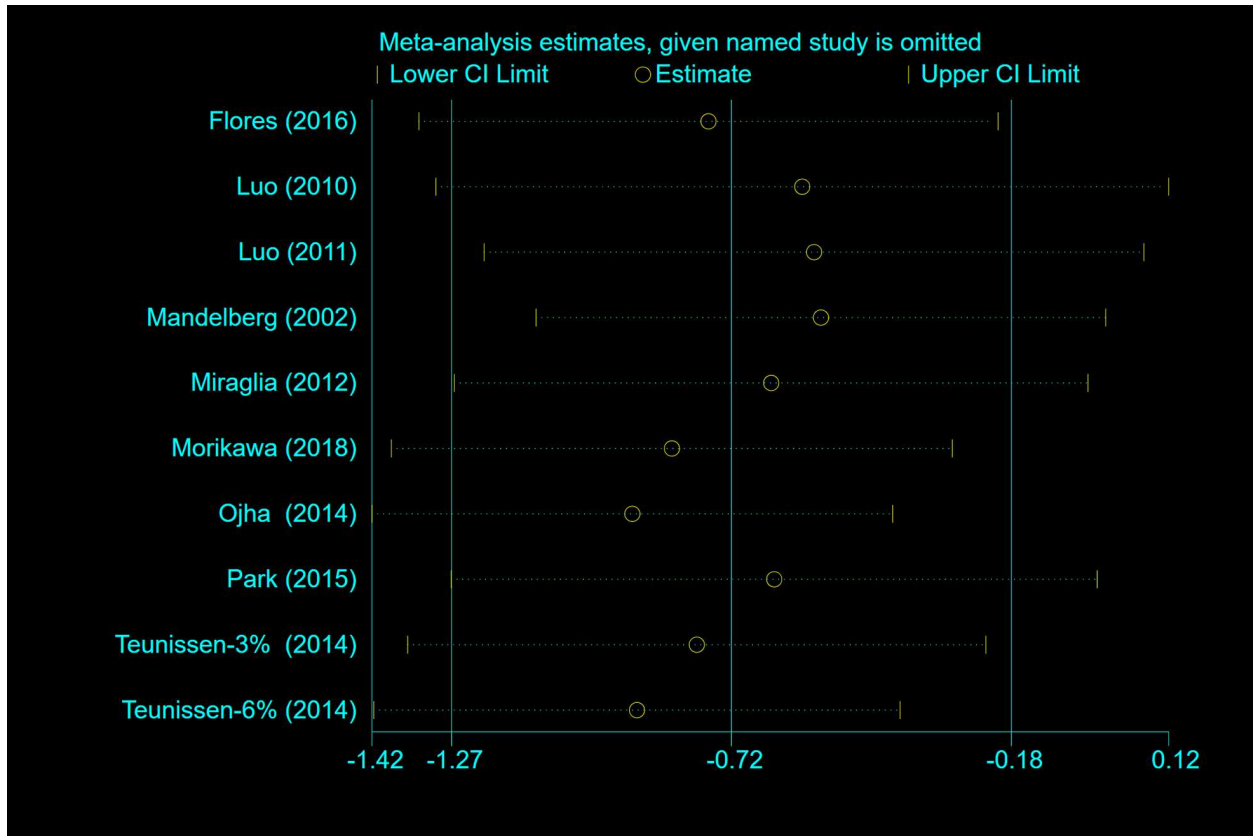
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Figure S14: Sensitivity analysis for 72h-CSS in bronchiolitis: exclusion of a single study in turn. The study being cited on the left is the one being left out in each analysis.