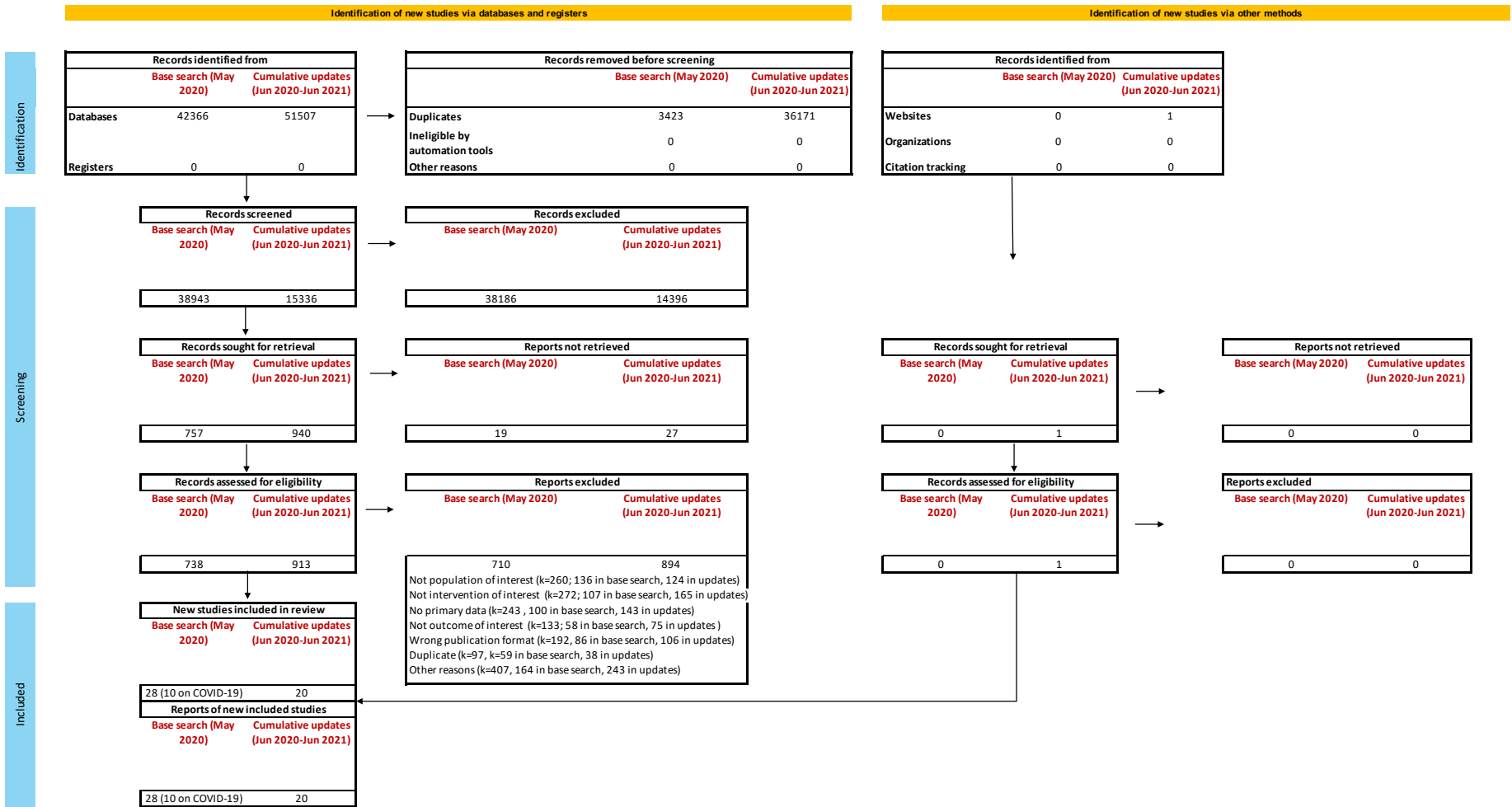# Supplementary Material*

Muti-Schüenemann GEU, Szczeklik W, Solo K, et al. Update alert 3: ventilation techniques and risk for transmission of coronavirus disease, including COVID-19. Ann Intern Med. 14 December 2021. [Epub ahead of print]. doi:10.7326/L21-0424

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Figure 1. Prisma diagram for living systematic reviews

Identification of new studies via databases and registers

Identification of new studies via other methods

Identification

Records identified from

	Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
Databases	42366	51507
Registers	0	0

Records removed before screening

	Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
Duplicates	3423	36171
Ineligible by automation tools	0	0
Other reasons	0	0

Records identified from

	Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
Websites	0	1
Organizations	0	0
Citation tracking	0	0

Screening

Records screened

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
38943	15336

Records excluded

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
38186	14396

Records sought for retrieval

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
757	940

Reports not retrieved

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
19	27

Records sought for retrieval

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
0	1

Reports not retrieved

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
0	0

Records assessed for eligibility

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
738	913

Reports excluded

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
710	894

Not population of interest (k=260; 136 in base search, 124 in updates)
Not intervention of interest (k=272; 107 in base search, 165 in updates)
No primary data (k=243 , 100 in base search, 143 in updates)
Not outcome of interest (k=133; 58 in base search, 75 in updates)
Wrong publication format (k=192, 86 in base search, 106 in updates)
Duplicate (k=97, k=59 in base search, 38 in updates)
Other reasons (k=407, 164 in base search, 243 in updates)

Records assessed for eligibility

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
0	1

Reports excluded

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
0	0

Included

New studies included in review

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
28 (10 on COVID-19)	20

Reports of new included studies

Base search (May 2020)	Cumulative updates (Jun 2020-Jun 2021)
28 (10 on COVID-19)	20

Supplement Table 1. Characteristics of included studies comparing different modalities of invasive and non-invasive ventilation

Study, analyzed design, Number of patients, Virus (preprint if indicated)	Ventilation	Age (mean & SD or median & IQR/range)	Eligibility criteria if reported	Degree of hypoxia based on PaO2/FiO2 ratio	Comorbidities	Radiographic pattern/findings	Risk of bias*
Duan 2020 (1), Cohort (n= 36), China, COVID-19#	NIV (CPAP or PEEP)	Mean ±SD 50 ±14	All the patients who used HFNC or NIV as first-line therapy.	PaO2/FiO2, mmHg 165 ±48	Hypertension (23%)	Not reported	8/9 No major concern
	HFNC	Mean ±SD 65 ±1	All the patients who used HFNC or NIV as first-line therapy.	PaO2/FiO2, mmHg 196 ±46	Hypertension (26%), diabetes (17%), chronic heart disease (27%), and chronic respiratory disease (4%)	Not reported	
Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	HFNC	Mean ±SD 65.7 ±14.7	Not reported	PaO2/FiO2, mmHg 166 ±65	Hypertension (47%), diabetes (20%), chronic cardiovascular disease (18%), obesity (21%), COPD (6%), CKD (8%), and cancer (11%)	Not reported	7/9 related to selection and comparability
	CPAP	Mean ±SD 70.3 ±12.1	Not reported	PaO2/FiO2, mmHg 151 ±90	Hypertension (55%), diabetes (20%), chronic cardiovascular disease (20%), obesity (11%), COPD (4%), CKD (6%), and cancer (10%)	Not reported	
	NIV	Mean ±SD 66.8 ±13.5	Not reported	PaO2/FiO2, mmHg 138 ±66	Hypertension (49%), diabetes (19%), chronic cardiovascular disease (13%), obesity (25%), COPD (15%), CKD (5%), and cancer (8%)	Not reported	
Grasselli 2020 (3), Cohort (n= 3988), Italy, COVID-19#	NIV vs IMV vs Oxygen	Median (IQR) 6 (56 – 69) for the entire cohort	Not reported	Overall PaO2, mmHG (not disaggregated by intervention): <76 (18%); 76-93 (18%); 94-127 (18%); >127 (18%).	Hypertension (41%), diabetes (13%), heart disease (13%), obesity (25%), COPD (2%), CKD (2%), and cancer (8%)	Not reported	6/9 Related to comparability and outcome assessment
Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	NIV (helmet)	Median (IQR) 66 (57 – 72)	PaO2/FIO2 ≤200, PaCO2 ≤45 mm Hg, no of history of chronic respiratory	PaO2/FIO2 ratio 105 (83-125); PaO2/FIO2 ratio ≤100 26 (48)	Hypertension (44%), diabetes (24%), smoking (9%), History of cancer (8%), Immunocompromised state (6%)	Bilateral infiltrates on enrollment chest x-ray: 100%	High risk of bias (death, need for invasive ventilation); some concerns (length of hospital stay, length of ICU

Study	Arm	Age	Inclusion criteria	Severity	Comorbidities	Imaging	Risk of bias
			failure or moderate to severe cardiac insufficiency, confirmed molecular diagnosis of COVID-19				stay) related to randomization process, deviation from intended intervention, and missing outcome
	HFNC	Median (IQR) 63 (55 – 69)	PaO2/FIO2 ≤200, PaCO2 ≤45 mm Hg, no of history of chronic respiratory failure or moderate to severe cardiac insufficiency, confirmed molecular diagnosis of COVID-19	PaO2/FIO2 ratio 102 (80-124); PaO2/FIO2 ratio ≤100 27 (49)	Hypertension (60%), diabetes (18%), smoking (20%), neurologic conditions (4%), Immunocompromised state (9%)	Bilateral infiltrates on enrollment chest x-ray: 100%	
Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Oxygen	Median (IQR) 52 (25 – 76)	Not reported	PaO2/FiO2, mmHg 32 (10 – 56)	Not reported	Not reported	6/9 (for mortality); 5/9 (for other outcomes) related to selection and comparability and outcome assessment
	NIV	Median (IQR) 70 (55 – 78)	Not reported	PaO2/FiO2, mmHg 35 (21 – 42)	Not reported	Not reported	
	IMV	Median (IQR) 58 (43 – 74)	Not reported	PaO2/FiO2, mmHg 21 (6 – 43)	Not reported	Not reported	
Kanthimathinathan 2020 (6), Cohort (n= 45), UK, COVID-19#	Supplemental Oxygen vs HFNC or CPAP vs IMV	Median (IQR) 3.5 (0.7 – 12) for the entire cohort	Not reported	Not reported	Three children (2 infants), 2 with comorbidities, required HFNC or CPAP. One infant, with preexisting congenital heart disease, required PICU admission for invasive mechanical ventilation.	Not reported	5/9 related to selection, comparability, and outcome assessment
Khalil 2020 (7), Cohort (n= 220), UK, COVID-19#	CPAP vs IMV	Mean ±SD	Not reported	Median (IQR)	Comorbidities presented overall, not per arm: asthma (11%), COPD (9%) hypertension (45%), diabetes (28%),	Imaging localised consolidation (19 %) and bilateral consolidation (57%) ,	7/9 Related to comparability and

Study	Group	Age	Crossover/Definition	PaO2/FiO2	Comorbidities	Severity	NOS score
		66.9 ±17 for the entire cohort		PaO2 /FiO2 ratio, mmHg: 240.1 (144.5 –306.7)	cardiovascular disease (11%), malignancy (13%), CKD (7%) and liver disease (3%)	and normal (11%) for the entire cohort	outcome assessment
Mukhtar 2020 (8), Cohort (n= 55), South Africa, COVID-19#	Oxygen	Mean ±SD 51 ±9	Not reported	PaO2/FiO2 (median, IQR): 250 (180 – 298)	Chronic cardiac disease (12%), Chronic pulmonary disease (0%), Chronic diabetes (50%), Chronic hypertension (62%), obesity (25%), smoking (18%)	Not reported	6/9 Related to selection and outcome assessment
	NIV	Mean ±SD 59 ±14	Not reported	PaO2/FiO2 (median, IQR): 170 (112 – 224)	Chronic cardiac disease (13%), Chronic pulmonary disease (3%), Chronic diabetes (43%), Chronic hypertension (53%), obesity (26%), smoking (3%)	Not reported	
	IMV	Mean ±SD 65 ±14	Patients who developed any feature of NIV failure was qualified for IMV.	PaO2/FiO2 (median, IQR): 175 (118 – 205)	Chronic cardiac disease (33%), Chronic pulmonary disease (22%), Chronic diabetes (77%), Chronic hypertension (55%), obesity (33%), smoking (55%)	Not reported	
Patel 2020 (9), Cohort (n= 104), USA, COVID-19#	HFNC	Mean ±SD 58.9 ±14.2	All patients on oxygen delivery via HFNT during the hospital course.	Not reported	Hypertension (38%), diabetes (35%), cardiovascular disease (20%), lung diseases (26%), CKD (14%)	Not reported	6/9 (for length of hospital stay); 7/9 (for death and length of ICU stay) related to comparability
	IMV	Mean ±SD 63.9 ±11.7	All patients on oxygen delivery via HFNT during the hospital course.	Not reported	Hypertension (57%), diabetes (33%), cardiovascular disease (27%), lung diseases (39%), CKD (21%)	Not reported	
Potalivo 2020 (10), Cohort (n= 520), Italy, COVID-19#	Oxygen	Mean ±SD 72 ±14.6	Not reported	Not reported	Not reported	Not reported	7/9 related to selection, comparability and outcome assessment
	NIV (CPAP)	Mean ±SD 64.5 ±12.7	Not reported	Not reported	Not reported	Not reported	

	IMV	Mean ±SD 67.3 ±9	respiratory fatigue, new hemodynamic instability, or worsening of gas exchange notwithstanding oxygen/NIV, also considering prognostic criteria and resources availability (e.g., ICU beds and mechanical ventilators)	PaO2/FiO2 ratio (before IMV):112.5 ± 50.4	Not reported	Not reported	
Sivaloganathan 2020 (11), Cohort (n= 103), UK, COVID-19#	NIV	Median (IQR) 50 (45 – 60)	Not reported	PaO2/FiO2 (median, IQR): 17 (14.3 – 20.4)	Not reported	Not reported	9/9
	IMV	Median (IQR) 61 (18 – 65)	Not reported	PaO2/FiO2 (median, IQR): 15.3 (12.7 – 18.1)	Not reported	Not reported	
Burns 2020 (12), Cohort (n= 28), UK, COVID-19‡	BiPAP	Median (range) 81.5 (54 – 91) for entire cohort	Not appropriate for escalation for invasive ventilation. Oxygen saturations not maintaining >94% despite 40% oxygen and a history of ventilatory failure.	SpO2 prior to NIPS= 89% (IQR=85–92.75) for the entire cohort	Comorbidities presented overall, not per arm: Hypertension (78.6%), ischaemic heart disease (35.7%), atrial fibrillation (28.6%), congestive cardiac failure (25%), diabetes mellitus (53.6%), chronic kidney disease (53.6%), COPD (17.9%), bronchiectasis (3.6%), asthma (21.4%), active malignancy (10.7%), dementia (3.6%), stroke (7.1%), and previous pulmonary or venous thromboembolism (7.1%).	Imaging 'Classical' = 16 (57.1%) and Imaging 'Indeterminate' = 8 (28.6%) for the entire cohort	5/9 Concern related to selection of participants and outcome follow-up
	CPAP	Median (range) 81.5 (54 – 91) for entire cohort	Not appropriate for escalation for invasive ventilation. Oxygen saturations not maintaining >94% despite 40% oxygen and a history of ventilatory failure.	SpO2 prior to NIPS= 89% (IQR=85–92.75) for the entire cohort	Comorbidities presented overall, not per arm: Hypertension (78.6%), ischaemic heart disease (35.7%), atrial fibrillation (28.6%), congestive cardiac failure (25%), diabetes mellitus (53.6%), chronic kidney disease (53.6%), COPD (17.9%),	Imaging 'Classical' = 16 (57.1%) and Imaging 'Indeterminate' = 8 (28.6%) for the entire cohort	5/9 Concern related to selection of participants and outcome follow-up

					bronchiectasis (3.6%), asthma (21.4%), active malignancy (10.7%), dementia (3.6%), stroke (7.1%), and previous pulmonary or venous thromboembolism (7.1%).		
Lalla 2020 (13), Cohort (n= 13), South Africa, COVID-19‡	HFNC vs IMV (intubation)	Not reported	Not reported	Not reported	Not reported	Not reported	3/9 Concern related to selection of participants and outcome follow-up
Wang 2020 (14), Cohort (n= 141), China, COVID-19‡	NIV vs IMV (EET)	Median (IQR) 64 (55-70) for the entire cohort	Not reported	Not reported	Comorbidities presented overall, not per arm: Hypertension (45%), diabetes (26%), cerebrovascular disease (92%), and coronary artery disease (8.5%)	Not reported	8/9 Concern related to selection of participants
Hong 2020 (15), Cohort (n= 9), China, COVID-19†	HFNC	Not reported	Not reported	Not reported	Not reported	Not reported	7/9 Concern related comparability
	IMV (Tracheotomy)	Not reported	Not reported	Not reported	Not reported	Not reported	
Li 2020 (16), RCT (n= 72), China, COVID-19†	HFNC	Mean ±SD 32 ±6.42	COVID19+ARDS	PaO2= 63.162 ±3.912mmHg	Not reported	Not reported	Some concerns due to randomization process,
	SOT	Mean ±SD 35 ±4.67	COVID19+ARDS	PaO2=62.886 ±3.243mmHg	Not reported	Not reported	
Oranger 2020 (17), Cohort (n= 66), France, COVID-19†	NIV (CPAP) + Oxygen therapy	Median (IQR) 63 (55 – 70)	• Confirmed SARS-CoV-2 infection • ARDS (respiratory rate ≥25, bilateral pulmonary infiltrates on chest X-ray or CTscan, need for standard oxygen between 3 and 6 L.min-1 to maintain SpO2 ≥ 92%). Among them, those requiring escalating oxygen therapy ≥ 6	SpO2 < 92%	No significant differences in respiratory and cardiovascular comorbidities, clinical data upon admission (body temperature, heart rate and arterial pression), biological data (white cell count, lymphocyte count, C-reactive protein, procalcitonin, D-dimers) or radiological data (bilateral infiltrates in 100% of cases). Prevalence not reported.	100% bilateral lung infiltrates	6/9 Concern related to comparability and outcome

			L.min-1 to maintain SpO2 ≥ 92% were included.				
	Oxygen therapy	Median (IQR) 62 (54 – 72)	• Confirmed SARS-CoV-2 infection • ARDS (respiratory rate ≥25, bilateral pulmonary infiltrates on chest X-ray or CT scan, need for standard oxygen between 3 and 6 L.min-1 to maintain SpO2 ≥ 92%). • Among them, those requiring escalating oxygen therapy ≥ 6 L.min-1 to maintain SpO2 ≥ 92% were included.	SpO2 < 92%	No significant differences in respiratory and cardiovascular comorbidities, clinical data upon admission (body temperature, heart rate and arterial pression), biological data (white cell count, lymphocyte count, C-reactive protein, procalcitonin, D-dimers) or radiological data (bilateral infiltrates in 100% of cases). Prevalence not reported.	100% bilateral lung infiltrates	
Shang 2020 (18), Cohort (n= 416), China, COVID-19†	NIV, IMV, SOT (helmet, oronasal or full-face mask)	Not reported	• Not reported	Not reported	Not reported	Not reported	7/9 Concern related to comparability
Tang 2020 (19), Cohort (n= 7), China, COVID-19†	NIV	Not reported	• Not reported	Not reported	Not reported	Not reported	6/9 Concern related to comparability and outcome
	HFNC	Not reported	• Not reported	Not reported	Not reported	Not reported	
Zheng 2020 (20), ohort (n= 34), China, COVID-19†	NIV	Median (IQR) 66 (51 – 72)	• Not reported	Not reported	63.2%Hypertension, 21.1%Diabetes, 5.3%Cardiovascular disease, 5.3%COPD, 15.8%Chronic liver disease, 5.3%Chronic kidney disease	Not reported	7/9 Concern related to comparability
	IMV	Median (IQR) 71 (60 – 83)	• Not reported	Not reported	66.7%Hypertension, 26.7%Diabetes, 20.0%Cardiovascular disease, 6.7%COPD, 6.7%Chronic liver disease, 6.7%Chronic kidney disease	Not reported	

Study	Intervention	Age	Severity		Comorbidities		Quality
Duca 2020 (21), Cohort (n = 320), Italy, COVID-19 (preprint)*	CPAP (Helmet)	Mean ±SD 69 ±11.5	Hypoxic and/or dyspneic on 15 L/min nonrebreather mask	Not reported	Not reported	Not reported	6/9 Concern related to the comparability of the arms and outcome follow-up
	NIV	Mean ±SD 71 ±12	Hypoxic and/or dyspneic on 15 L/min nonrebreather mask	Not reported	Not reported	Not reported	
	IMV	Mean ±SD 69 ±12	Hypoxic and/or dyspneic on 15 L/min nonrebreather mask	Not reported	Not reported	Not reported	
He 2020 (22), Cohort (n= 37), China, COVID-19*	SOT vs HFNC vs NIV	Not reported	Not reported	Not reported	Not reported	Not reported	6/9 Concern related to selection and comparability of the arms
Hua 2020 (23), Cohort (n= 45), China, COVID-19*	HFNC	Mean ±SD 38.1 ±0.7	Not reported	Not reported	Not reported	Not reported	5/9 Concern related to selection, comparability of the arms and outcome follow-up
	SOT	Mean ±SD 37.8 ±0.8	Not reported	Not reported	Not reported	Not reported	
Liao 2020 (24), Cohort (n = 81), China, COVID-19 (preprint)*	HFNC, NIV, SOT (nasal catheter & mask)	Median (IQR) 50 (39 – 65)	Dyspnea with respiratory rate ≥ 30; pulse oxygenation < 93%; PaO2:FiO2 < 300; lung infiltrates >50% within 24 to 48 hours; respiratory failure, septic shock, and/or multi-organ failure	PaO2:FiO2 ratio (<300 mmHg)	Hypertension (18.5%), Diabetes (22.2%), chronic pulmonary disease (13.6%), chronic heart failure (4.9%),	Lung infiltrates > 50% in 4.9%	5/9 Concern related to selection, comparability of the arms and outcome follow-up
Liu 2020 (25), Cohort (n= 47), China, COVID-19*	NIV vs IMV	Age >60 years: 89%	Not reported	Not reported	Heart failure (51.1%), renal failure (31.2%)	Not reported	4/9 Concern related to selection, comparability, and outcome follow up
Liu 2020 (26), Cohort (n= 32), China, COVID-19*	NIV vs HFNC	Not reported	Not reported	Not reported	Not reported	Not reported	5/9 Concern related to selection, comparability, and outcome follow up
Mo 2020 (27), Cohort (n= 38), China, COVID-19*	HFNC	Mean ±SD 59.8 ±10.6	Not reported	Not reported	Not reported	Not reported	6/9 Concern related to selection and

Study	Arm	Age	Description	Baseline	Comorbidities	Findings	Risk of bias
							comparability of arms
	SOT	Mean ±SD 60.3 ±16.3	Not reported	Not reported	Not reported	Not reported	
Wang 2020 (28), Cohort (n = 27), China, COVID-19*	HFNC	Median (IQR) 65 (56 – 75)	• Patients with pneumonia secondary to COVID-19 who required HFNC, NIV or invasive ventilation (severe respiratory failure)..	At baseline, the number of patients with PaO2/ FiO2 > 200 and ≤ 200 mmHg was 6 and 11, respectively	Hypertension (18%), Diabetes (18%), Chronic heart failure (18%)	Pulmonary infiltrates 100%	6/9 Concern related to selection and comparability of the arms and outcome follow-up
	NIV	Not reported	• Not reported	Not reported	Not reported	Not reported	
Wang 2020 (29), Cohort (n= 548), China, COVID-19*	NIV vs IMV vs HFNC	Not reported	• Not reported	Not reported	Baseline data available only for initial cohort with 548 pts: Comorbidities n (%): Hypertension 166 (30), coronary heart disease 34 (6), diabetes mellitus 83 (15), chronic kidney disease 10 (2), asthma 5 (1), COPD 17 (3)	Not reported	6/9 Concern related to selection and comparability of the arms
Wu 2020 (30), Cohort (n = 201), China, COVID-19*	SOT, NIV, IMV, IMV with ECMO	Median (IQR) 51 (43 – 60) for entire cohort	• not reported	not reported	not reported	not reported	6/9 Concern related to selection and comparability of the arms

*: initial review (grey). †: first update (green). ‡: second update (blue). #: current update (orange). CPAP: continuous positive airway pressure. NIV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; MV: mechanical ventilation; ECMO; Extracorporeal membrane oxygenation; SOT: standard oxygen therapy; HFNC; High flow oxygen by nasal canula. Risk of bias per outcome for randomized studies was assessed using the Cochrane Risk of Bias 2.0 tool (overall risk of bias rating is presented here); risk of bias for non-randomized studies was assessed using Newcastle-Ottawa scale (overall risk of bias rating is presented here).

Supplement Table 2. Results of randomized, adjusted and unadjusted studies of COVID-19 patients comparing no ventilation, invasive mechanical ventilation and non-invasive mechanical ventilation by hard outcome and subgroups

Comparison	Name of study	Outcome (duration follow-up)	Intervention	Comparator	Effect estimate [OR (95%CI)] with subgroups or narrative for adjusted studies
BiPAP vs CPAP	Burns 2020 (12), Cohort (n= 28), UK, COVID-19‡	Mortality (30 days)	12/23	2/5	n.r
CPAP vs oxygen	Kanthimathinathan 2020 (6), Cohort (n= 45), UK, COVID-19#	Mortality (41 days)	0/1	0/9	n.r
	Oranger 2020 (17), Cohort (n= 66), France, COVID-19†	Mortality (7 days)	0/38	2/14	n.r
		Mortality (14 days)	0/38	2/14	n.r
		Need for invasive ventilation (7 days)	9/38	6/14	n.r
		Need for invasive ventilation (14 days)	9/38	6/14	n.r
CPAP vs IMV	Kanthimathinathan 2020 (6), Cohort (n= 45), UK, COVID-19#	Mortality (41 days)	0/1	0/1	n.r
	Khalil 2020 (7), Cohort (n= 220), UK, COVID-19#	Mortality (28 days)	15/41	13/34	n.r
CPAP vs HFNC	Duan 2020 (1), Cohort (n= 36), China, COVID-19#	Mortality (90 days)	1/13	1/23	n.r
	Duan 2020 (1), Cohort (n= 36), China, COVID-19#	Need for invasive ventilation (90 days)	2/13	4/23	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Mortality (30 days)	100/330	26/163	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Need for invasive ventilation (71 days)	82/330	47/163	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Length of hospital stay (71 day)	19.8 ±12.1	19.2 ±13.3	n.r

	Study	Outcome			
	Kanthimathinathan 2020 (6), Cohort (n= 45), UK, COVID-19#	Mortality (41 days)	0/1	0/2	n.r
	He 2020 (22), Cohort (n= 37), China, COVID-19*	Need for invasive ventilation (n.r)	2/6	2/21	n.r
	Liu 2020 (25), Cohort (n= 32), China, COVID-19*	Hospital mortality (n.r)	3/10	0/8	n.r
		Need for invasive ventilation (n.r)	1/10	0/8	n.r
	Wang 2020 (28), Cohort (n = 27), China, COVID-19*	Need for invasive ventilation (n.r)	1/9	2/17	n.r
	Liao 2020 (24), Cohort (n = 81), China, COVID-19 (preprint)*	Recovery (28 days)	5/8	8/13	n.r
CPAP vs NIV	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Mortality (30 days)	100/330	54/177	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Need for invasive ventilation (71 days)	82/330	49/177	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Length of hospital stay (71 day)	19.8 ±12.1	21.5 ±15.1	n.r
	Khalil 2020 (7), Cohort (n= 220), UK, COVID-19#	Mortality (28 days)	15/41	2/4	n.r
HFNC vs oxygen	Kanthimathinathan 2020 (6), Cohort (n= 45), UK, COVID-19#	Mortality (41 days)	0/2	0/9	n.r
	Li 2020 (16), RCT (n= 72), China, COVID-19†	Need for invasive ventilation (12 h)	1/37	6/35	n.r
	He 2020 (22), Cohort (n= 37), China, COVID-19*	Need for invasive ventilation (n.r)	2/21	1/10	n.r
	Hua 2020 (23), Cohort (n= 45), China, COVID-19*	Time to improvement in CT in days (absorption of lesion area ≥ 30% (n.r)	4.8±2.4	8±2.8	n.r
	Mo 2020 , Cohort (n= 38), China, COVID-19*	Need for invasive ventilation (n.r)	5/22	5/16	n.r
	Liao 2020 (24), Cohort (n = 81), China,	Recovery (28 days)	5/8	3/4 (mask)	n.r

	COVID-19 (preprint)*				
	Liao 2020 (24), Cohort (n = 81), China, COVID-19 (preprint)*	Recovery (28 days)	5/8	34/51 (nasal)	n.r
HFNC vs NIV	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Mortality (28 days)	10/55	8/54	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Mortality (60 days)	12/55	13/54	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	ICU mortality (n.r.)	14/55	11/54	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	In-hospital mortality (n.r.)	14/55	13/54	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Need for invasive ventilation (28 days)	28/55	16/54	HR: 2.04 (1.12 – 3.7)
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Length of hospital stay (n.r.)	22 (13 – 44)	21 (14 – 30)	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Length of ICU stay (n.r.)	10 (5 – 23)	9 (4 – 17)	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Respiratory support-free days (n.r.)	18 (0 – 22)	20 (0 – 25)	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Invasive ventilation-free days (28 days)	25 (4 – 28)	28 (13 – 28)	n.r
	Grieco 2021 (4), RCT (n= 110), Italy, COVID-19#	Invasive ventilation-free days (60 days)	60 (43 – 60)	57 (19 – 60)	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Mortality (30 days)	26/163	54/177	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Need for invasive ventilation (71 days)	47/163	49/177	n.r
	Franco 2020 (2), Cohort (n= 670), Italy, COVID-19#	Length of hospital stay (71 day)	19.2 ±13.3	21.5 ±15.1	n.r

	Tang 2020 (19), Cohort (n= 7), China, COVID-19†	Mortality (n.r.0)	0/5	1/2	n.r
HFNC vs IMV	Kanthimathinathan 2020 (6), Cohort (n= 45), UK, COVID-19#	Mortality (41 days)	0/2	0/1	n.r
	Patel 2020 (9), Cohort (n= 104), USA, COVID-19#	Mortality (10 days)	2/67	13/27	n.r
	Patel 2020 (9), Cohort (n= 104), USA, COVID-19#	Length of hospital stay (10 day)	9.7 ±4.6	13.67 ±7.97	n.r
	Patel 2020 (9), Cohort (n= 104), USA, COVID-19#	Length of ICU stay (10 day)	4.05 ±2.64	10.45 ±6.12	n.r
	Lalla 2020 (13), Cohort (n= 13), South Africa, COVID-19‡	Mortality (n.r.)	1/7	6/6	n/a
	Hong 2020 (15), Cohort (n= 9), China, COVID-19†	Hospital Mortality (n.r)	0/8	0/1	n.r
	Wang 2020 (29), Cohort (n= 548), China, COVID-19*	Mortality (15 days)	9/24	16/25	HR 1.11 (0.43 – 2.83)[1]
NIV vs IMV	Khalil 2020 (7), Cohort (n= 220), UK, COVID-19#	Mortality (28 days)	2/4	13/34	n.r
	Grasselli 2020 (3), Cohort (n= 3988), Italy, COVID-19#	Mortality (n.r.)	127/350	1514/2929	HR 0.81 (0.65 – 1)[2]
	Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Mortality (83 days)	0/4	2/11	n.r
	Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Length of hospital stay (83 day)	Mean (range) 15 (12 – 18)	Mean (range) 32 (17 – 65)	n.r
	Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Length of ICU stay (83 day)	Mean (range) 5 (2 – 7)	Mean (range) 25 (10 – 56)	n.r

Study	Outcome			
Mukhtar 2020 (8), Cohort (n= 55), South Africa, COVID-19#	Mortality (46 days)	3/30	7/9	n.r
Mukhtar 2020 (8), Cohort (n= 55), South Africa, COVID-19#	Length of ICU stay (46 day)	Median (IQR) 7 (4 – 8)	Median (IQR) 7 (3 – 18)	n.r
Potalivo 2020 (10), Cohort (n= 520), Italy, COVID-19#	Mortality (60 days)	9/46	15/41	HR 0.6 (0.356 – 1.011)[3]
Sivaloganathan 2020 (11), Cohort (n= 103), UK, COVID-19#	Mortality (71 days)	0/31	6/21	n.r
Wang 2020 (14), Cohort (n= 141), China, COVID-19‡	Mortality (n.r.)	n.r	n.r	0.34 (0.16 – 0.71)[4]
Shang 2020 (18), Cohort (n= 416), China, COVID-19†	Mortality (n.r)	19/68	12/14	n.r
Zheng 2020 (20), Cohort (n= 34), China, COVID-19†	Mortality (n.r)	0/19	0/15	n.r
Duca 2020 (21), Cohort (n = 320) Italy, COVID-19 (preprint)*	Mortality (up to 24 days)	46/71 (Helmet CPAP) 4/7 (NIV)	2/7	n.r.
Liu 2020 (25), Cohort (n= 47), China, COVID-19*	Length of hospital stay (Before death)	7 (4 – 9.75)	13 (7 – 21)	n.r.
Wang 2020 (29), Cohort (n= 548), China, COVID-19*	Mortality (15 days)	46/78	16/25	HR 1.61 (0.84 – 3.09) [1]
Wu 2020 (30), Cohort (n = 201), China, COVID-19*	Mortality (n.r.)	38/61	5/5	n.r.

NIV vs oxygen	Grasselli 2020 (3), Cohort (n= 3988), Italy, COVID-19#	Mortality (n.r.)	127/350	13/76	HR 0.55 (0.17 – 1.75) [2]
	Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Mortality (83 days)	0/4	0/7	n.r
	Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Length of hospital stay (83 day)	Mean (range) 15 (12 – 18)	Mean (range) 14 (6 – 24)	n.r
	Gundem 2020 (5), Cohort (n= 26), Norway, COVID-19#	Length of ICU stay (83 day)	Mean (range) 5 (2 – 7)	Mean (range) 4 (2 – 8)	n.r
	Mukhtar 2020 (8), Cohort (n= 55), South Africa, COVID-19#	Mortality (46 days)	3/30	0/16	n.r
	Mukhtar 2020 (8), Cohort (n= 55), South Africa, COVID-19#	Length of ICU stay (46 day)	Median (IQR) 7 (4 – 8)	Median (IQR) 3 (2 – 3)	n.r
	Potalivo 2020 (10), Cohort (n= 520), Italy, COVID-19#	Mortality (60 days)	9/46	94/408	HR 1.77 (0.79 – 3.98) [3]
	Potalivo 2020 (10), Cohort (n= 520), Italy, COVID-19#	Need for invasive ventilation (60 days)	25/71	32/440	n.r
NIV vs no IMV including conventional oxygen therapy	Liao 2020 (24), Cohort (n = 81), China, COVID-19 (preprint)*	Recovery (28 days)	8/13	3/4 (mask)	n.r
	Liao 2020 (24), Cohort (n = 81), China, COVID-19 (preprint)*	Recovery (28 days)	8/13	34/51 (nasal catheter)	n.r
	He 2020 (22), Cohort (n= 37), China, COVID-19*	Need for invasive ventilation (n.r)	2/6	1/10	n/a

*: initial review. †: first update: ‡: second update. #: current update. CPAP: continuous positive airway pressure. NIV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; MV: mechanical ventilation; ECMO; Extracorporeal membrane oxygenation; SOT: standard oxygen therapy; HFNC; High flow oxygen by nasal canula; HCW: healthcare worker: ICU: intensive care unit; NIPPV: noninvasive positive pressure ventilation

a: median (IQR);

b: median (minimum & maximum)

1: adjusted by: age, SaO$_2$, WBC count, lymphocyte count, LDH, multi-organ dysfunction, treatment with corticosteroids, arbidol, ribavirin, & lopinavir/ritonavir

2: adjusted by: age, sex, hypertension, heart disease, hypercholesterolemia, Diabetes T2, malignancy, COPD, FiO_2, PaO_2/FiO_2, PEEP at admission, statin, & ACE, ARB, & Diuretics therapy

3: adjusted by age, sex, and administration of steroids, canakinumab, and tocilizumab

4: adjusted by: age, sex, D-dimer, prothrombin time, CRP

5: Adjusted for age, baseline PaO2/FiO2, number of comorbidities and steroid usage

Supplement Table 3. Evidence Profile Non-invasive ventilation compared to invasive mechanical ventilation for COVID-19 and acute hypoxemic respiratory failure

Author(s) of this table: Giovanna Elsa Ute Muti Schuenemann, Assem Khamis, Karla Solo, Holger Schünemann

Question: Non-invasive ventilation compared to invasive mechanical ventilation for COVID-19 and acute hypoxemic respiratory failure

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty	Importance
Mortality (at different time intervals)									
4	observational studies	serious[a]	very serious	serious[b]	Serious[c]	none	The meta-analysis of hazard ratios these four studies showed a hazard ratio of 0.74 (0.46, 1.18).	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations
a. There are concerns regarding selection of participants (possible selection bias).

b. There are concerns regarding the assessment of the outcome (duration of follow up).

c. There was unexplained inconsistency in the study results.

Supplement Table 4. Evidence Profile non-invasive ventilation compared to oxygen only for COVID-19 and acute hypoxemic respiratory failure

Author(s) of this table: Giovanna Elsa Ute Muti Schuenemann, Assem Khamis, Karla Solo, Holger Schünemann

Question: Non-invasive ventilation compared to no mechanical ventilation for COVID-19 and acute hypoxemic respiratory failure

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Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			

Mortality

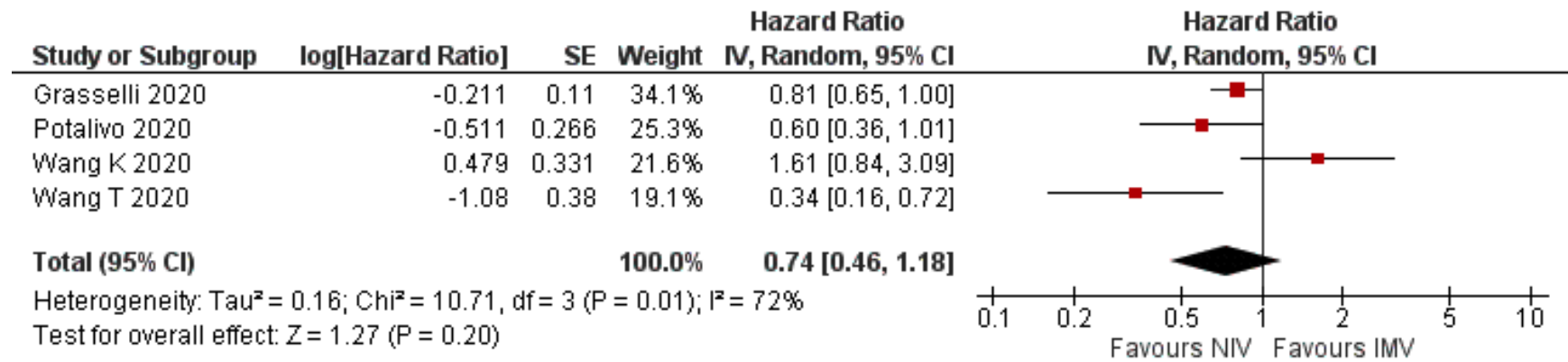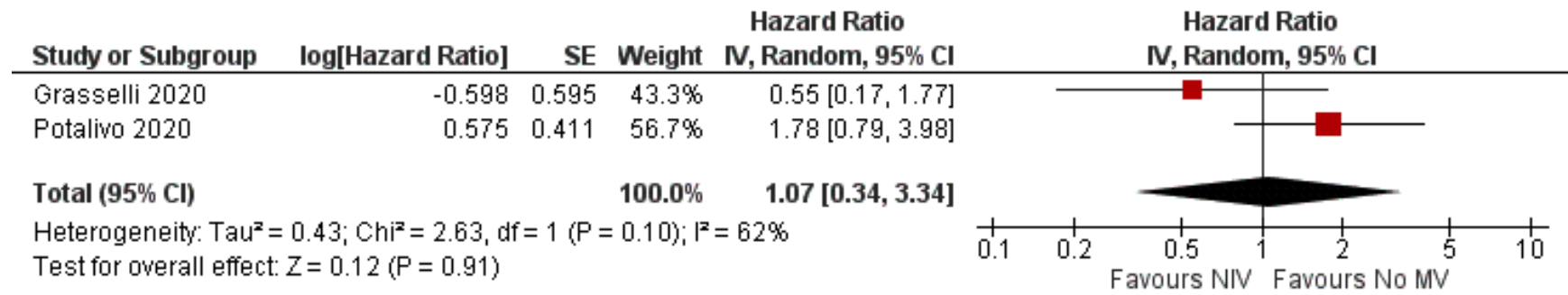| № of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty	Importance
2	observational studies	serious[a]	serious[b]	not serious	serious	none	The meta-analysis showed a pooled HR of 1.07 (0.34, 3.34). Individually, both studies demonstrated conflicting results wihere Grasselli et al. showed a hazard ratio of 0.55 (0.17, 1.77) and Potalivo demonstrated a hazard ratio of 1.78 (0.79, 3.98.	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. Concerns regarding comparability of interventions and outcome assessment.
b. There was unexplained inconsistency in the study results
c. The confidence interval of the pooled effect is wide. Although this is in part due to inconsistency, the number of participants and events is also small and we rated down for imprecision in addition to inconsistency.

Supplement Figure 2. Forest plot showing adjusted HRs of NIV (vs IMV) for mortality (4 studies included; Grasselli 2020 and Potalivo 2020 are the newly added studies).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Grasselli 2020	-0.211	0.11	34.1%	0.81 [0.65, 1.00]
Potalivo 2020	-0.511	0.266	25.3%	0.60 [0.36, 1.01]
Wang K 2020	0.479	0.331	21.6%	1.61 [0.84, 3.09]
Wang T 2020	-1.08	0.38	19.1%	0.34 [0.16, 0.72]
Total (95% CI)			100.0%	0.74 [0.46, 1.18]

Heterogeneity: Tau² = 0.16; Chi² = 10.71, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 1.27 (P = 0.20)

Supplement Figure 3. Forest plot showing adjusted HRs of NIV (vs no MV) for mortality (2 studies included; Grasselli 2020 and Potalivo 2020 are the newly added studies).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Grasselli 2020	-0.598	0.595	43.3%	0.55 [0.17, 1.77]
Potalivo 2020	0.575	0.411	56.7%	1.78 [0.79, 3.98]
Total (95% CI)			100.0%	1.07 [0.34, 3.34]

Heterogeneity: Tau² = 0.43; Chi² = 2.63, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.12 (P = 0.91)

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