Supplemental Table 1. Studies Excluded after Full-Text Review

Study	Reason for exclusion	Exclusion classification[a]
Arons et al (1) (1999)	Sub-study of included study	D
Boyle et al (2) (1997)	Infection status of patients not reported; no permissive fever control group; mortality not reported	NS
Boyle et al (3) (2011)	Infection status of patients not reported; mortality not reported; no permissive fever control group	NS
Chandralekha et al (4) (2008)	Not relevant to antipyretic therapy	A
Clemmer et al (5) (1992)	Not relevant to antipyretic therapy	A
Creechan et al (6) (2001)	No permissive fever group	C
Cruz et al (7) (2002)	Included non-septic patients; no permissive fever control group; mortality not reported	NS
De Maat et al (8) (2010)	Included non-septic patients; no permissive fever control group; mortality not reported	NS
Gozzoli et al (9) (2001)	Mortality not reported specifically for subset of infected patients and this data could not be obtained	NS
Gozzoli et al (10) (2004)	Included non-septic patients; no permissive fever control group; mortality not reported	NS
Greenberg et al (11) (2010)	Included non-septic patients; mortality not reported	NS
Hammond et al (12) (2011)	Mortality not reported for antipyretic and control groups	M
Hammond et al (13) (2013)	Mortality not reported for antipyretic and control groups	M
Henker et al (14) (2001)	Included non-septic patients; no permissive fever control group; mortality not reported	NS
Hersch et al (15) (2008)	No permissive fever control group; mortality not reported	C
Honarmand et al (16) (2012)	Mortality not reported specifically for subset of infected patients and this data could not be obtained	NS
Kiekkas et al (17) (2007)	Included non-septic patients; not relevant to antipyretic therapy; mortality not reported	NS
Kiekkas et al (18) (2010)	Included non-septic patients; not relevant to antipyretic therapy; mortality not reported	NS
Krajcova et al (19) (2013)	Included non-septic patients; mortality not reported	NS
Krudsood et al (20) (2010)	Included non-septic patients	NS
Laupland et al (21) (2012)	Included non-septic patients; not relevant to antipyretic therapy	NS
Manthous et al (22) (1995)	Included non-septic patients; no permissive fever control group; mortality not reported	NS
Matsuda et al (23) (1995)	No permissive fever control group; mortality not reported	C
Mohr et al (24) (2010)	Duplicate data as of included study	D
Mohr et al (25) (2011)	Duplicate data as of included study	D
Mohr et al (26) (2013)	Duplicate data as of included study	D
Morris et al (27) (2010)	Mortality not reported specifically for subset of infected patients and this data could not be obtained	NS
Mourvillier et al (28) (2013)	Not relevant to antipyretic therapy	A
Niven et al (29) (2011)	Included non-septic patients; mortality not reported	NS
Niven et al (30) (2012)	Duplicate data as of included study	D
Niven et al (31) (2012)	Included non-septic patients; mortality not reported	NS
O'Donnell et al (32) (1997)	Included non-septic patients; mortality not reported	NS
Pernerstorfer et al (33) (1995)	No permissive fever control group	C
Pernerstorfer et al (34) (1999)	Non-septic patients included; mortality not reported	NS
Poblete et al (35) (1997)	Included non-septic patients; included patients with head injury; no permissive fever control group; mortality not reported	NS
Promes et al (36) (2011)	Included non-septic patients	NS
Rokyta et al (37) (2004)	No permissive fever control group	C
Satsuta et al (38) (2013)	Insufficient data to include in meta-analysis	I

Supplemental Table 1. Studies Excluded after Full-Text Review (continued)

Study	Reason for exclusion	Exclusion classification[a]
Schulman et al (39) (2005)	Included non-septic patients	NS
Young et al (40) (2011)	No control group; mortality not reported for antipyretic and control groups	C
Yang et al (41) (2013)	No permissive fever control group	C

[a]Exclusion classification symbols are as follows: D, duplicate data or sub-study of included study; NS, non-septic patients included in the study; A, study not relevant to anti-pyretic therapy; C, study did not include a permissive fever control group; M, mortality not reported as an outcome; I, insufficient data reported to analyze.

Supplemental Table 2. Descriptive Characteristics of Randomized and Observational Studies

Author (year)	Study Design	Number of centers; countries	Setting	Sample size[a]	Main inclusion criteria	Intervention or antipyretic therapy evaluated	Control	Duration of intervention	Primary outcome
Bernard et al (42) (1991)	RCT	2; United States	ICU	30	Severe sepsis	Ibuprofen 800 mg rectally every 4 hours	Placebo	12 hours	Urinary eicosanoid metabolite concentrations
Haupt et al (43) (1991)	RCT	4; United States	Medical ICU	29	Severe sepsis	Ibuprofen 600 mg or 800 mg IV once, then Ibuprofen 800 mg rectally every 6 hours	Placebo	24 hours	Not specified
Bernard et al (44) (1997)	RCT	7; United States, Canada	Medical/ Surgical ICU	455	Severe sepsis	Ibuprofen 10 mg/kg (maximum dose 800 mg) IV every 6 hours	Placebo	48 hours	30-day mortality
Memis et al (45) (2004)	RCT	1; Turkey	ICU	40	Severe sepsis, positive culture data	Lornoxicam 8 mg IV every 12 hours	Placebo	72 hours	Not specified
Schortgen et al (46) (2012)	RCT	7; France	Medical/ Surgical ICU	200	Septic shock, fever (≥ 38.4°C)	External cooling to achieve normothermia (36.5-37.0°C)	Physical cooling only if temperature > 41.0°C	48 hours	Proportion of patients with a 50% decrease in baseline vasopressor dose
Niven et al (47) (2013)	RCT	2; Canada	Medical/ Surgical ICU	26	Fever (two consecutive values ≥ 38.3°C two hours apart or a single value ≥ 39.5°C)[b]	Acetaminophen 650 mg enterally every 6 hours as needed for temperatures ≥ 38.3°C and physical cooling as needed for temperatures ≥ 39.5°C	Acetaminophen 650 mg enterally every 6 hours only if temperatures ≥ 40.0°C and physical cooling for temperatures ≥ 40.5°C	ICU length of stay	28-day mortality
Janz et al (48) (2015)	RCT	1; United States	Medical ICU	51	Severe sepsis, detectable cell-free hemoglobin	Acetaminophen (1 g) enterally every 6 hours	Placebo	3 days	Plasma F2-Isoprostane

Supplemental Table 2. Descriptive Characteristics of Randomized and Observational Studies (continued)

Author (year)	Study Design	Number of centers; countries	Setting	Sample size[a]	Main inclusion criteria	Intervention or antipyretic therapy evaluated	Control	Duration of intervention	Primary outcome
Young et al (49) (2015)	RCT	23; Australia, New Zealand	Medical/ Surgical ICU	700	Sepsis, fever (≥ 38.0°C)	Acetaminophen 1 g IV every 6 hours; physical cooling as needed for temperatures ≥ 39.5°C	Placebo	28 days or until ICU discharge, fever resolution, cessation of antimicrobial therapy, death, or development of contraindication to the study drug	ICU-free days to day 28
Pestaña et al (50) (2007)	Historically controlled	1; Spain	Surgical ICU	30	Septic shock, fever (≥ 39.5°C)	CVVHD aimed at a core temperature of 38.0°C	No CVVHD	Mean (SD) 51 (40) hours	28-day mortality
Selladurai et al (51) (2011)	Cross-sectional	1; Australia	Medical/ Surgical ICU	106	Sepsis	Acetaminophen	Absence of acetaminophen	First 7 days of ICU stay	Not specified
Lee et al (52) (2012)	Prospective cohort	25; Japan, Korea	Medical/ Surgical ICU	1425	ICU admission > 48 hours[b]	Antipyretic medication and physical cooling	Absence of antipyretic medication or physical cooling	ICU length of stay	28-day in-hospital mortality
Mohr et al (53) (2012)[c]	Retrospective cohort	1; United States	ED	171	Severe sepsis, fever (≥ 38.3°C)	Antipyretic medication	Absence of antipyretic medication	ED length of stay	28-day in-hospital mortality
Mohr et al (54) (2012)	Retrospective cohort	1; United States	Hospital (71% ICU)	278	Severe sepsis, fever (≥ 38.3°C), Gram-negative bacteremia	Antipyretic medication	Absence of antipyretic medication	Between 4 hours before and 6 hours after positive blood culture	28-day in-hospital mortality
Janz et al (55) (2013)	Case-control	1; United States	Medical/ Surgical ICU	391	Sepsis	Acetaminophen	Absence of acetaminophen	First 96 hours of ICU stay	Hospital mortality

Supplemental Table 2. Descriptive Characteristics of Randomized and Observational Studies (continued)

Author (year)	Study Design	Number of centers; countries	Setting	Sample size[a]	Main inclusion criteria	Intervention or antipyretic therapy evaluated	Control	Duration of intervention	Primary outcome
Zhang et al (56) (2015)	Case-control	1; United States	Medical/ Surgical ICU	15268	Sepsis	Antipyretic medication and physical cooling	Absence of antipyretic medication or physical cooling	ICU length of stay	ICU mortality
Suzuki et al (57) (2015)	Retrospective cohort	4; Australia	Medical/ Surgical ICU	15818	ICU admission[b]	Acetaminophen	Absence of acetaminophen	ICU length of stay	Hospital mortality

[a]Total number of patients enrolled in the study. [b]Outcome data available for subgroup of septic patients. [c]Abstract only available. RCT, randomized controlled trial; IV, intravenous; ICU, intensive care unit; CVVHD, continuous venovenous hemofiltration; ED, emergency department.

Supplemental Table 3. Patient Baseline Characteristics of Randomized Studies

Author (year)	Study group	Sample size[a]	Male, No. (%)	Age[b] (years)	Fever,[c] No. (%)	Illness severity scores[b]	Mechanical ventilation, No. (%)	Vaso-pressors, No. (%)	Baseline body temperature[b,d] (°C)	Baseline heart rate[b] (bpm)	Baseline minute ventilation[b] (L/min)
Bernard et al (42) (1991)	Intervention	16	-	54 (14)	-	-	13 (81)	8 (50)	38.1 (1.2)	112 (20)	13.9 (4.4)
	Control	14	-	54 (15)	-	-	11 (79)	7 (50)	38.1 (1.1)	108 (22)	13.4 (6.0)
Haupt et al (43) (1991)	Intervention	16	10 (63)	48 (16)	-	-	13 (81)	10 (63)	38.5 (1.6)	118 (16)	15.8 (6.4)
	Control	13	6 (46)	55 (14)	-	-	11 (85)	7 (54)	38.5 (1.4)	126 (14)	18.9 (10.5)
Bernard et al (44) (1997)	Intervention	224	94 (42)	54 (18)	200 (89)	APACHE II: 16 (7)	175 (78)	146 (65)	37.9 (1.5)	113 (15)	14.3 (6.0)
	Control	231	79 (34)	56 (16)	211 (91)	APACHE II: 15 (7)	176 (76)	147 (64)	38.0 (1.5)	114 (15)	13.9 (6.1)
Memis et al (45) (2004)	Intervention	20	13 (65)	49 (19-87)[e]	-	APACHE II: 17 (4) SOFA: 6 (2)	-	7 (35)	37.8 (0.8)	98 (24)	-
	Control	20	9 (45)	51 (20-89)[e]	-	APACHE II: 18 (4) SOFA: 6 (2)	-	8 (40)	37.6 (0.6)	95 (17)	-
Schortgen et al (46) (2012)	Intervention	101	75 (74)	62 (51-70)	101 (100)[f]	SOFA: 11 (9-14) SAPS3: 77 (67-85)	101 (100)	101 (100)	38.8 (38.6-39.2)	-	-
	Control	99	67 (68)	61 (49-70)	99 (100)[f]	SOFA: 11 (9-14) SAPS3: 79 (68-87)	99 (100)	99 (100)	38.9 (38.5-39.3)	-	-
Niven et al (47) (2013)	Intervention	14	8 (57)	53 (43-67)	14 (100)	APACHE II: 18 (7)	14 (100)	3 (21)	37.8 (0.7)[g]	-	-
	Control	12[h]	8 (6)	58 (49-69)	12 (100)	APACHE II: 19 (6)	12 (100)	7 (58)	37.5 (0.3)[g]	-	-
Janz et al (48) (2015)	Intervention	18	9 (50)	50 (41-64)	8 (44)[i,j]	APACHE II: 21.0 (16-29) SOFA: 6 (4-9)	8 (44)	8 (44)	37.7 (37.0-38.5)[k]	103 (21)[j]	-
	Control	22	12 (55)	58 (47-63)	9 (41)[i,j]	APACHE II: 22 (17-24) SOFA: 6 (5-8)	6 (27)	10 (45)	37.9 (37.2-38.4)[k]	96 (18)[j]	-
Young et al (49) (2015)	Intervention	347	224 (65)	59 (17)	347 (100)[i]	APACHE II: 19 (7)	176 (51)	174 (50)	38.8 (0.6)[k]	100 (21)	10.3 (4.0)
	Control	344	225 (65)	58 (17)	344 (100)[i]	APACHE II: 19 (8)	182 (53)	181 (53)	38.7 (0.6)[k]	100 (21)	9.8 (3.3)

Dashes indicate information not provided. [a]Number of patients included in analysis of baseline characteristics. [b]Continuous variables reported as mean (standard deviation) or median (interquartile range) unless otherwise indicated. [c]Fever defined as a temperature ≥ 38.3°C unless otherwise specified. [d]Baseline point measurement unless otherwise specified. [e]Median (range) reported. [f]Fever defined as temperature ≥ 38.4°C. [g]Baseline daily mean temperature. [h]Includes three patients without sepsis. [i]Fever defined as temperature ≥ 38.0°C. [j]Information provided via personal communication with author. [k]Baseline maximum temperature. APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment; SAPS3, Simplified Acute Physiology Score 3.

Supplemental Table 4. Outcome Data for Randomized Studies

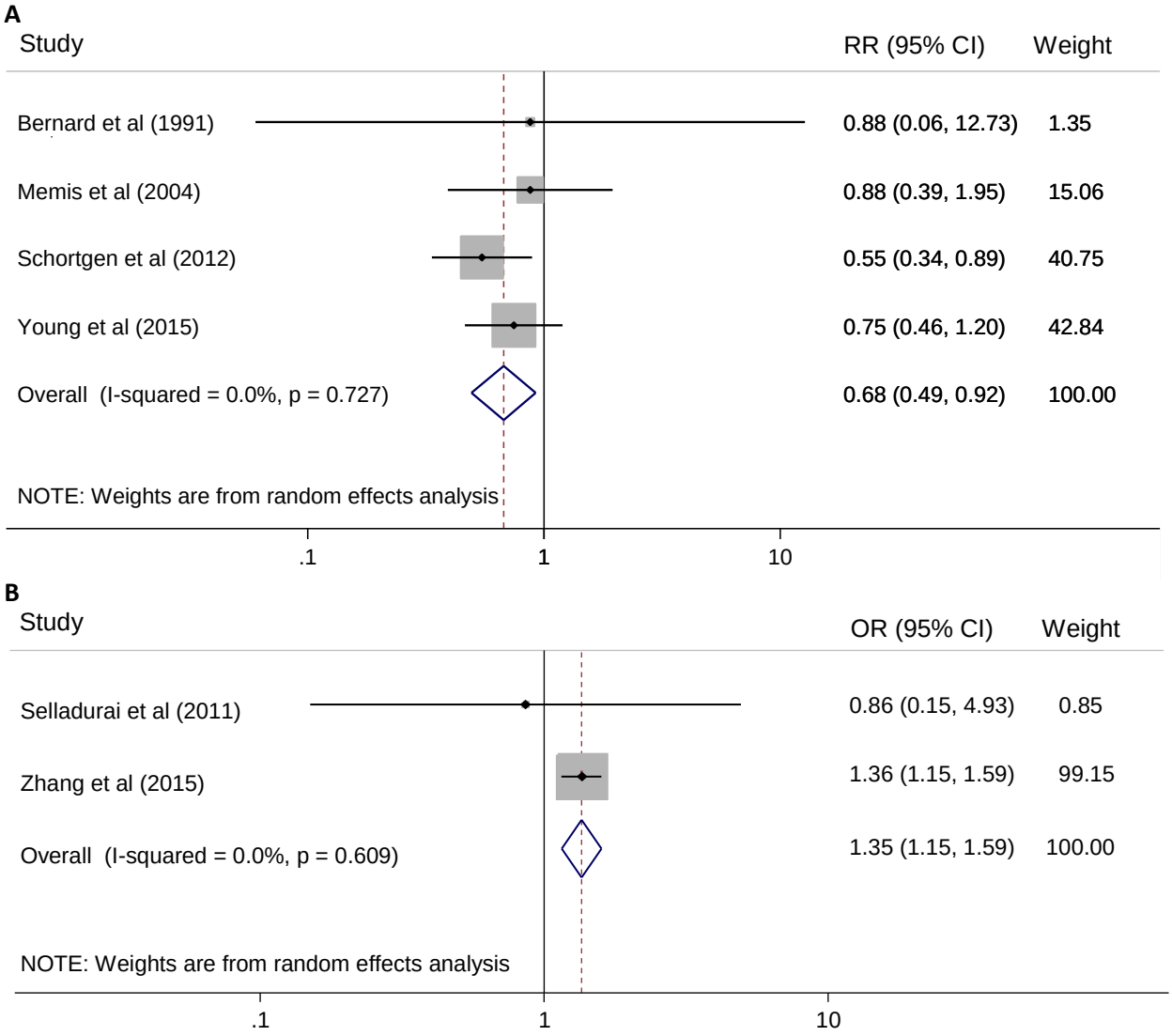
Author (year)	Study group	Sample size[a]	28-day mortality, No. (%)	Hospital mortality, No. (%)	ICU mortality, No. (%)	Other reported mortality, No. (%)	Shock reversal, No./total with shock (%)	Incidence of nosocomial infections, No. (%)	Post-intervention body temperature[b,c] (°C)	Post-intervention heart rate[b] (bpm)	Post-intervention minute ventilation[b] (L/min)
Bernard et al (42) (1991)	Intervention	16	3 (19)[d]	-	-	5-day: 1 (6)	7/8 (88)	-	37.0 (0.4)	93 (16)	13.3[e]
	Control	14	6 (43)[d]	-	-	5-day: 1 (7)	3/7 (43)	-	38.1 (1.5)	107 (22)	15.1[e]
Haupt et al (43) (1991)	Intervention	16	-	9 (56)	-	-	4/10 (40)	3 (19)	37.0 (0.8)	103 (16)	14.9 (6.4)
	Control	13	-	4 (31)	-	-	5/7 (71)	1 (8)	38.1 (1.1)	113 (22)	13.3 (5.8)
Bernard et al (44) (1997)	Intervention	224	83 (37)	-	-	-	-	18 (8)	36.9 (1.5)	99 (15)	13.4 (6.0)
	Control	231	92 (40)	-	-	-	-	26 (11)	37.5 (1.5)	104 (15)	13.5 (6.1)
Memis et al (45) (2004)	Intervention	20	-	7 (35)	7 (35)	-	-	-	37.9 (0.4)	96 (22)	-
	Control	20	-	8 (40)	8 (40)	-	-	-	37.8 (0.5)	97 (22)	-
Schortgen et al (46) (2012)	Intervention	101	-	43 (43)	35 (35)	14-day: 19 (19)	87/101 (86)	32.6/1000 ICU days[f]	36.8 (0.6)	-	-
	Control	99	-	48 (48)	43 (43)	14-day: 34 (34)	72/99 (73)	23.8/1000 ICU days[f]	37.6 (1.2)	-	-
Niven et al (47) (2013)	Intervention	14	3 (21)	-	-	-	-	0 (0)	38.0 (0.7)[g]	-	-
	Control	12[h]	2 (22)[h,i]	-	-	-	-	0 (0)[h,i]	37.7 (0.7)[g]	-	-
Janz et al (48) (2015)	Intervention	18	-	1 (6)	-	-	-	-	36.9 (36.9-37.1)[j]	97 (17)[i]	-
	Control	22	-	4 (18)	-	-	-	-	37.1 (36.9-37.4)[j]	88 (24)[i]	-
Young et al (49) (2015)	Intervention	346	48 (14)	-	-	14-day: 27 (8) 90-day: 55 (16)	-	-	36.9 (0.7)[g]	-	-
	Control	344	47 (14)	-	-	14-day: 36 (10) 90-day: 57 (17)	-	-	37.2 (0.8)[g]	-	-

Dashes indicate information not provided. [a]Number of patients included in analysis of outcomes. [b]Continuous variables reported as mean (standard deviation) or median (interquartile range). [c]Post-intervention point measurement unless otherwise specified. [d]30-day mortality reported. [e]No measure of dispersion provide. [f]For meta-analysis, converted to number of patients based on mean ICU length of stay in each group. [g]Post-intervention daily mean temperature on study day 2. [h]Three patients without sepsis were not included in analysis of mortality and incidence of nosocomial infections for this meta-analysis. [i]Information provided via personal communication with author. [j]Maximum temperature on study day 3. ICU, intensive care unit.

Supplemental Table 5. Risk of Bias Assessment of Randomized Studies Using the Cochrane Collaboration Risk of Bias Tool

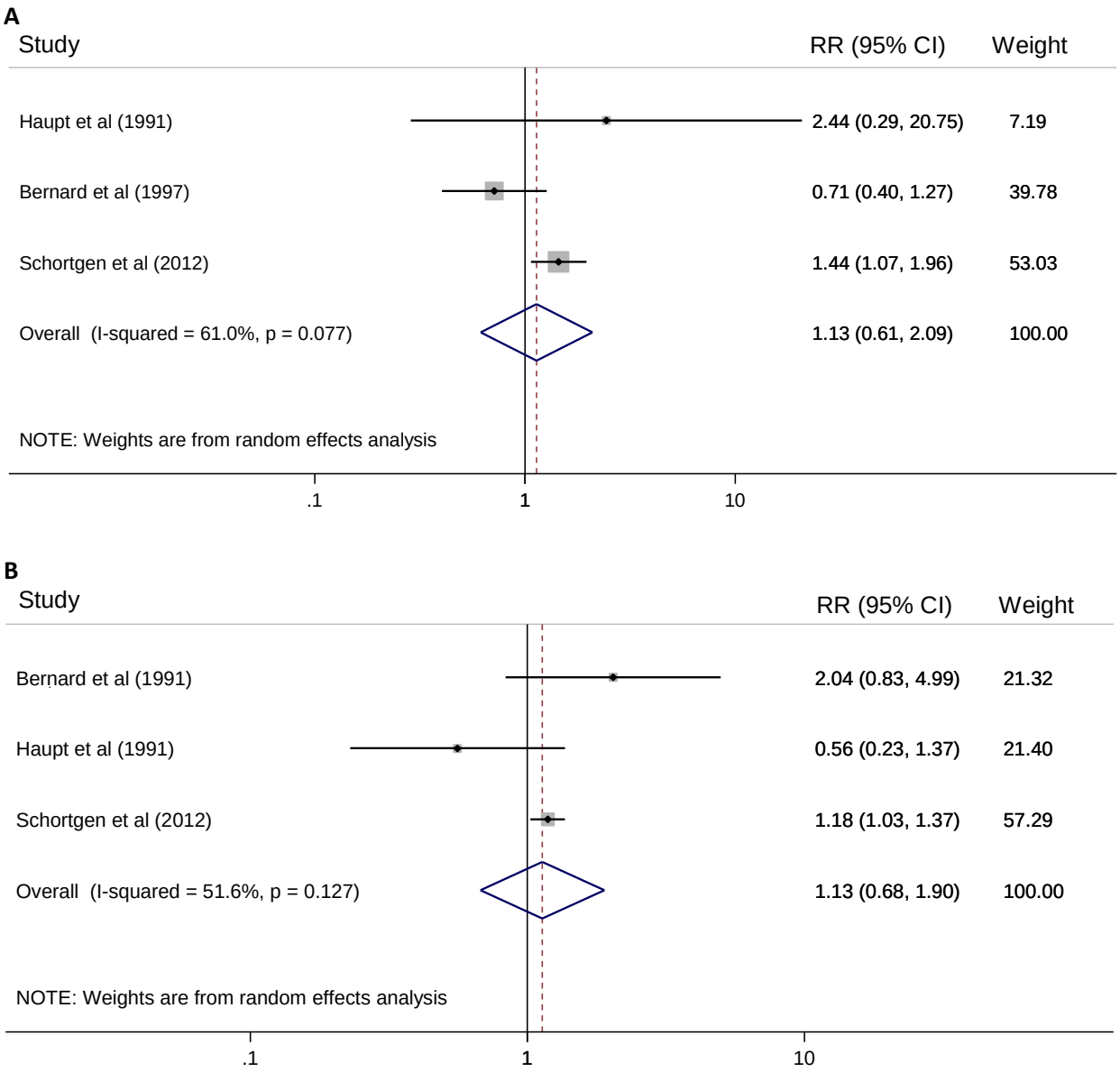
	Sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bernard et al (42) (1991)	Low	Low	Low	Low	Low	Unclear	Low
Haupt et al (43) (1991)	Low	Low	Low	Low	Unclear	Unclear	Low
Bernard et al (44) (1997)	Low	Low	Low	Low	Low	Low	Low
Memis et al (45) (2004)	Low	Low	Low	Low	Unclear	Unclear	Low
Schortgen et al (46) (2012)	Low	Low	High	High	Low	Unclear	Low
Niven et al (47) (2013)	Low	Low	High	Low	Low	Low	Low
Janz et al (48) (2015)	Low	Low	Low	Low	Low	Unclear	Low
Young et al (49) (2015)	Low	Low	Low	Low	Low	Low	Low

Supplemental Figure 1. Results of Meta-Analyses of Early Mortality



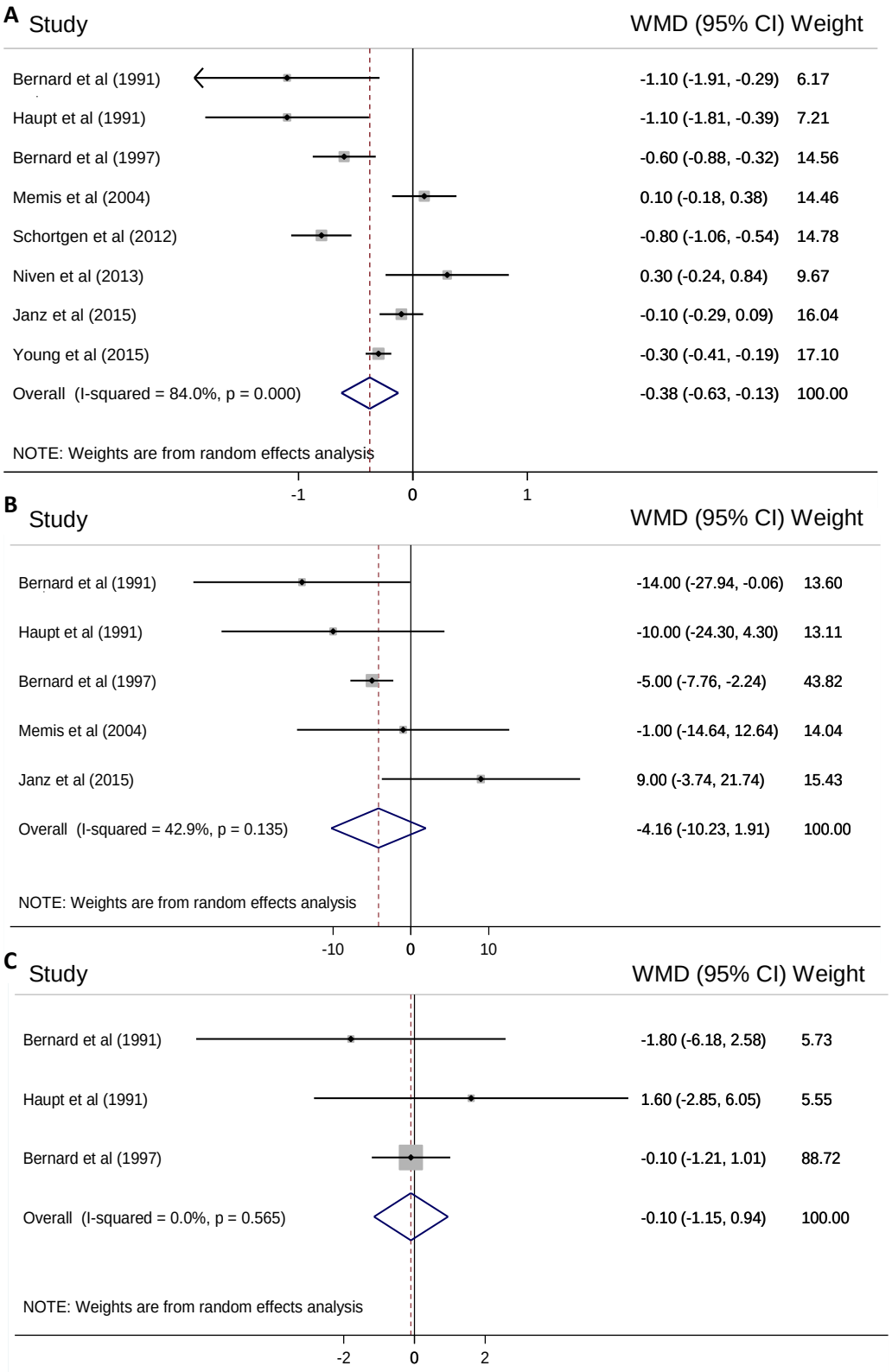
Meta-analysis results of early mortality (occurring within 14 days or in the intensive care unit) in patients treated with antipyretic therapy vs control in (A) randomized studies and (B) observational studies. A relative risk (RR) or odds ratio (OR) < 1 favors antipyretic therapy. The size of the grey box corresponds to weight in the random effects analysis. RR, relative risk; 95% CI, 95% confidence interval; OR, odds ratio.

Supplemental Figure 2. Results of Meta-Analyses of Acquisition of Nosocomial Infections and Shock Reversal



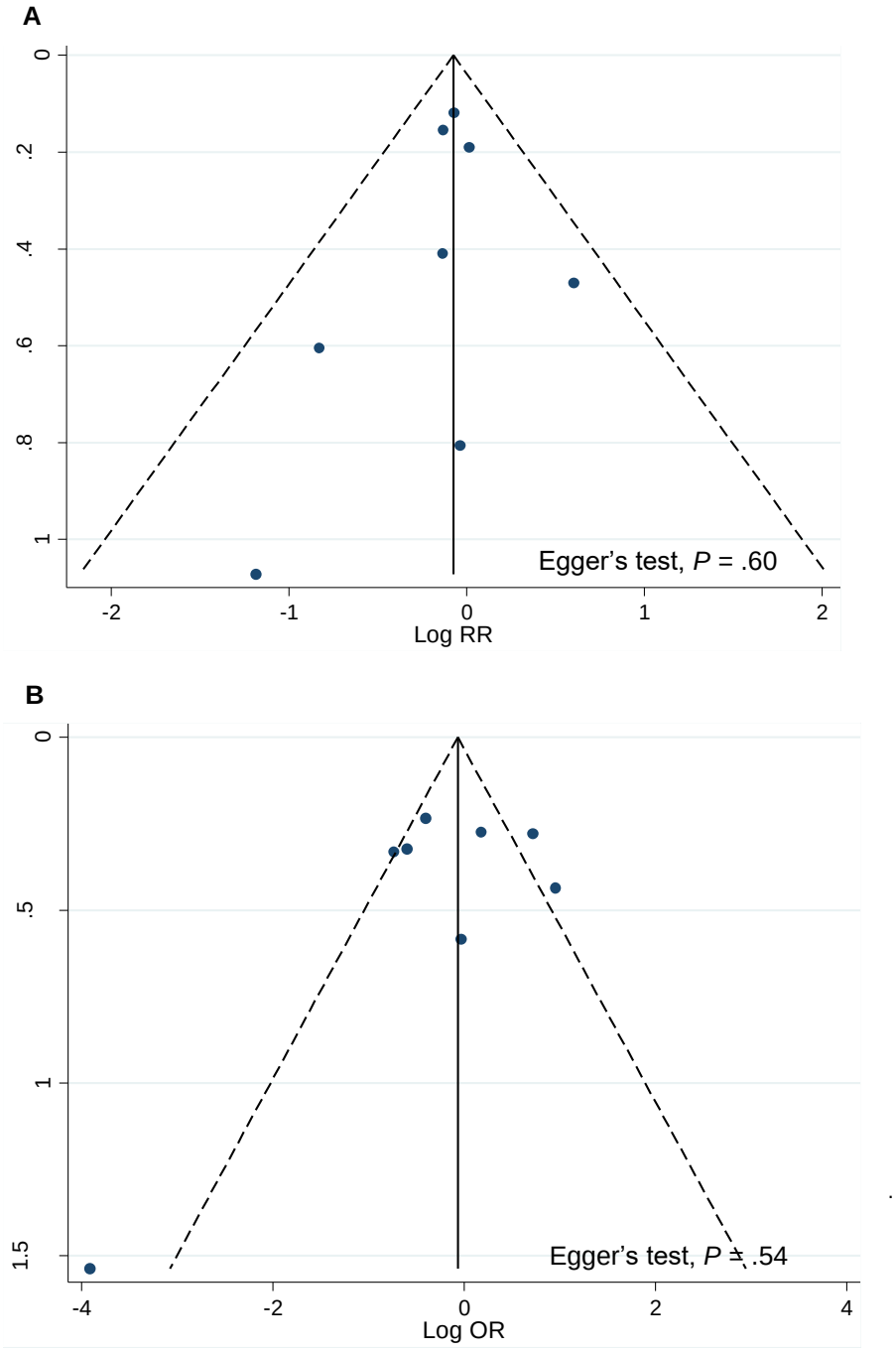
Meta-analysis results of (A) acquisition of nosocomial infections and (B) shock reversal in patients treated with antipyretic therapy vs control in randomized studies. A relative risk (RR) < 1 favors antipyretic therapy. The size of the grey box corresponds to weight in the random effects analysis. RR, relative risk; 95% CI, 95% confidence interval; OR, odds ratio.

Supplemental Figure 3. Results of Meta-Analyses of Post-Intervention Physiological Parameters



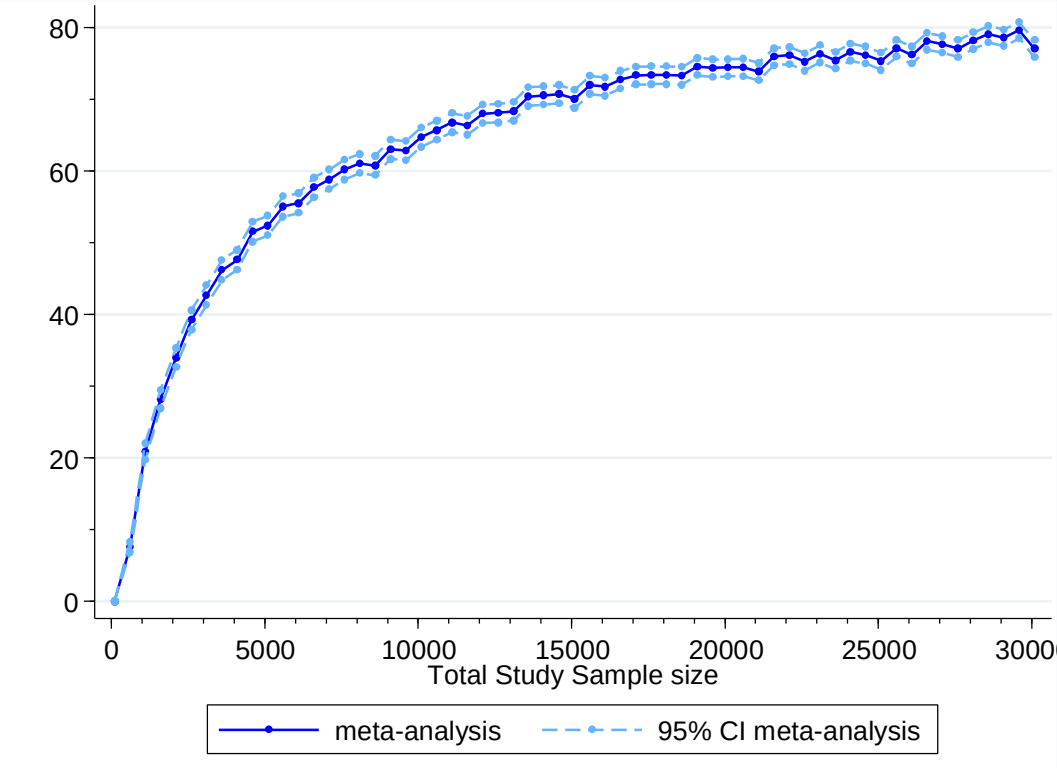
Meta-analysis results of (A) post-intervention body temperature, (B) post-intervention heart rate, and (C) post-intervention minute ventilation. Results reported as weighted mean differences (WMD) between the antipyretic and control groups expressed in (A) °C, (B) beats per minute, or (C) L/min. The size of the grey box corresponds to weight in the random effects analysis. A WMD < 0 indicates a decrease in the parameter. WMD, weighted mean difference; 95% CI, 95% confidence interval.

Supplemental Figure 4. Funnel plots of 28-day/Hospital Mortality in Randomized and Observational Studies Comparing Antipyretic Therapy to Control



Funnel plots demonstrating effect sizes and standard errors of effect sizes for 28-day/hospital mortality as reported in the included (A) randomized and (B) observational studies. RR, relative risk; OR, odds ratio.

Supplemental Figure 5. Simulation-Based Power Curve for 28-day/Hospital Mortality



Power curve for 28-day/hospital mortality based on relative risk using a fixed-effects model. It demonstrates the total sample sizes required of an additional study to achieve varying levels of power to change the results of the meta-analysis to favor antipyretic therapy. An additional study would need to enroll approximately 29,000 patients to achieve a power of 80%.

Supplemental Table 6. Patient Baseline Characteristics of the Observational Studies[a]

Author (year)	N[b]	Male, No. (%)	Age[c] (years)	Fever, No. (%)	Fever definition[d] (C°)	Illness severity scores[c]	Mechanical ventilation, No. (%)	Vasopressors, No. (%)
Pestaña et al (50) (2007)	30	21 (70)	61 (14)	30 (100)	≥ 39.5	APACHE II: 21 (5) SOFA: 10 (2)	30 (100)	30 (100)
Selladurai et al (51) (2011)	106	63 (59)	64 (16)	36 (34)	≥ 38.1	APACHE III: 59 (48-74)	47 (44)	-
Lee et al (52) (2012)	606	385 (64)	67 (55-75)	267 (44)	≥ 38.5	APACHE II: 21 (16-25)	429 (71)	-
Mohr et al (53) (2012)	171	-	-	171 (100)	-	-	-	-
Mohr et al (54) (2012)	278	145 (52)	58 (16)	278 (100)	≥ 38.3	APACHE II: 24 (7)	122 (44)	116 (42)
Janz et al (55) (2013)	292	155 (53)	58 (49-68)	-	-	APACHE II: 28 (21-33)	-	-
Zhang et al (56) (2015)	15268	8175 (54)	65 (20)	11433 (75)	≥ 37.3	SAPS: 15 (5) SOFA: 6 (4)	-	-
Suzuki et al (57) (2015)	15818[e]	10199 (64)[e]	64 (51-73)[e]	4397 (28)[e]	≥ 38.1	APACHE II: 17 (7)[e] SAPS II: 30 (22)[e]	11513 (73)[e]	-

Dashes indicate information not provided. [a]For studies in which only a subset of patients was included in the analysis of the relationship between antipyretic therapy and mortality in septic patients, baseline characteristics are provided for that subset, unless otherwise noted. [b]Number of patients included in analysis of baseline characteristics. [c]Continuous variables reported as mean (standard deviation) or median (interquartile range). [d]Body temperature threshold used to stratify patients into febrile and afebrile groups. [e]Baseline characteristics reported for entire study population, not for subset of infected patients (n = 681) included in the analysis of the relationship between antipyretic therapy and mortality. APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment; SAPS, Simplified Acute Physiology Score.

Supplemental Table 7. Methodological Quality Assessment of Observational Studies Using the Newcastle-Ottawa Scale

Author (year)	Patient Selection[a]	Comparability[b]	Outcome/Exposure[c]	Total
Pestaña et al (50) (2007)	★★★	★	★★★	7
Selladurai et al (51) (2011)	★★★★		★★★	7
Lee et al (52) (2012)	★★★★	★★	★★★	9
Mohr et al (53) (2012)	★★★★	★	★★★	8
Mohr et al (54) (2012)	★★★★	★	★★★	8
Janz et al (55) (2013)	★★★	★★	★★★	8
Zhang et al (56) (2015)	★★★	★★	★★★	8
Suzuki et al (57) (2015)	★★★★	★★	★★★	9

Points represented by stars. [a]For case-control studies, evaluates adequacy of case and control definitions, representativeness of the cases, and selection of controls; for cohort studies, evaluates representativeness of exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study; maximum four points. [b]Evaluates comparability of cases and controls or exposed and non-exposed cohorts; maximum two points. [c]For case-control studies, evaluates ascertainment of exposure, method of ascertainment for cases and controls, and non-response rate; for cohort studies, evaluates method of outcome assessment, length of follow-up, and adequacy of follow-up; maximum three points.

Supplemental Table 8. Outcome Data for Observational Studies

Author (year)	N[a]	Antipyretic exposure, No. (%)	Mortality reported	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Variables included in multivariable model
Pestaña et al (50) (2007)	30	Physical cooling: 19 (63)	28-day mortality	0.02 (0.001, 0.41)	-	-
Selladurai et al (51) (2011)	106	Acetaminophen: 74 (70)	ICU mortality	0.86 (0.15, 4.93)	-	-
Lee et al (52) (2012)	606[b]	Acetaminophen: 116 (19) NSAIDs: 31 (5) Physical cooling: 307 (51)	28-day in-hospital mortality	Acetaminophen: 2.30 (1.48, 3.58) NSAIDs: 2.32 (1.10, 4.91) Physical cooling: 1.00 (0.68, 1.46)	Acetaminophen: 2.05 (1.19, 3.55) NSAIDs: 2.61 (1.11, 6.11) Physical cooling: 1.2 (0.70, 2.05)	Age, APACHE II score, perioperative admission, requirement for mechanical ventilation, cardiac or vascular disease, thoracic or respiratory disease, maximum body temperature during ICU stay, type of antipyretic treatment
Mohr et al (53) (2012)	171	Antipyretic medication: 135 (79)	28-day in-hospital mortality	0.40 (0.16, 1.01)	0.97 (0.31, 3.06)	APACHE II score, intubation status, fever magnitude
Mohr et al (54) (2012)	278	Antipyretic medication: 130 (47)	28-day in-hospital mortality	0.51 (0.30, 0.87)	0.55 (0.29, 1.03)	APACHE II score, pneumonia, hypotension (per 10 mmHg), dialysis, surgery
Janz et al (55) (2013)	292[b]	Acetaminophen: 146 (50)	Hospital mortality	0.42 (0.23, 0.78)	0.48 (0.25, 0.92)	Age, presence of chronic liver disease, APACHE II score, cell-free hemoglobin concentration
Zhang et al (56) (2015)	15268	Antipyretic medication: 1027 (7) Physical cooling: 1006 (7)	ICU mortality	Any antipyretic therapy: 1.60 (1.39, 1.83) Physical cooling: 2.24 (1.91, 2.63)	Any antipyretic therapy: 1.36 (1.15, 1.59) Physical cooling: 1.51 (1.23, 1.84)	Age, SOFA score, sex, ICU type, presence of elevated lactate, missing values, temperature load
Suzuki et al (57) (2015)	681[b]	-	Hospital mortality	-	0.67 (0.42, 1.05)	APACHE II score, hospital, APACHE III diagnosis group, treatment limitation, propensity score for receiving paracetamol

Dashes indicate information not provided or not applicable. [a]Number of infected patients included in the analysis of the relationship between antipyretic therapy and mortality. [b]Subgroup of patients included in meta-analysis. OR, odds ratio; 95% CI, 95% confidence interval; ICU, intensive care unit; NSAID, non-steroidal anti-inflammatory drug; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

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