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Original Article

Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression^{\star}



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ABSTRACT

Background and aims: Diabetes Mellitus (DM) is chronic conditions with devastating multi-systemic complication and may be associated with severe form of Coronavirus Disease 2019 (COVID-19). We conducted a systematic review and meta-analysis in order to investigate the association between DM and poor outcome in patients with COVID-19 pneumonia.

Methods: Systematic literature search was performed from several electronic databases on subjects that assess DM and outcome in COVID-19 pneumonia. The outcome of interest was composite poor outcome, including mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care, and disease progression.

Results: There were a total of 6452 patients from 30 studies. Meta-analysis showed that DM was associated with composite poor outcome (RR 2.38 [1.88, 3.03], p < 0.001; I^2 : 62%) and its subgroup which comprised of mortality (RR 2.12 [1.44, 3.11], p < 0.001; I^2 : 72%), severe COVID-19 (RR 2.45 [1.79, 3.35], p < 0.001; I^2 : 45%), ARDS (RR 4.64 [1.86, 11.58], p = 0.001; I^2 : 9%), and disease progression (RR 3.31 [1.08, 10.14], p = 0.04; I^2 : 0%). Meta-regression showed that the association with composite poor outcome was influenced by age (p = 0.003) and hypertension (p < 0.001). Subgroup analysis showed that the association was weaker in studies with median age \geq 55 years-old (RR 1.92) compared to <55 years-old (RR 3.48), and in prevalence of hypertension \geq 25% (RR 1.93) compared to <25% (RR 3.06). Subgroup analysis on median age <55 years-old and prevalence of hypertension <25% showed strong association (RR 3.33) *Conclusion*: DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19.

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1. Introduction

Coronavirus Disease 2019 (COVID-19) has been declared as a public health emergency by the World Health Organization (WHO) on January 30, 2020. At the time this paper is written, COVID-19 has inflicted more than 1.2 million people globally with overall mortality rate of 5.7% [1]. Although the majority of COVID-19 patients present with mild or no symptoms, some patients will develop severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death. Clinical predictors may provide vital

clues regarding efficient resource planning and allocation during a pandemic. (see Table 1)

Diabetes Mellitus (DM) is one of the most prevalent chronic conditions with devastating multi-systemic complication and was estimated to have inflicted 463 million people in 2019 [2]. It is not yet known whether people with DM are more susceptible to COVID-19, but several studies have reported the association between severe COVID-19 infection with DM [3,4]. It was postulated that the angiotensin converting enzyme 2 (ACE2) may be the plausible explanation of this association [5].

In this study, we aimed to perform a systematic review and meta-analysis in order to investigate the association between DM and poor outcome in patients with COVID-19 pneumonia. Our hypothesis is that DM is associated with poor outcome in patients with COVID-19 pneumonia. To the best of the authors knowledge, this is the first systematic review, meta-analysis, and meta-

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Table 1			
Characteristics	of the	included	studies.

Authors	Study Design	Samples	Male (%)	Overall Age (Mean/Median) (years)	Hypertension (%)	CAD/CVD (%)	DM (%)	COPD (%)	Outcome
Akbari A	Observational	440 (13/	56.4 (61.5	48	7.9 (15.3 vs	5.7 (15.3 v	7.5 (30.8	N/A	Mortality
Bai T 2020	Observational	427) 127 (36/	63 (77.8 vs	55 (67 vs 50)	28.3 (41.7 vs	2.4 (5.6 vs 1.1)	11.8 (13.9	N/A	Mortality
Cao J 2020	Retrospective Observational	91) 102 (17/	57.1) 52 (76.5 vs	54 (72 vs 53)	23.1) 27.5 (64.7 vs	(CVD) 4.9 (17.6 vs	vs 11.0) 10.8 (35.3	9.8 (23.5	Mortality
Chen 2020	Observational	85) 123 (31/	47.1) 49 (71 vs	56 (72 vs 53)	20) 33.3 (48.4 vs	2.4) 12.2 (25.8 vs	vs 5.9) 11.4 (19.4	4.9 (9.7 vs	Mortality
Chen T	Retrospective Observational	92) 274	42) 62 (73 vs	62 (68.0 vs 51.0)	38.3) 34 (48 vs 24)	7.6) 8 (14 vs 4)	vs 8.7) 17 (21 vs	3.3) 7 (10 vs 4)	Mortality
2020	Retrospective	(113/ 161)	55)			(CVD)	14)	(CLD)	
Fu L 2020	Observational Retrospective	200 (34/ 166)	49.5 (16.2 vs 67.7)	<49 (5.9 vs 28.3), 50–59 (23.5 vs 27.1), 60–69 (20.6 vs 31.3), >70 (5 vs 13.2)	50.5 (21.8 vs 12.1)	N/A	N/A	4 (50.0 vs 15.6) (CLD)	Mortality
Li K 2020	Observational Retrospective	102 (15/ 87)	58 (73 vs 55)	57 (69 vs 55)	30 (47 vs 28)	4 (13 vs 2)	15 (13 vs 15)	2 (7 vs 1)	Mortality
Luo XM	Observational	403	47.9 (57 vs	56 (71 vs 49)	28 (60 vs	8.9 (16 vs 6.6)	14.1 (25 vs	6.9 (17 vs	Mortality
2020	Reffospective	303)	44.9)	20 (20 E5)	17.5)	11 (20 0)	10.6)	5.0)	
Yuan M 2020	Retrospective	27 (10/ 17)	45 (47 vs 40)	60 (68 vs 55)	19 (50 vs 0)	11 (30 vs 0)	22 (60 vs 0)	N/A	Mortality
Zhou 2020	Observational Retrospective	191 (54/ 137)	62 (70 vs 59)	56 (69.0 vs 52.0)	30.4 (48 vs 23)	8 (24 vs 1)	19 (31 vs 14)	3 (7 vs 1)	Mortality
Guan 2020	Observational Retrospective	1099 (173/	58.1 (57.8 vs 38.2)	47 (52.0 vs 45.0)	15.0 (23.7 vs 13.4)	2.5 (5.8 vs 1.8)	7.4 (16.2 vs 5.7)	1.1 (3.5 vs 0.6)	Severe COVID-19
Hu I. 2020	Observational	926) 323	514(529	61 (65 vs 56)	32.5 (38.3 vs	12.7 (19.2 vs	146(192	(35 vs 0)	Severe
114 2 2020	Retrospective	(172/	vs 49.7)		25.8)	5.3) (CVD)	vs 9.3)		COVID-19
Li Q 2020	Observational Potrospoctivo	325 (26/	51.4 (76.9	51 (65 vs 49)	24 (46.2 vs	5.5 (19.2 vs	9.2 (19.2	1.2 (7.7 vs	Severe
Liu J 2020	Prospective	61 (17/	50.8 (58.8	40 (56 vs 41)	19.7 (35.3 vs	1.6 (5.9 vs 0)	8.2 (1.6 vs	8.2 (1.6 vs	Severe
Liu Lei	Observational	44) 51 (7/44)	vs 47.7) 62.7 (57.1	45 (52 vs 44)	13.6) 7.8 (14.3 vs	(CVD) N/A	4.5) 7.8 (57.1	4.5) N/A	Severe
2020 Ma LK	Retrospective Observational	84 (20/	vs 63.7) 57.1 (60 vs	48 (58 vs 46.5)	6.8) 14.3 (20.0 vs	6 (10 vs 4.7)	vs 0) 11.9 (35 vs	6.0 (10.0 vs	COVID-19 Severe
2020 Qin 2020	Retrospective Observational	64) 452	56.3) 52.0 (54.2	58 (61 vs 53)	12.5) 29.5 (36.7 vs	5.9 (8.4 vs 1.8)	4.7) 16.4 (18.5	4.7) (CLD) 2.6 (3.1 vs	COVID-19 Severe
	Retrospective	(286/ 166)	vs 48.2)		18.1)	(CVD)	vs 13.3)	1.8)	COVID-19
Wan 2020	Observational Retrospective	135 (40/ 135)	53.3 (52.5	47 (56 vs 44)	9.6 (10 vs 9.4)	5.2 (15 vs 1)	8.9 (22.5 vs 3 1)	0.7 (2.5 vs 0)	Severe
Wang Dan	Observational	143 (71/	51 (62 vs	58 (65 vs 44)	25.2 (43.7 vs	11.2 (16.9 vs	9.1 (12.7	7.0 (9.9 vs	Severe
2020 Wang Y	Retrospective Observational	72) 110 (38/	40.3) 43 (63.2 vs	≤40 (53%), 41−60 (21%), >60 (36%)	6.9) 20.9 (39.5 v	5.6) N/A	vs 5.6) 13.7 (21.0	4.2) 5.4 (10.5 v	COVID-19 Severe
2020	Retrospective	72)	33.3)	≤40 (7.9 vs 69.4), 41−60 (21.0 vs 18.1), >60 (71.0 vs 12.5)	11.1)		v 9.7)	2.8)	COVID-19
Yuan B 2020	Observational Retrospective	417 (92/ 325)	47.5 (53.2 vs 42.8)	45 (58 vs 41)	15.1 (28.3 vs 11 4)	N/A	7.7 (17.4 vs 4 9)	1.9 (1.1 vs 2.1)	Severe COVID-19
Zhang	Observational	221 (55/	48.9 (63.6 vs 44.0)	55 (62 vs 51)	24.4 (47.3 vs	10 (23.6 vs	10 (12.7 vs	2.7 (7.3 vs	Severe
2020	Observational	140 (59	507(500	-20 (1 7	20 (27 0	5.4)	12.1 (12.9	1.2)	COVID-15
2020	Retrospective	140 (58 vs 82)	vs 46.3)	<30(1.7 vs 4.9), 30-49(15.5 vs 34.1), 50-69 (48.3 vs 50), \geq 70 (34.5 vs 11.0)	30 (37.9 VS 24.4)	5 (6.9 VS 3.7)	vs 11.0)	1.4 (3.4 VS U)	COVID-19
Liu Y 2020	Observational Retrospective	109 (53 vs 56)	59 (52.8 vs 55.4)	55 (61 vs 49)	37 (21 vs 26)	6.4 (5.7 vs 7.1)	11 (20.8 vs 1.8)	3.7 (3.8 vs 3.6)	ARDS
Wu C 2020	Observational Retrospective	201 (84/ 117)	63.7 (71.4 vs 58.1)	51 (58.5 vs 48)	19.4 (27.4 vs 13.7)	4 (6 vs 2.6)	10.9 (19 vs 5.1)	2.5 (CLD)	ARDS
Cao 2020	Observational Retrospective	198 (19/ 176)	51 (89.5 vs 46.9)	50.1 (63.7 vs 48.6)	21.2 (31.6 vs 20.1)	6.0 (26.3 vs 3.9) (CVD)	7.6 (10.5 vs 7.3)	N/A	ICU Care
Huang 2020	Observational	41 (13/	73 (85 vs	49.0 (49.0 vs 49.0)	14.6 (15 vs	14.6 (23 vs	19.5 (8 vs	2.4 (8 vs 0)	ICU Care
Wang,	Observational	138 (36	54.3 (61.1	56 (66 vs 51)	31.2 (58.3 vs	14.5 (25 vs	10.1 (22.2	2.9 (8.3 vs	ICU Care
Dawei 2020	Ketrospective	vs 102)	vs 52.0)		21.6)	10.8)	vs 5.9)	1.0)	
Feng 2020	Observational Retrospective	141 (15/ 126)	51.1 (46.7 vs 51.6)	44 (58 vs 41)	14.9 (40.0 vs 11.9)	2.1 (6.7 vs 1.6) (CVD)	5.7 (13.3 vs 4.8)	2.8 (13.3 vs 1.6)	Disease Progression
Liu W 2020	Observational Retrospective	78 (11/ 67)	50 (63.6 vs 47.8)	38 (55 vs 37)	40 (18.2 vs 9.0)	N/A	25 (18.2 vs 4.5)	10 (9.1 vs 1.5)	Disease Progression

CAD: Coronary artery disease; COVID-19: Coronavirus disease 2019; CLD: Chronic Lung/Pulmonary Disease; CVD: Cardiovascular Disease; ICU: Intensive Care Unit; N/A: Not available.

regression that comprehensively describe the association between DM and outcome in COVID-19.

1.1. Subjects

Research articles that evaluate the association between COVID-19 and clinically validated definition of mortality, severe COVID-19, ARDS, intensive care unit (ICU care), and disease progression.

2. Material and methods

2.1. Eligibility criteria

We included all research articles in adult patients diagnosed with COVID-19 with information on DM and clinical grouping or outcome of the clinically validated definition of mortality, severe COVID-19, ARDS, ICU care, and disease progression. The following types of article were excluded: articles other than original research (e.g., review articles, letters, or commentaries); original research with samples below 20 or case reports and series; articles not in the English language; articles on research in pediatric populations (17 years of age or younger).

2.2. Search strategy and study selection

We performed systematic literature search from PubMed and EuropePMC with the search terms (1) "COVID-19" OR "SARS-COV-2" AND "Characteristics", (2) "COVID-19" OR "SARS-COV-2" AND "Diabetes", English, MEDLINE. Duplicate results were removed. The remaining articles were independently screened for relevance by its abstracts with two authors (MAL and IH). The full text of residual articles was assessed according to the inclusion and exclusion criteria. The search was finalized on April 8th, 2020 The study was carried out per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

2.3. Data extraction

Data extraction was performed independently by two authors (IH and RP), we used standardized forms that include author, year, study design, age, gender, cardiovascular diseases, hypertension, DM, need for ICU care, and severe COVID-19.

The outcome of interest was composite poor outcome that comprised of mortality, severe COVID-19, ARDS, need for ICU care, and disease progression. ARDS was defined as per World Health Organization (WHO) interim guidance of Severe Acute Respiratory Infection (SARI) of COVID-19, including the acute onset, chest imaging, and origin of pulmonary infiltrates, and oxygenation impairment [6]. Severe COVID-19 was defined as patients who had any of the following features at the time of, or after, admission: (1) respiratory distress (\geq 30 breaths per min); (2) oxygen saturation at rest \leq 93%; (3) ratio of partial pressure of arterial oxygen (PaO2) to fractional concentration of oxygen inspired air (fiO2) \leq 300 mmHg; or (4) critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) [7].

2.4. Statistical analysis

The software review Manager 5.3 (Cochrane Collaboration) and Stata version 16 were used for meta-analysis. Dichotomous variables were calculated using Mantel-Haenszel formula with random effects models regardless of heterogeneity. The effect estimate was reported as risk ratios (RRs) along with its 95% confidence intervals (Cls) for dichotomous variables, respectively. P-value was twotailed, and the statistical significance set at \leq 0.05. Random effects meta-regression was performed using restricted-maximum likelihood for pre-specified variables including age, gender, hypertension, cardiovascular disease, and COPD. Subgroup analysis was performed for each component of composite poor outcome. To assess the small-study effect, we performed regression-based Harbord's test for dichotomous outcome. Begg's funnel-plot analysis was performed to qualitatively assess the risk of publication bias.

3. Results

3.1. Study selection and characteristics

Initial search yields 298 records, and 281 records remained after the removal of duplicates. 238 records were excluded after screening the title/abstracts. After evaluating 43 full-text for eligibility, 13 full-text articles were excluded because: no outcome of interest: severe, mortality, ARDS, disease progression. 30 studies were included in the qualitative synthesis and meta-analysis [Fig. 1] [3,8–36]. There were a total of 6452 patients from 30 studies.

3.2. Diabetes and outcome

This meta-analysis showed that DM was associated with composite poor outcome (RR 2.38 [1.88, 3.03], p < 0.001; I^2 : 62%, p < 0.001) [Fig. 2]. Subgroup analysis showed that DM was associated with mortality (RR 2.12 [1.44, 3.11], p < 0.001; I^2 : 72%, p < 0.001), severe COVID-19 (RR 2.45 [1.79, 3.35], p < 0.001; I^2 : 45%, p = 0.04), ARDS (RR 4.64 [1.86, 11.58], p = 0.001; I^2 : 9%, p = 0.29), and disease progression (RR 3.31 [1.08, 10.14], p = 0.04; I^2 : 0%, p = 0.75). DM was not associated with increased need for ICU care (RR 1.47 [0.38, 5.67], p = 0.57; I^2 : 63%, p = 0.07).

3.3. Meta-regression

Meta-regression showed that the association between DM and composite poor outcome was affected by age (p = 0.003) [Fig. 3A] and hypertension (p < 0.001) [Fig. 3B], but not gender (p = 0.895), cardiovascular diseases (p = 0.5) [Fig. 3C], and COPD (p = 0.47). Multivariable meta-regression by including two covariates in single analysis showed age (p = 0.334) and hypertension (p = 0.107) effect is probably dependent on each other.

3.4. Subgroup analysis

Subgroup analysis for studies with median age \geq 55 years-old (RR 1.92 [1.56, 2.37], p < 0.001; l²: 10%, p = 0.35) showed a lower RR for composite poor outcome compared to <55 years-old (RR 3.48 [2.55, 4.77], p < 0.001; l²: 21%, p = 0.22).

Subgroup analysis for studies with prevalence of hypertension \geq 25% (RR 1.93 [1.48, 2.52], p < 0.001; I²: 58%, p < 0.003) showed a lower RR for composite poor outcome compared to prevalence of hypertension <25% (RR 3.06 [2.19, 4.26], p < 0.001; I²: 33%, p = 0.10).

Subgroup analysis for studies with median age <55 years-old and prevalence of hypertension <25% showed association with poor outcome (RR 3.33 [2.35, 4.73], p < 0.001; I^2 : 28%, p = 0.17).

3.5. Publication bias

The funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot for the association between DM and composite poor outcome [Fig. 4A]. Regression-based Harbord's test showed indication of small-study effects for DM and composite poor outcome (p = 0.004) [Fig. 4B].



Fig. 1. Prisma flowchart.

4. Discussion

This comprehensive meta-analysis of 30 studies showed that DM was associated with poor outcome that comprises of mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19. This association was influenced by age and hypertension. Further analysis based on meta-regression showed that magnitude of risk linked to DM as a single factor was greater in studies with younger and non-hypertensive patients, which is yet to be addressed by the existing literature.

Meta-regression showed that the association between DM and poor outcome was influenced by age and hypertension. Age and prevalence of hypertension was inversely proportional with the effect of DM on poor outcome. In other words, the effect estimate of DM was less in older and hypertensive patients. Subgroup analysis further demonstrates the vast difference in RR. Meta-regression also showed that age and prevalence of hypertension seemed to be dependent on one another, this is further demonstrated by subgroup analysis showing that the RR for age <55 years-old, prevalence of hypertension <25%, and both of them combined varies only slightly. The association between DM (as a single risk factor) with composite poor outcome in COVID-19 was greater in younger people and without hypertension. The presence of older age and hypertension may attenuate the association of DM with composite poor outcome. Hence, the total risk is expected to be higher in older patients with HT, but the magnitude of DM as a single risk factor is greater in younger people without hypertension.

It is not yet known whether people with DM are more susceptible to COVID-19, but several studies have reported a greater risk of severe COVID-19 in diabetic patients [3,4]. Diabetic individuals have a greater risk of respiratory infections due to compromised immune system, especially the innate immunity [5,37]. Even transient hyperglycaemia may temporarily affect innate immune responses to infection [38]. It was hypothesized that ACE2 may be the key pathfinder of COVID-19 severity in diabetic individuals [5].

ACE2 is a type 1 integral membrane glycoprotein expressed in the epithelial cells of cardiovascular, pulmonary, renal, brain and intestinal tissue, it acts by breaking down angiotensin II into angiotensin 1–7 [37,39,40]. This enzyme acts by counteracting the inflammatory actions of angiotensin II, lowering the concentration of pro-inflammatory cytokine interleukin (IL)-6, increasing the anti-inflammatory, and increasing the antioxidant action of angiotensin 1-7, escalating the levels of surfactant protein D and promoting vasodilation [41]. The novel coronavirus responsible for COVID-19 is expected to act similarly to Severe Acute Respiratory Syndrome (SARS-CoV). Both utilize ACE2 to bind and gain entry to the host pneumocytes [39]. Viral surface spike (S) protein of COVID-19 binds to ACE2 after spike protein activation by transmembrane protease serine 2 (TMPRSS2) [40]. Routine use of ACEI and ARB as a medication for chronic conditions upregulates ACE2 expression [5,37], thereby facilitating entry of SARS-CoV-2 into the

Study or Subgroup Events Total Verify Total Weight M-H. Random, 95%; C1 M-H. Random, 95%; C1 Atsat 2020 4 13 29 423 3.0% 4.481 [1.85, 10.91] Atsat 2020 6 17 5 85 2.25% 6.001 [2.07, 17.43] Cho J 2020 6 17 5 8.5 2.25% 6.001 [2.07, 17.43] Fu L 2020 7 15 2.44 87.4 116 60.9, 2.21 Lix X020 26 100 3.2 305 5.5% 2.27 [1.48, 3.79] Van M 2020 26 100 3.2 305 5.5% 2.27 [1.28, 4.03] Zhou 2020 17 5.4 196 4.05% 2.27 [1.28, 4.03] Study core 2.31 (1 = 9 (P = 0.0002); P = 72% 2.81 [1.84, 4.34] Classover COVD-19 2.31 (P = 0.0001); P = 72% 2.30 [0.86, 5.0] Gauzo 7 7 4.4 <t< th=""><th></th><th>Diabetes Mellit</th><th>us (+)</th><th>Diabetes Mell</th><th>itus (-)</th><th></th><th>Risk Ratio</th><th>Risk Ratio</th></t<>		Diabetes Mellit	us (+)	Diabetes Mell	itus (-)		Risk Ratio	Risk Ratio		
6.1.1 Mortality Actent 2020 4 13 22 442 3.6% 4.49 [1.86, 10.91] Bal T 2020 5 36 10 91 3.1% 1.26 [0.46, 3.44] Chan 2020 6 31 8 22 3.2% 2.23 [0.44, 5.91] Chan 2020 2 6 31 13 22 3.2% 2.23 [0.44, 5.91] Chan 2020 2 7 100 32 110 5.5% 2.37 [1.48, 3.70] Tub X020 2 7 100 32 100 5.2 40 5% 2.37 [1.48, 3.70] Tub X020 2 7 100 32 110 5.5% 2.37 [1.44, 3.41] Chan 2020 17 2 44 10 137 5.5% 2.27 [1.42, 4.3, 7.9] Tub X020 17 43 10 137 5.5% 2.27 [1.42, 4.3, 7.9] Tub X020 17 43 10 137 5.5% 2.27 [1.42, 4.3, 7.9] Tub X020 17 43 10 17 0.7% 2.12 [1.42, 4.3, 7.9] Tub X020 17 43 10 137 5.5% 2.27 [1.42, 4.3, 7.9] Tub X020 17 43 10 17 0.7% 2.12 [1.42, 4.3, 7.9] Tub X020 17 43 10 17 0.7% 2.12 [1.42, 4.3, 7.9] Tub X020 17 43 10 2.9 11 Heterogenety: Tat ² = 0.23 (1.6 ² = 9 0.000.); F = 72% Tub X020 3 17 2 53 926 5.7% 2.28 [1.94, 4.34] Tub X020 3 17 2 54 151 4.5% 2.07 [1.15, 5.72] Tub X020 3 17 2 54 155 4.5% 2.07 [1.15, 5.72] Tub X020 3 17 2 54 155 4.5% 2.07 [1.15, 5.72] Tub X020 3 17 2 54 155 4.5% 2.07 [1.15, 5.72] Tub X020 4 7 0 3 64 2.4% 7.47 [1.12, 28.21] Ma KL 2020 7 7 20 3 64 2.4% 7.47 [1.12, 28.21] Ma KL 2020 7 7 20 3 64 2.4% 7.47 [1.12, 28.21] Ma KL 2020 7 7 20 3 64 2.4% 7.47 [1.12, 28.21] Ma KL 2020 7 7 55 15 168 3.7% 1.41 [0.61, 52.7] Yuan B 2020 8 38 7 77 3.4% 2.24 [0.64, 53] Tub X020 8 38 7 77 3.4% 2.24 [1.64, 4.70] Yuan 2020 18 38 7 77 3.4% 2.24 [1.64, 53] Tub X020 19 7 55 15 168 3.7% 1.41 [0.61, 52.7] Zhang J 2020 18 64 6 117 3.5% 3.77 [1.41 [0.61, 52.7] Yuan 2020 18 64 6 117 3.5% 3.77 [1.41 [0.61, 52.7] Yuan 2020 18 64 6 117 3.5% 3.77 [1.41 [0.61, 52.7] Tub X020 19 64 6 117 3.5% 3.77 [1.41 [0.61, 52.7] Panag J 2020 19 64 6 117 3.5% 3.77 [1.41 [0.61, 52.6] Tub X020 19 7 55 15 168 3.7% 1.44 [0.63, 5.67] Tub X020 10 64 6 17 3.5% 3.77 [1.41 [0.61, 5.56] Subbola (9% C) 7 13 7 7 173 4.7% 4.54 [1.68, 11.68] Tub X020 10 64 6 17 7 3.5% 3.77 [1.41 [0.61, 5.56] Tub X020 10 64 6 17 7 3.5% 4.37 [1.41 [0.14] 7.2 2.60] F 2.60 (1.40 Con Char = 1.0, dr = 1.9 = 0.75); P = 0.5% Tub X020 10 8 38 6 102 3.2	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI		
Abbri 2020 4 13 20 4 13 20 423 3.6% 4.69 [1.85, 10.91] To 2020 5 36 10 91 3.5% 5.2% 2.23 [0.46, 5.41] Chan 2020 6 17 5 85 2.9% 6.00 [2.07, 17.43] Chan 2020 2 113 23 114 5.5% 1.46 [0.08, 3.27] Chan 2020 2 113 23 114 5.5% 1.46 [0.08, 3.27] Lu SM 2020 2 5 100 32 303 5.5% 2.37 [1.48, 3.79] To 31 events 125 231, df = 9 (P = 0.0002); H = 72% Ext 2020 17 54 19 137 5.0% 2.27 [1.28, 4.03] Subtotal (95% C1) 423 112 4.61 9.4% 2.40 (9.68, 3.27] To 31 events 125 231, df = 9 (P = 0.0002); H = 72% Ext 2020 3 172 54 9.4% 2.43 [1.64, 4.34] To 21 events 22.3 C μ^{-2} 0.2001 (F = 72% Ext 2020 3 172 54 9.4% 2.43 [1.64, 4.34] To 24 events 22.3 2.20 = 0.0001; H = 72% Ext 2020 3 172 24 51 4.5% 3.88 [1.7, 12.34] Lu 2020 3 172 24 51 4.5% 3.88 [1.7, 12.34] Lu 2020 3 172 24 51 4.5% 3.88 [1.7, 12.34] Lu 2020 3 172 24 51 4.5% 3.88 [1.7, 12.34] Lu 2020 3 172 24 4.5% 3.27 [1.15, 3.72] Can 2020 5 26 25 299 3.6% 2.20 [1.15, 3.72] Lu 2020 3 172 244 155 4.5% 2.30 [1.2, 12.34] Lu 2020 3 172 244 155 4.5% 2.30 [1.2, 12.34] Lu 2020 3 172 244 155 4.5% 2.30 [1.2, 12.34] Lu 2020 3 172 244 155 4.5% 3.20 [1.2, 12.34] Lu 2020 3 7 20 34 2.4% 7.47 (2.13, 8.21] Can 2020 9 40 3 95 2.4% 7.17 (1.2, 13, 8.21] Can 2020 9 40 3 95 2.4% 7.17 (1.2, 13, 8.21] Can 2020 9 40 3 95 2.4% 7.17 (1.2, 13, 8.21] Can 2020 9 40 3 95 2.4% 7.17 (1.2, 13, 8.21] Can 2020 9 40 3 95 2.4% 7.71 (1.2, 13, 8.21] Can 2020 9 40 3 95 2.4% 7.71 (1.2, 13, 8.21] Can 2020 1 16 53 1 56 15 186 3.7% 1.40 [1.0, 12, 1.2, 12, 1.2, 1.2, 1.2, 1.2, 1.2,	6.1.1 Mortality									
Bail 2020 5 36 10 91 3.1% 1.26 [0.46, 3.44] Chen 2020 6 31 8 92 3.2% 2.23 [0.46, 5.81] Chen 2020 24 34 113 23 161 5.5% 1.40 [0.82, 2.61] Ful 2020 25 34 111 168 6.6% 1.14 [0.82, 2.61] Ful 2020 7 10 24 87 4.5% 1.36 [0.84, 3.61] Ful 2020 7 10 24 87 4.5% 1.36 [0.84, 3.61] Ful 2020 7 10 24 87 4.5% 1.36 [0.84, 3.61] Total avents 128 281 Heterogeneity: Tau ² - 0.35 (CH ² = 3.23, 1.6f = 9 ($P = 0.0002$); $P = 72\%$ Tast for overall effect 2 = 3.29 ($P = 0.0001$) 6.12 Severe COVID-19 Guan 2020 9 17 20 3 64 2.4% 7.47 [2.13, 8.61] Heterogeneity: Tau ² - 0.35 (CH ² = 3.23, 1.6f = 9 ($P = 0.0002$); $P = 72\%$ Tast for overall effect 2 = 3.29 ($P = 0.0001$) 6.12 Severe COVID-19 Guan 2020 5 26 9 ($P = 0.0002$); $P = 72\%$ Tast for overall effect 2 = 3.29 ($P = 0.0001$) 6.12 Severe COVID-19 Guan 2020 4 17 20 3 64 2.4% 7.47 [2.13, 8.61] Wang Dan 2020 9 7 10 4.47 7 20 3 64 2.4% 7.47 [2.13, 8.61] Wang Dan 2020 9 7 10 4.47 7.27% 2.280 [1.84, 4.34] Tast for overall effect 2 = 3.29 ($P = 0.0001$) 6.12 AUD Wang Dan 2020 9 7 14 7.2 3.4% 2.17 [0.85, 5.52] Wang Dan 2020 16 92 116 325 4.6% 3.53 [1.94, 6.78] Tast for overall effect 2 = 3.29 ($P = 0.0001$) 6.14 AUD 7.15 (1.05 (1.05 4.10), $P = 4.17$, 2.4% (1.10, 2.1, 3.27] Tast for overall effect 2 = 3.29 ($P = 0.0001$) 6.14 AUD 7.16 (1.05 4.5 2.1] 7.16 (1.05 4.5 2.2] 7.16 (1.05 4.5 4.4 2.4 4.5 1.5 2.5 4.4 4.5 4.5 4.5 4.5 4.5	Akbari 2020	4	13	29	423	3.6%	4.49 [1.85, 10.91]			
Cao J 2020 6 17 5 88 2 94% $6.00 [2.07, 17.4]$ Chen 7020 24 113 23 161 5.3% 1.40 [0.89, 2.60] Chen 7020 26 34 111 66 66% 1.41 (0.92, 1.42] Li K 2020 7 15 24 87 4.7% 1.60 [0.89, 3.21] Li K 2020 25 100 32 303 55% 2.37 [1.43, 3.79] Yuan M 2020 6 10 0 17 0.7% 2.127 [1.32, 3.41.64] Total sents 128 261 Heterogeneity 17 0.2% Che ² 3.231, df = 9 [$e = 0.0002$]; $\mu = 25\%$ Test for overall effect 2 = 3.82 ($\mu = 0.0003$); $\mu = 1.0\%$ Van M 2020 5 26 200 33 17 2 44 0.5% 2.27 [1.44, 3.11] Total sents 128 283 [1.84, 4.34] Total sents 190 Tot 38 41 38 58 2.45% [7.12 [1.28, 2.32 [1.34] Total sents 190 Tot 38 41 38 59 2.45% [7.12 [1.28, 2.32 [1.34] Total sents 190 Tot 38 48 5 2.45% [7.12 [1.28, 2.36] Total sents 190 Tot 38 48 5 2.46% [7.12 [1.28, 2.36] Total sents 28 3.20 ($\mu = 0.001$); $\mu = 0.200$; $\mu = 0.001$; $\mu = 0.$	Bai T 2020	5	36	10	91	3.1%	1.26 [0.46, 3.44]			
Chen 2020 6 31 8 92 3.2% 2.23 [0.84, 591] Fu L 2020 26 34 113 23 161 6.6% 1.14 [0.98, 2.42] Fu L 2020 7 15 24 67 4.7% 1.68 [0.98, 2.59] Fu L 2020 7 15 24 67 4.7% 1.68 [0.98, 2.59] Lu X A020 25 100 32 303 5.5% 2.37 [1.48, 3.79] Zhou 2020 6 10 0 17 0.7% 21.27 [1.28, 4.31] Zhou 2020 17 54 19 137 5.0% 2.27 [1.28, 4.31] Total events 128 2.31, df = 9 (P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.23, Ch ⁻ = 32.31, df = 9 (P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.23, Ch ⁻ = 32.31, df = 9 (P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁻ = 32.31, df = 9 (P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 32.31, df = 9 (P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 32.31, df = 9 (P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 1.79, df = 12, P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 1.79, df = 12, P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 1.79, df = 12, P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 1.79, df = 12, P = 0.002), P = 72% Haterogenety, Tau ⁺ = 0.32, Ch ⁺ = 1.79, df = 12, P = 0.002), P = 45%, Tatal (1.06, 1.327), Tatal (1.06, 1.337), Tatal (1.06, 1.337), Tatal (1.06, 1.337), Tatal (1.36, 1.	Cao J 2020	6	17	5	85	2.9%	6.00 [2.07, 17.43]			
Chen T2020 24 113 23 161 5.3% 1.49 [0.88, 2.80] T 12020 26 34 111 166 6.6% 1.14 [0.92, 1.42] Li K 2020 7 15 24 67 4.7% 1.66 [0.98, 3.21] Li K 2020 25 100 32 303 55% 2.57% 1.248, 3.79] Yaan M 2020 6 10 0 17 0.7% 21.27 [1.32, 34.184] Total events 126 23.31 df = 9 ($P = 0.0002$); $P = 7.8\%$ Test for overal effect: $Z = 3.82$ ($P = 0.000$) E.1.28 events 2.1 df = 9 ($P = 0.0002$); $P = 7.8\%$ Test for overal effect: $Z = 3.82$ ($P = 0.000$) Li U 2020 5 26 26 25.7% 2.83 [1.84, 4.34] T 12 2020 5 26 26 25.2% 3.86% 2.30 [0.86, 5.50] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.50] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.50] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.50] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.70] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.70] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.70] Li U 2020 5 26 26 22.98 3.6% 2.30 [0.86, 5.70] Li U 2020 4 7 0 44 7.0 44 0.7% 50.63 [3.01.88.2.41] Wan 2020 5 3 266 22.166 55% 1.44 (0.88, 2.21] Wan 2020 5 3 266 22.166 55% 1.44 (0.88, 2.21] Wan 2020 5 3 266 22.166 55% 1.44 (0.88, 2.21] Wan 2020 6 3 38 7.7 2.5 44.8% 2.47 [0.168, 2.21] Wan 2020 7 5 5 16 166 3.2% 1.26 [0.20, 7.77] Zhang 2.007 7 55 16 166 3.2% 1.26 [0.27, 7.78] Zhang 2.020 16 8 48 9 122 3.6% 2.30 [0.47, 1.07] Zhang 2.020 17 55 176 166 3.2% 3.7% 1.44 [0.61, 3.27] Zhang 2.020 16 8 46 1.17 3.3% 3.71 [1.52, 3.08] Wu 2.020 11 53 1 56 1.2% 1.162 [1.55, 66.55] Wu 2.020 11 53 1 56 1.2% 3.6% 2.30 [0.21, 2.56] Wu 2.020 11 53 1 56 1.2% 3.6% 2.30 [0.21, 2.56] Wu 2.020 11 53 1 56 1.2% 3.7% 1.44 [0.51, 3.57] Total events 11 26 Heterogenety: Tat' = 0.06; Ch' = -1.0, df = 1 ($P = 0.2.9$); $P = 9\%$ Test for overal effect: $Z = 5.63$ ($P = 0.0.01$); $P = 63\%$ Test for overal effect: $Z = 5.69$ ($P = 0.0.01$); $P = 63\%$ Test for overal effect: $Z = 2.05$ ($P = 0.0.01$); $P = 63\%$ Test for overal effect: $Z = 0.26$ ($P = 0.0.01$); $P = 63\%$ Test for overal effect: $Z = 0.00$; $P = 0.00$; $P = 0.000$; $P = 0.000$; $P = 0.0000$; $P = 0.0000$; $P = 0.0000$; $P = 0.0000$; $P = 0.00000$;	Chen 2020	6	31	8	92	3.2%	2.23 [0.84, 5.91]			
Full 2020 26 34 111 166 6.6% 1.14 [0.62 1.42] Luk 2020 7 16 24 87 4.7% 1.60 [0.89, 3.21] Luc XM 2020 6 10 0 32 303 5.5% 2.37 [1.48, 3.79] Zhou 2020 17 54 19 137 5.0% 2.27 [1.28, 34.184] Zhou 2020 17 54 19 137 5.0% 2.27 [1.28, 34.184] Zhou 2020 17 54 19 137 5.0% 2.27 [1.28, 34.184] Zhou 2020 17 54 19 137 5.0% 2.27 [1.28, 34.184] Total events 128 ($p = 0.0001$) F 0.0002($p = 0.0002$), $p = 0.0002$, $p = 0.002$,	Chen T 2020	24	113	23	161	5.3%	1.49 [0.88, 2.50]			
Lik 2020 7 15 24 87 4.7% 169 [0.8, 3.21] Lik 2020 25 100 32 303 5.5% 2.37 [1.43, 37] Yuan M 2020 6 10 0 17 0.7% 21.27 [1.32, 31.144] Subtal (95% Ct) 2 43 152 40.6% 21.27 [1.32, 31.144] Subtal (95% Ct) 2 43 173 53 926 5.7% 2.83 [1.84, 4.34] Heterogeneity: Tau ² 0.25, Ch ² = 32.31, d ² = 9 (P = 0.0002); P = 72% Tast for overall effect Z = 3.26 (P = 0.0001) 61.2 Severe COVID-19 Guan 2020 5 26 25 299 36% 2.30 [0.46, 5.50] Liu L 2020 3 17 2 44 151 4.5% 2.07 [1.15, 3.72] Liu L 2020 3 17 2 44 15% 4.88 [0.71, 2.12] Liu L 2020 3 17 2 44 15% 4.88 [0.71, 2.12] Liu L 2020 3 17 2 44 15% 4.88 [0.71, 2.12] Liu L 2020 3 17 2 44 10 5% 5.65 [2.5] Wang Dan 2020 9 47 3 0 44 0.5% 50.65 [3.01, 82.64 [1] Wang Dan 2020 9 71 4 72 2.7% 2.28 [1.64, 3.47] Wang Dan 2020 9 77 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang Jourg 100 173 Heterogeneity: Tau ² = 0.15; Ch ² = 21.75, df = 12 (P = 0.04); P = 45% Tast for overall effect Z = 3.68 (P < 0.0001) 6.13 ANDS Subtal (95% Ct) 1055 2566 44.8% 2.45 [1.79, 3.35] Liu V 2020 16 53 (P < 0.0001) 6.13 ANDS Liu V 2020 11 53 1 66 12% 11.62 [1.55, 66.95] Subtal (95% Ct) 1055 2566 44.8% 2.45 [1.79, 3.35] Chall events 190 173 Heterogeneity: Tau ² = 0.80; (P = 0.07); P = 9% Tast for overall effect Z = 5.63 (P < 0.0001) 6.13 ANDS Liu Y 2020 1 1 53 1 66 12% 11.62 [1.55, 66.95] Wang Dan 200 9 2 19 13 77 173 4.7% 4.54 [1.86, 11.56] Altan 2 = 5.63 (P < 0.0001) 6.13 ANDS Liu Y 2020 1 1 53 1 166 12% 11.45 [1.55, 65.95] Wang Dan 200 9 2 19 13 77 173 4.7% 4.54 [1.86, 11.56] Altan 2 = 5.63 (P < 0.0001) 6.13 ANDS Liu Y 2020 1 1 53 1 166 12% 12% 11.62 [1.55, 66.95] Wang Dan 20 (P = 0.07); P = 9.07; P = 9.05 Tast for overall effect Z = 3.26 (P = 0.07); P = 6.37; Heterogeneity: Tau ² = 0.80 (P = 0.57); 6.15 Dissere Copy (P = 0.40; P = 0.7); P = 0.07;	Fu L 2020	26	34	111	166	6.6%	1.14 [0.92, 1.42]	-		
Luo XM 2020 25 100 32 303 5.5% 2.37 [1.48, 3.79] Zhuo 2020 17 54 19 137 5.0% 2.27 [1.28, 341.30] Zhuo 2020 17 54 19 137 5.0% 2.27 [1.28, 341.30] Zhuo 2020 17 54 19 137 5.0% 2.27 [1.28, 341.30] Zhuo 2020 17 2.31, df = 9 ($P = 0.0002$); $P = 72\%$ Test for overall effect. Z = 3.82 ($P = 0.0002$); $P = 0.0002$; $P = 72\%$ Total events 126 2.3; $df = 9 (P = 0.0002)$; $P = 72\%$ Test for overall effect. Z = 3.82 ($P = 0.0002$); $P = 0.0002$; $P = 72\%$ Total events 127 44 151 4.4% 2.07 [1.15, 3.72] Lu J 2020 5 228 25 29 3.6% 2.30 [0.96, 5.50] Lu J 2020 4 7 0 44 7.5% 3.88 [0.71, 22.4] Ma KL 2020 7 20 3 64 2.4% 7.47 [2.13, 22.4] Ma KL 2020 7 20 3 64 2.4% 7.47 [2.13, 22.4] Wang Dan 2020 9 7 12 0 3 64 2.4% 7.47 [2.13, 22.4] Wang Dan 2020 9 7 14 72 2.4% 2.40 [0.48, 5.52] Zhang 2020 16 328 7 72 3.4% 2.17 [0.85, 5.52] Zhang 2020 16 59 2.69 2.80 [% 1.28, 0.14] Wang Dan 2020 16 59 2.83 (% 1.26 [1.40, 1.32] Zhang 2020 16 59 2.83 (% 1.26 [1.40, 1.32] Zhang 2020 16 59 2.83 (% 1.26 [1.40, 1.32] Zhang 2020 11 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang 2020 16 98 4 0 13 2596 4.43% 2.45 [1.48, 11.58] Total events 190 Total events 190 Total events 190 Total events 27 7 Total events 11 28 ($P = 0.0001$) 5.1 ARDS Luv 2020 11 55 1 28% 1.45 [0.35, 5.65] Huang 210.5 ($D^{H} = 21, 75, df = 12 (P = 0.04); P = 45\%$ Test for overall effect. Z = 5.80 ($P = 0.0001$) 5.1 ARDS Luv 2020 11 55 (1.16 2.2 = 0.16 ($P = 0.75$; $P = 9\%$ Test for overall effect. Z = 5.20 ($P = 0.001$) 5.1 ALCU Care Can 2020 2 1 15 6 128 19% 2.80 (0.62, 12.65] Huang 2020 1 2 15 6 128 19% 2.80 (0.62, 12.65] Huang 2020 2 2 15 6 128 19% 2.80 (0.62, 12.65] Huang 2020 2 2 15 6 128 19% 2.80 (0.62, 12.65] Huang 2020 2 2 15 6 128 19% 2.80 (0.62, 12.65] Huang 2020 2 2 15 6 128 19% 2.80 (0.62, 12.65] Huang 2020 ($P = 0.00$) Test for overall effect. Z = 0.00 ($P = 0.75$; $P = 0\%$ Test for overall effect. Z = 0.00 ($P = 0.75$; $P = 0\%$ Test for overall effect. Z = 0.00 ($P = 0.75$; $P = 0\%$ Test for overal effect. Z = 0.00 ($P = 0.75$;	Li K 2020	7	15	24	87	4.7%	1.69 [0.89, 3.21]			
Yuan M 2020 6 10 0 17 0.7% 21.27 [1.32, 341.44] Subtol (26% C) 7 4 54 19 137 5.0% 2.27 [1.32, 341.44] Subtol (26% C) 7 4 23 1 1562 40.6% 2.12 [1.44, 3.11] Label events 126 251 Heterogeneity: Tau ² = 0.23, 0.1 ⁴ = 9 (P = 0.0002); P = 72% Tast for overall effect 2 = 3.28 (P = 0.0001) 6.1.2 Severe COVID-19 Guan 2020 2 26 173 53 926 5.7% 2.83 [1.84, 4.34] Lu 2020 3 172 14 151 4.9% 2.07 [1.15, 3.72] Lu 2020 3 172 2 44 17 4.9% 2.07 [1.15, 3.72] Lu 2020 3 177 2 44 1.5% 3.88 [0.17, 21.24] Lu 1.2020 3 177 2 44 1.5% 3.88 [0.17, 21.24] Lu Lu 2020 3 177 2 44 0.7% 50.85 [1.01, 6.52, 14] Ma 1.2020 7 203 64 2.27 166 5.5% 1.40 [0.88, 2.21] Ma 2.2020 9 7 45 15 166 5.5% 1.40 [0.88, 2.21] Ma 2.2020 9 7 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang 2.020 8 58 9 82 3.6% 1.26 [1.58, 5.52] Zhang 2.020 8 58 9 82 3.6% 1.26 [1.58, 5.52] Zhang 2.020 16 525 4.46% 3.7% 1.41 [0.61, 3.27] Zhang 2.020 8 58 9 82 3.6% 1.26 [1.58, 5.52] Zhang 2.020 17 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang 2.020 18 58 9 82 3.6% 1.26 [1.58, 5.52] Zhang 2.020 11 53 1 56 1.2% 11.82 [1.55, 86.95] Subtol (6% C) 1 105 7 2.60 4.48% 2.45 [1.78, 3.36] Tat for overall effect 2 = 3.28 (P = 0.000)! 6.1.3 ARDS Lu Y 2020 11 53 1 166 1.2% 11.82 [1.55, 86.95] Wu C 2020 16 84 6 117 3.4% 4.48 [1.86, 11.58] Alterogeneity: Tau ² = 0.03; Ch ² = 1.75, df = 12 (P = 0.04); P = 45% Tast for overall effect 2 = 3.28 (P = 0.07); P = 9\% Tast for overall effect 2 = 3.28 (P = 0.07); P = 9.0% Tast for overall effect 2 = 3.28 (P = 0.07); P = 9.0% Tast for overall effect 2 = 3.28 (P = 0.07); P = 0.07]; P = 3% Tast for overall effect 2 = 3.29 (P = 0.07); P = 0.07]; P = 6.3% Tast for overall effect 2 = 3.29 (P = 0.07); P = 6.3% Tast for overall effect 2 = 2.09 (P = 0.57); P = 0.0% Tast for overall effect 2 = 2.09 (P = 0.07); P = 0.0% Tast for overall effect 2 = 2.09 (P = 0.07); P = 0.0% Tast for overall effect 2 = 2.09 (P = 0.07); P = 0.0% Tast for overall effect 2 = 2.09 (P = 0.07); P = 0.0% Tast for overall effect 2 = 2.09 (P = 0.07); P = 0.0% Tast for over	Luo XM 2020	25	100	32	303	5.5%	2.37 [1.48, 3.79]	-		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Yuan M 2020	6	10	0	17	0.7%	21.27 [1.32, 341.84]			
Subtal (95% C) 423 152 40.8% 2.12 [1.44, 3.11] Heterogeneity: Tau" = 0.23; Chi" = 32.31; d = 9 (P = 0.0002); P = 72% Test for overall effect Z = 3.82 (P = 0.001) 6.12 Severe COVID-19 Guan 2020 28 173 53 926 5.7% LU Q 2020 3 172 41 151 4.9% 2.07 [1.15, 3.72] LU Q 2020 5 26 25 299 3.8% 2.30 [0.96, 5.50] LU Q 2020 4 7 0 44 0.7% 50.63 [3.01, 682, 14] Ma KL 2020 7 7 20 3 64 2.4% 7.47 [2.13, 28.61] Ma KL 2020 7 7 20 3 64 2.4% 7.47 [2.13, 28.1] Ma KL 2020 9 71 4 72 2.4% 1.40 [0.88, 2.11] Ma KL 2020 9 71 4 72 2.4% 1.40 [0.88, 2.21] Wang Dan 2020 9 71 4 72 2.4% 1.47 [2.13, 28.5] Wang Y 2020 8 38 7 72 3.4% 2.217 [0.85, 5.52] Yuan B 2020 16 92 16 325 4.4% 3.53 [1.84, 6.79] Zhang J 2020 8 58 9 62 3.6% 1.28 [0.74, 7.07] Wang Y 2020 8 58 9 62 3.6% 1.28 [0.74, 7.07] Yuan B 2020 16 92 16 325 4.4% 3.53 [1.84, 6.79] Zhang J 2020 8 58 9 62 3.6% 1.28 [0.52, 3.06] 2.45 [1.76, 3.32] Total events 190 713 Heterogeneity: Tau" = 0.4%; Chi" = 21.7%, df = 12 (P = 0.04); P = 45% Test for overall effect Z = 5.63 (P < 0.0001) 6.13 ARDS Lu Y 2020 1 1 53 1 56 12% Hueng 2020 2 1 1 6 31 1 56 1.2% Total events 27 7 7 Heterogeneity: Tau" = 0.6%; Chi" = 5.44, df = 2 (P = 0.07); P = 63% Test for overall effect Z = 0.56 (P = 0.07); 6.13 Clu Events 27 Total events 11 26 Hueng 2020 1 1 3 7 28 1.2% 0.37 [1.15, 9.09] Hueng 2020 2 1 15 6 128 Hueng 2020 1 1 3 7 128 3.4% 3.31 [1.06, 1.15] For overall effect Z = 0.56 (P = 0.07); 6.15 Disease Progression Feng 2020 2 15 6 128 Heterogeneity: Tau" = 0.86; Chi" = 5.44, df = 2 (P = 0.07); P = 63% Test for overall effect Z = 0.56 (P = 0.57) 6.15 Disease Progression Feng 2020 2 1 15 6 128 Heterogeneity: Tau" = 0.06; Chi = 5.44, df = 2 (P = 0.07); P = 63% Test for overall effect Z = 0.36 (P = 0.001) 6.14 Lift Stability (PSK C)) 170 708 7.473 100.0% 2.38 [1.88, 3.03] Hueng 2020 4 0 16 (P = 0.001); P = 63% Total events 4 9 Heterogeneity: Tau" = 0.2; Chi = 5.56, df = 20 (P = 0.0001); P = 62% Total events 4 0 9 Heterogeneity: Tau" = 0.2; Chi = 7.56, df = 29	Zhou 2020	17	54	19	137	5.0%	2.27 [1.28, 4.03]	-		
Total events 126 261 Heterogeneity: Tau" = 0.23; Ch" = 21, df = 9 (P = 0.0002); P = 72%. Test for overall effect: $2 = 3.82$ ($P = 0.0001$) 6.1.2 Severe COVID-19 Cuan 2020 33 172 14 151 4.9% 2.07 [1.15, 3.72] LU 2020 3 172 244 15% 3.88 [0.71, 21.24] LU 1.2020 4 7 0 44 0.7% 50.656 [30.1 68.21] Ma KJ 2020 7 20 3 64 2.4% 7.47 [2.13, 26.21] Ma KJ 2020 7 20 3 64 2.24% 7.47 [2.13, 26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13, 26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13, 26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13, 26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13, 26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13, 26.21] Wang Da 2020 16 92 616 56% 1.44.00 [38, 2.23] Wang Da 2020 7 55 15 166 3.7% 4.210 [0.85, 5.52] Una 8.2020 16 92 105 2506 44.8% 2.45 [1.78, 3.35] Total events 190 173 Heterogeneity: Tau" = 0.43; Ch" = 21.75, df = 12 ($P = 0.04$); $P = 45\%$ Test for overall effect: $2 = 5.03$ ($P = 0.001$) 6.1.3 AROS Lu 2020 1 1 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C.2020 1 1 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C.2020 1 1 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C.2020 1 1 53 1 66 3.3% 3.71 [1.52, 9.09] Subtotal (95% CI) 1 37 7 7 Heterogeneity: Tau" = 0.06; Ch" = 1.10, df = 1 ($P = 0.29$); $P = 9\%$ Test for overall effect: $2 = 0.50$ ($P = 0.07$); $P = 63\%$ Test for overall effect: $2 = 0.50$ ($P = 0.07$); $P = 63\%$ Test for overall effect: $2 = 0.50$ ($P = 0.07$); $P = 63\%$ Test for overall effect: $2 = 0.50$ ($P = 0.07$); $P = 63\%$ Total events 1 1 2 6 Heterogeneity: Tau" = 0.8; Ch" = 5.44, df = 2 ($P = 0.07$); $P = 63\%$ Test for overall effect: $2 = 0.50$ ($P = 0.07$); $P = 63\%$ Total events 1 1 2 6 Heterogeneity: Tau" = 0.05; Ch" = 5.44, df = 2 ($P = 0.07$); $P = 63\%$ Total events 1 1 2 6 Heterogeneity: Tau" = 0.05; Ch" = 0.0, df = 1 ($P = 0.75$; $P = 0\%$ Test for overall effect: $2 = 2.00$ ($P = 0.000$) Total events $4 = 9$ Heterogeneity: Tau" = 0.23; ($P = 0.0000$); $P = 0.0000$ Total events $4 = 0.23; (P = 0.00000); P = 0.00000Total events 256 = 156, d = 26(P = 0.0$	Subtotal (95% CI)		423		1562	40.6%	2.12 [1.44, 3.11]	◆		
Heterogeneity: Tau" = 0.23; Chr" = 22.31; df = 9 ($P = 0.0002$); $P = 72%$. Test for overall effect Z = 3.82 ($P = 0.0001$) 6.1.2 Severe COVID-19 Guan 2020 28 173 53 926 5.7% 2.83 [1.84, 4.34] HL 2020 35 26 25 299 3.8% 2.30 [0.96, 5.50] LU Q 2020 5 26 25 299 3.8% 2.30 [0.96, 5.50] LU Q 2020 4 7 0 44 0.7% 50.6313.01, 822.14] Ma KL 2020 7 20 3 64 2.4% 7.47 [2.13, 2.821] Char 2020 9 40 3 95 2.4% 7.47 [2.13, 2.821] Char 2020 9 71 4 72 2.4% 2.28 [1.84, 6.79] Vana 2020 9 71 4 72 3.4% 2.17 [0.86, 5.22] Vana 9200 8 38 7 7.23 3.4% 2.217 [0.86, 5.22] Vana 9200 16 92 16 3.25 4.46% 3.55 [1.84, 6.79] Vana 0200 7 55 15 15 66 3.7% 1.41 [0.61, 3.27] Zhang J 2020 8 58 9 262 3.6% 1.28 [0.52, 3.06] Zhang Guap 2020 7 55 15 15 64 3.3% 1.28 [0.52, 3.06] Subtotal (f5% Ct) 105 2566 44.8% Subtotal (f5% Ct) 105 7 2.7% 7 Heterogeneity: Tau" = 0.8; Chr" = 21.75, df = 12 ($P = 0.04$); $P = 45\%$ Test for overall effect Z = 5.63 ($P < 0.00001$) 6.1.3 ARDS Lu V 2020 1 1 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C 2020 2 11 53 1 73 173 4.7% 4.64 [1.86, 11.56] Total events 11 26 (2.9); $P = 0\%$ Test for overall effect Z = 0.56 ($P = 0.07$); $P = 6\%$ Test for overall effect Z = 0.56 ($P = 0.07$); $P = 6\%$ Test for overall effect Z = 0.56 ($P = 0.07$); $P = 6\%$ Test for overall effect Z = 0.56 ($P = 0.7$); 6.1.3 Discase Progression Feng 2020 2 15 6 128 1.9% 2.80 [0.62, 12.65] LU W 2020 2 1 13 7 1.2% 1.45 [0.35, 5.95] Huang 2020 2 15 6 128 1.9% 2.80 [0.62, 12.65] LU W 2020 2 1 1 3 7 1.2% 1.45 [0.35, 5.95] Huang 2020 2 2 15 6 128 1.9% 2.80 [0.62, 12.65] LU W 2020 2 2 15 6 128 1.9% Subtotal (65% Ct) 2 2 5 6.7 1.9% Test for overall effect Z = 0.9 ($P = 0.001$): For a coreal effect Z = 0.9 ($P = 0.001$): For a (4.64 (1.66, 1.76, 1.16] Subtotal (65% Ct) 2 2.6 1.3 3 .4% 3.31 [1.08, 10.14] Total events 11 26 ($P = 0.000$; $P = 0.0000$; $P = 0.0000000000000000000000000000000000$	Total events	126		261						
Test for overall effect: $2 = 3.82$ ($P = 0.0001$) 6.1.2 Severe COVID-19 Count 2020 33 172 14 151 4.9% 2.07 (1.15.3.72) U 2020 5 26 25 299 3.6% 2.03 (1.64.4.34) 10 2020 3 172 2 44 15% 3.88 [0.71.21.24] U 1.1 (2020 4 7 0 44 0.7% 5.05.65] (0.1 (2000)) Mark 2020 7 2.0 3 64 2.4% 7.47 [2.13.26.21] Mark 2020 7 2.0 3 64 2.2% 7.47 [2.13.26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13.26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13.26.21] Wang Da 2020 9 71 4 72 2.4% 7.47 [2.13.26.21] Wang Da 2020 9 71 4 72 2.2% 2.28 [0.74.70] Wang Da 2020 16 92 16 3.25 4.5% 3.53 [1.64.67.9] Wang Da 2020 16 92 16 3.25 4.5% 3.53 [1.64.67.9] Wang Da 2020 17 55 15 166 3.3% 4.217 [0.65.5.52] The start of the start of	Heterogeneity: Tau ² =	0.23; Chi ² = 32.31	1, df = 9 ((P = 0.0002); l ² =	= 72%					
	Test for overall effect:	Z = 3.82 (P = 0.00	001)							
Cuen 2020 28 173 53 926 5.7% 2.83 [1.84, 4.34] Hu L 2020 3 172 14 151 4.9% 2.07 [1.15, 3.72] U Q 2020 5 26 25 299 3.6% 2.010.66, 5.60] U Q 2020 3 17 2 44 1.5% 3.88 [0.71, 2.44] U L Li U 2020 4 7 0 44 0.7% 50.83 [3.01, 652.14] Ma KL 2020 7 20 3 64 2.4% 7.47 [2.13, 26.21] Man 2020 9 40 3 95 2.4% 7.47 [2.13, 26.21] Wang Dan 2020 9 71 4 72 2.7% 2.28 [0.74, 7.07] Wang Y 2020 8 38 7 72 3.4% 2.17 [0.85, 5.52] Wang Dan 2020 16 92 16 3.55 4.6% 1.40 [0.86, 2.7] Wang Y 2020 8 38 7 72 3.4% 2.57 [0.85, 5.52] Yuan B 2020 16 92 16 3.55 4.6% 2.46 [1.48, 6.78] Zhang Ju202 7 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang Ju202 7 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang Ju202 7 55 15 166 3.7% 1.41 [0.61, 3.27] Total events 190 173 Heterogeneity: Tau ² = 0.53 (P < 0.0001) 6.1.3 ARDS Lu Y 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtotal (95% C) 137 173 4.7% 4.64 [1.86, 11.58] Vu C 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtotal (95% C) 2 19 13 179 2.0% 1.45 [0.35, 5.65] Wang Dan 2020 2 1 1 53 7 28 1.2% 0.31 [0.40, 2.25] Wang D2020 1 13 7 7 2 4.12% 0.31 [0.40, 2.25] Wang D2020 1 13 7 7 2 4.12% 0.31 [0.40, 2.25] Wang D2020 1 1 3 7 72 8 1.2% 0.31 [0.40, 2.25] Wang D2020 1 1 3 7 7 8 1.2% 0.31 [0.40, 2.25] Wang D2020 1 1 3 7 7 8 1.2% 0.31 [0.40, 2.25] Wang D2020 1 1 3 7 7 8 1.2% 0.31 [0.40, 2.25] Wang D2020 2 2 15 6 128 1.9% 2.280 [0.62, 12.65] Lu Y 2020 1 6 8 36 6 102 3.2% 3.76 [1.41, 10.16] Subtotal (95% C) 26 9.0.7); P = 63% Test for overall effect: Z = 0.30; C P = 0.57); P = 0.07; P = 63% Test for overall effect: Z = 0.00; C HP = 0.10; P = 0.57; P = 0.63% Total events 4 9 9 Heterogeneity: Tau ² = 0.00; C HP = 0.10; P = 0.75; P = 0.63% Total events 4 0.6 [0.76, 2.161] Subtotal (95% C) 28 193 3.4% 3.331 [1.06, 10.14] Total events 4 40 [0.76, 2.161] Subtotal (95% C) 10 709 473 100.0% 2.38 [1.88, 3.03] Total events 5 4.6 (f = 2.0P = 0.000; P	6.1.2 Severe COVID-	19								
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Guan 2020	28	173	53	926	5.7%	2.83 [1.84, 4.34]			
Li Q 2020 5 26 26 29 36% 2.30 $(0.96, 5.5)$ Li U 2020 4 7 0 44 07% 50.63 $(3.01, 852, 14)$ Li U 12020 4 7 20 3 64 2.4% 7.47 $(2.13, 26, 21)$ Ma KL 2020 7 20 3 64 2.4% 7.47 $(2.13, 26, 21)$ Wang Dan 2020 9 40 3 95 2.4% 7.13 $(2.00, 2.486)$ Wang Dan 2020 9 71 4 72 2.7% 2.28 $(1.44, 6.79)$ Wang Dan 2020 16 92 16 3.2% 4.3% 2.37 $(1.44, 6.79)$ Zhang Quqin 2020 7 55 15 166 3.7% 1.44 $(0.63, 2.3.6)$ Subtotal (95% CI) 1055 2506 44.8% 2.45 $(1.79, 3.35)$ Total events 190 773 Heterogeneity: Tau ² = 0.13; Ch ² = 2.175, df = 12 (P = 0.04); P = 45% Test for overall effect: Z = 5.63 (P < 0.0001) 6.1.3 ARDS Li U Y 2020 16 84 6 117 3.5% 3.37 $(1.45, 1.98)$ Total events 27 7 7 7 Heterogeneity: Tau ² = 0.15; P = 1.10, df = 1 (P = 0.29); P = 9% Test for overall effect: Z = 5.63 (P < 0.0001) 6.1.4 CU Care Cas 2020 2 1 1 5 6 126 1.2% $(1.45, 0.35, 5.95)$ Huterogeneity: Tau ² = 0.8; Ch ² = 2.17; P = 0.07); P = 9% Test for overall effect: Z = 5.63 (P = 0.07); P = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Fere 2020 2 1 5 6 126 1.9% 2.80 $(0.62, 12.65)$ Huterogeneity: Tau ² = 0.05; Ch ² = 5.44; df = 2 (P = 0.07); P = 0% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Fere 2020 2 1 1 3 67 1.6% 4.06 $(0.76, 21.61)$ Subtotal (9% CI) 2 17 7 0 474 3 100.0% 2.38 $(1.38, 3.03)$ Total events 4 9 Heterogeneity: Tau ² = 0.00; Ch ² = 0.10; Ch ² = 0.07); P = 0% Test for overall effect: Z = 0.00; Ch ² = 0.00; P	Hu L 2020	33	172	14	151	4.9%	2.07 [1.15, 3.72]			
Liu J 2020 3 17 2 44 15% 338 ($0.71, 21.24$) Liu Lai 2020 4 7 0 44 0.7% 5063 (30.182.14) Liu Lai 2020 7 20 3 64 2.4% 7.47 (2.13, 26.21) Clin 2020 9 40 3 95 2.4% 7.47 (2.13, 26.21) Van 2020 9 40 3 95 2.4% 7.13 (2.03, 2.436) Wang Y 2020 8 38 7 7.2 3.4% 2.17 ($0.28, 2.21$) Vang Y 2020 8 38 7 7.2 3.4% 2.17 ($0.28, 5.52$] Vang S 2020 16 92 16 325 4.6% 3.53 (1.4, 6.79) Vang Y 2020 8 58 9 82 3.6% 1.26 ($0.52, 3.66$) Subtotal (95% CI) 1055 2206 44.8% 2.45 ($1.79, 3.35$] Total events 190 173 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 ($P = 0.29$); $P = 9\%$ Test for overall effect: $Z = 5.64$, $P = 0.001$) 6.1.4 ICU Care Cao 2020 2 1 16 84 6 117 3.5% 3.77 (1.52, 9.09) Subtotal (95% CI) 137 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 ($P = 0.29$); $P = 9\%$ Test for overall effect: $Z = 5.29 (P = 0.001$) 6.1.4 ICU Care Cao 2020 2 1 19 13 179 2.0% 1.45 (0.35, 5.95] Huang 2020 1 1 37 128 4.2% 3.37 (1.44, 1.0.16) Subtotal (95% CI) 68 309 6.4% 1.47 (0.38, 5.67] Total events 11 26 Cao 2020 2 1 19 13 179 2.0% 1.45 (0.35, 5.95] Huang 2020 1 1 36 7 1.6% 4.06 (0.76, 21.61] Subtotal (95% CI) 68 309 6.4% 1.47 (0.38, 5.67] Total events 11 26 Huang 2020 2 1 15 6 126 1.9% 2.80 (0.62, 12.65] Liu Y 2020 2 15 6 (1.9 - 0.77); $P = 63\%$ Test for overall effect: $Z = 0.50 (P - 0.57)$ 6.1.5 Disease Progression Feng 2020 2 1 15 6 126 1.9% 2.80 (0.62, 12.65] Liu W 2020 2 2 15 6 (1.9% 4.06 (0.76, 21.61] Subtotal (95% CI) 26 (P = 0.57); $P = 0\%$ Test for overall effect: $Z = 0.50 (P - 0.57)$ For a 2020 2 2 15 6 (1.9% 4.06 (0.76, 21.61] Subtotal (95% CI) 26 (P = 0.07); $P = 63\%$ Test for overall effect: $Z = 2.09 (P = 0.04)$ Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 57, 59, d ² = 0\% Test for overall effect: $Z = 2.19 (P = 0.04)$; $P = 62\%$ Total events 358 476 Heterogeneity: Tau ² = 0.20; (Chi ² = 2, $P < 0.0001$); $P = 62\%$	Li Q 2020	5	26	25	299	3.6%	2.30 [0.96, 5.50]			
Lu Lei 2020 4 7 0 44 0.7% 50.83 [301, 852.14] Ma KL 2020 7 20 3 64 2.4% 7.47 [213, 26.21] Qin 2020 53 286 22 166 5.6% 1.40 [0.88, 2.21] Wang Dan 2020 9 71 4 72 2.4% 7.47 [213, 26.21] Wang Dan 2020 9 71 4 72 2.4% 7.47 [213, 26.21] Wang Dan 2020 9 71 4 72 2.4% 7.47 [10.85, 5.52] Yuang S2020 16 92 16 325 4.6% 3.53 [1.84, 6.79] Zhang J2020 7 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang J2020 8 6 58 9 62 3.6% 1.28 [0.52, 3.06] Subtotal (95% CI) 1055 2506 44.8% 2.45 [1.79, 3.35] Total events 190 173 Heterogeneity: Tau ² = 0.13; Ch ² = 21.75, df = 12 (P = 0.04); P = 45% Test for overall effect: Z = 5.63 (P < 0.0001) 6.1.3 ARDS Liu Y 2020 16 84 6 117 3.5% 3.71 [1.52, 9.08] Subtotal (95% CI) 137 77 4.7% 4.64 [1.86, 11.58] Total events 27 7 7 Heterogeneity: Tau ² = 0.05; Ch ² = 1.0, df = 1 (P = 0.29); P = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 CU Care Cao 2020 2 1 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Wang 2020 1 1 22 (19 13 7 28 1.2% 0.31 [0.04, 2.25] Wang 2020 2 1 19 13 77 28 1.2% 0.31 [0.04, 2.25] Wang 2020 2 115 6 126 1.9% 2.80 [0.62, 12.65] Huang 2020 1 2 19 13 37 28 3.78 [1.41, 10.15] Heterogeneity: Tau ² = 0.05; Ch ² = 2.4 (P = 0.07); P = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 115 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 115 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 115 6 126 1.9% 3.34 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.05; Ch ² = 0.00; Ch ² = 2.09 (P = 0.00); P = 0% Test for overall effect: Z = 2.09 (P = 0.04) Total events 4 9 Heterogeneity: Tau ² = 0.05; Ch ² = 0.00; Ch ²	Liu J 2020	3	17	2	44	1.5%	3.88 [0.71, 21.24]	+		
In a RL 2020 7 20 3 64 2.4% $7.47[21;3;262]$ Qin 2020 53 286 22 166 56% 7.13[20;3;24:95] Wang 2020 9 71 4 72 2.4% 7.13[20;3;24:95] Wang Y 2020 8 38 7 72 2.4% 2.71[085,552] Yuan 8 2020 16 92 16 325 4.6% 3.53[1:46,679] Zhang Guin 2020 7 55 15 166 3.7% 1.44[1061,3:27] Zhang Guin 2020 7 55 15 166 1.2% 1.26[0.52;3:06] Subtotal (95% CI) 1055 2506 44.8% 2.45 [1.79, 3.35] 1.26 [0.52;3:06] Total events 190 173 Hetrogeneity: Tau* = 0.5; Ch* = 21.75; df = 12 (P = 0.04); P = 45% Test for overall effect: Z = 5.63 (P < 0.00001)	Liu Lei 2020	4	7	0	44	0.7%	50.63 [3.01, 852,14]	· · · · · · · · · · · · · · · · · · ·		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Ma KL 2020	7	20	3	64	2.4%	7.47 [2.13, 26,21]			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Qin 2020	53	286	22	166	5.6%	1.40 [0.88, 2.21]	-		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Wan 2020	9	40	3	95	2.4%	7.13 [2.03, 24,95]			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Wang Dan 2020	9	71	4	72	2.7%	2.28 [0.74, 7.07]			
Yuan B 2020 16 92 16 325 4.6% 3.53 [1.84, 6.79] Zhang Jougo 7 55 15 166 3.7% 1.41 [0.61, 3.27] Zhang Jougo 8 58 9 82 3.6% 1.26 [0.52, 3.06] Subtotal (95% CI) 1055 2506 44.8% 2.45 [1.79, 3.35] Total events 190 173 Heterogeneity: Tau ² = 0.13; Ch ² = 21.75, df = 12 (P = 0.04); P = 45% Test for overall effect: $Z = 5.63$ (P < 0.00001) 6.1.3 ARDS Liu Y 2020 11 53 1 56 1.2% 11.62 [1.55, 86.95] Viu C 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtotal (95% CI) 137 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Ch ² = 1.10, df = 1 (P = 0.29); P = 9% Test for overall effect: $Z = 3.29$ (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 8 36 6 102 3.2% 3.78 [1.41, 10.5] Subtotal (95% CI) 6.8 309 6.4% 1.47 [0.38, 5.67] Heterogeneity: Tau ² = 0.8; Ch ² = 5.4, df = 2 (P = 0.07); P = 63% Test for overall effect: $Z = 0.56$ (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Liu W 2020 3 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 4 3 16 1.9 (0.61) Total (95% CI) 70 64 1.9 9 Heterogeneity: Tau ² = 0.05; Ch ² = 0.10; df = 1 (P = 0.75); P = 0% Test for overall effect: $Z = 2.09$ (P = 0.04) Total (95% CI) 70 26 193 3.4% 3.31 [1.08, 10.14] Total (95% CI) 70 26 192 6.9 (0.57) Total (95% CI) 70 26 192 6.9 (0.57) Total (95% CI) 70 26 9.9 (0.00001); P = 62% Total (95% CI) 70 70 9 4743 100.0% 2.38 [1.88, 3.03] Total events 368 476 Heterogeneity	Wang Y 2020	8	38	7	72	3.4%	2.17 [0.85, 5.52]	— —		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Yuan B 2020	16	92	16	325	4.6%	3.53 [1.84, 6.79]			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhang Gugin 2020	7	55	15	166	3.7%	1 41 [0 61 3 27]	—		
Subtotal (95% CI) 1055 2506 44.8% 2.45 [1.78, 3.35] Total events 190 173 Heterogeneity: Tau ² = 0.15, Ch ² = 21.75, df = 12 (P = 0.04); P = 45% Test for overall effect: Z = 5.63 (P < 0.00001) 6.1.3 ARDS Liu Y 2020 11 53 1 56 1.2% 11.62 [1.55, 66.95] Wu C 2020 16 84 6 117 3.5% 3.71 [1.52, 90.9] Subtotal (95% CI) 137 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 7 Heterogeneity: Tau ² = 0.06; Ch ² = 1.10, df = 1 (P = 0.29); P = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 88 309 6.4% 1.47 [0.38, 5.67] Heterogeneity: Tau ² = 0.08; Ch ² = 5.44, df = 2 (P = 0.07); P = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 2.1.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Ch ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.99 (P = 0.000) Total events 4 9 Heterogeneity: Tau ² = 0.00; Ch ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.99 (P = 0.000) Total events 358 476 Heterogeneity: Tau ² = 0.21; Ch ² = 0.29; P = 0.00001); P = 62%	Zhang J 2020	8	58	9	82	3.6%	1 26 [0 52 3 06]			
Total events 190 173 Heterogeneity: Tau ² = 0.13; Chi ² = 21.75, df = 12 (P = 0.04); P = 45% Test for overall effect: Z = 5.63 (P < 0.00001) 6.1.3 ARDS Liu Y 202 11 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtotal (95% CI) 137 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); P = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 ICU Care Cao 2020 2 1 9 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 137 7 28 1.2% 0.31 [0.04, 2.25] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); P = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 202 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 202 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.09 (P = 0.07); P = 63% Test for overall effect: Z = 2.09 (P = 0.07); P = 0% Test for overall effect: Z = 2.09 (P = 0.07); P = 0% Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.09 (P = 0.07); P = 0% Total events 4 9 Heterogeneity: Tau ² = 0.21; Chi ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.09 (P = 0.0001); P = 62%	Subtotal (95% CI)	Ũ	1055	Ū	2506	44.8%	2.45 [1.79, 3.35]	•		
Total events 11 26 Heterogeneity: Tau ² = 0.13; Chi ² = 21.75, df = 12 (P = 0.04); P = 45% Test for overall effect: Z = 5.63 (P < 0.00001) 6.1.3 ARDS Liu Y 2020 11 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtoal (95% Cl) 1 37 7 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); P = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 ICU Care Cao 2020 2 1 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 3 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtoal (95% Cl) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.86; Chi ² = 5.44, df = 2 (P = 0.07); P = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtoal (95% Cl) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.09 (P = 0.04) Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.09 (P = 0.04) Total events 4 76 Heterogeneity: Tau ² = 0.21; Chi ² = 50, df = 29 (P < 0.0001); P = 62%	Total events	190		173						
Total events $110 = 0.15, 0.01 = 1.10, 0.01 = 1.00, 0.01 = 0.00, 0.00, 0.$	Heterogeneity: Tau ² =	0.13 Chi ² = 21.7	5 df = 12	$P(P = 0.04) \cdot l^2 =$	45%					
6.1.3 ARDS Liu Y 2020 11 53 1 56 1.2% 11.62 [1.55, 86.95] Vu C 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtotal (95% CI) 137 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); P ² = 9% Test for overall effect: Z = 3.29 (P = 0.001) 61.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 1.45 [0.56, 21.65] 1.47 [0.38, 5.67] 6.1.5 Disease Progression Feng 2020 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] 3.31 [1.08, 10.14]	Test for overall effect:	Z = 5.63 (P < 0.00	0001)	. (1 0.01), 1	1070					
Liu Y 2020 11 53 1 56 1.2% 11.62 [1.55, 86.95] Wu C 2020 16 84 6 117 3.5% 3.71 [1.52, 9.09] Subtotal (95% CI) 137 77 Heterogeneity: Tau ² = 0.06; Ch ² = 1.10, df = 1 (P = 0.29); l ² = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Ch ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Ch ² = 0.10, df = 1 (P = 0.75); l ² = 0% Test for overall effect: Z = 2.09 (P = 0.04) Total events 558 476 Heterogeneity: Tau ² = 0.21; Ch ² = 76.59, df = 29 (P < 0.0001); l ² = 62%	6.1.3 ARDS									
Wu C 2020 16 84 6 117 3.5% 3.71 [1.52 , 9.09] Subtotal (95% CI) 137 173 4.7% 4.64 [1.86 , 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); i ² = 9% 7 Test for overall effect: Z = 3.29 (P = 0.001) 6.14 ICU Care 20% 1.45 [0.35 , 5.95] Gao 2020 2 19 13 79 2.0% 1.45 [0.35 , 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04 , 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41 , 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38 , 5.67] Total events 11 26 126 1.9% 2.80 [0.62 , 12.65] 1.10 Liu W 2020 2 11 3 67 1.6% 4.06 [0.76 , 21.61] 4.06 5.71 Subtotal (95% CI) 26 193 3.4% 3.31 [1.08 , 10.14] 4.64 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); i ² = 0% <td>Liu Y 2020</td> <td>11</td> <td>53</td> <td>1</td> <td>56</td> <td>1.2%</td> <td>11.62 [1.55, 86.95]</td> <td></td>	Liu Y 2020	11	53	1	56	1.2%	11.62 [1.55, 86.95]			
Subtotal (95% CI) 137 173 4.7% 4.64 [1.86, 11.58] Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); l ² = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% 1.8% 4.06 [0.76, 21.61] Test for overall effect: Z = 0.56 (P = 0.57) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 9 9 1.108, 10.14] 100.0% 2.38 [1.88, 3.03] 4 Total events 358 476 4743 100.0% 2.38 [1.88, 3.03] 4 4 Total events 358 476 1000 <td>Wu C 2020</td> <td>16</td> <td>84</td> <td>6</td> <td>117</td> <td>3.5%</td> <td>3.71 [1.52, 9.09]</td> <td></td>	Wu C 2020	16	84	6	117	3.5%	3.71 [1.52, 9.09]			
Total events 27 7 Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); I ² = 9% Test for overall effect: Z = 3.29 (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); I ² = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); I ² = 0% Test for overall effect: Z = 2.09 (P = 0.04) Total events 358 476 Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.00001); I ² = 62%	Subtotal (95% CI)		137		173	4.7%	4.64 [1.86, 11.58]	•		
Heterogeneity: Tau ² = 0.06; Chi ² = 1.10, df = 1 (P = 0.29); l ² = 9% Test for overall effect: $Z = 3.29$ (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 133 7 28 1.2% 0.31 [0.04, 2.25] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.86; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: $Z = 0.56$ (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.65] Liu W 2020 2 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% Test for overall effect: $Z = 2.09$ (P = 0.04) Total events 358 476 Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.0001); l ² = 62%	Total events	27		7						
Test for overall effect: $Z = 3.29$ (P = 0.001) 6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: $Z = 0.56$ (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% Test for overall effect: $Z = 2.09$ (P = 0.04) Total events 358 476 Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.00001); l ² = 62%	Heterogeneity: Tau ² =	0.06; Chi ² = 1.10,	df = 1 (F	P = 0.29); I ² = 9%	6					
6.1.4 ICU Care Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Image: Colored colore	Test for overall effect:	Z = 3.29 (P = 0.00	01)							
Cao 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% Cl) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: $Z = 0.56$ (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% Cl) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% Test for overall effect: $Z = 2.09$ (P = 0.04) Total events 358 476 Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.00001); l ² = 62%	6 1 4 ICU Care									
Lad 2020 2 19 13 179 2.0% 1.45 [0.35, 5.95] Huang 2020 1 13 7 28 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); I ² = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] • Total events 4 9 • • Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); I ² = 0% 2.38 [1.88, 3.03] • • Total (95% CI) 1709 4743 100.0% 2.38 [1.88, 3.03] • • •	Cap 2020	2	10	10	170	2.00/	1 45 10 25 5 051			
Huang 2020 1 13 7 26 1.2% 0.31 [0.04, 2.25] Wang D 2020 8 36 6 102 3.2% 3.78 [1.41, 10.15] Subtotal (95% CI) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% 2.80 [0.62, 12.65] Test for overall effect: Z = 0.56 (P = 0.57) 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% CI) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% 2.38 [1.88, 3.03] Total (95% CI) 1709 4743 100.0% 2.38 [1.88, 3.03] Total events 358 476 Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.00001); l ² = 62% 0.001 0.1 100 1000	Cao 2020	2	19	13	179	2.0%	1.45 [0.35, 5.95]			
Wang D 2020 6 36 6 102 3.7% 3.76 [1.41, 10.15] Subtotal (95% Cl) 68 309 6.4% 1.47 [0.38, 5.67] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% Cl) 26 193 3.4% 3.31 [1.08, 10.14] • Total events 4 9 + + + Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% 2.38 [1.88, 3.03] • Total events 358 476 + + Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.00001); l ² = 62% 2.001 0.4 1 1000	Huang 2020	1	13	1	28	1.2%	0.31 [0.04, 2.25]			
Subtract (35, 6, 1) Color Sols C.4.% T.4.7 [0.50, 5.57] Total events 11 26 Heterogeneity: Tau ² = 0.88; Chi ² = 5.44, df = 2 (P = 0.07); l ² = 63% Test for overall effect: Z = 0.56 (P = 0.57) 6.1.5 Disease Progression Feng 2020 2 15 6 126 1.9% 2.80 [0.62, 12.65] Liu W 2020 2 11 3 67 1.6% 4.06 [0.76, 21.61] Subtotal (95% Cl) 26 193 3.4% 3.31 [1.08, 10.14] Total events 4 9 Heterogeneity: Tau ² = 0.00; Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% Test for overall effect: Z = 2.09 (P = 0.04) Total events 358 476 Heterogeneity: Tau ² = 0.21; Chi ² = 76.59, df = 29 (P < 0.00001); l ² = 62%	Wang D 2020 Subtotal (95% CI)	8	30	0	300	3.2% 6.4%	3.78 [1.41, 10.15]			
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Fig. 2. Diabetes Mellitus and Poor Outcome. Forest-plot shows that diabetes mellitus was associated with increased composite poor outcome and its subgroup which comprises of mortality, severe COVID-19, ARDS, need for ICU care, and disease progression in patients with COVID-19. ARDS: Acute Respiratory Distress Syndrome, COVID-19: Coronavirus Disease 2019, ICU: Intensive Care Unit.



Fig. 3. Bubble-plot for Meta-regression. Meta-regression analysis showed that the association between diabetes mellitus and composite poor outcome was affected by age [A] and hypertension [B], but not by cardiovascular diseases [C].

pneumocytes and consequently cause severe and fatal infection [42]. Among other diabetic medications, the use of liraglutide and pioglitazone have also been found to be related with increased ACE2 regulation in animal studies [42,43].

The interconnection between ACE2, renin-angiotensin system (RAS) signalling, aging, DM, hypertension, and severity of COVID-19 may not be as simple as it may seem. As we discussed previously, our meta-regression analysis showed that the association between DM and poor outcome was interdependent with age and hypertension. One of the possible rationale behind this finding is the use of medications, particularly ACEI or ARB in the hypertensive

individuals. The risks and benefits associated with ACEI/ARB use in COVID-19 patients remains controversial [44], a specific type of ARB has been shown to ameliorate lung injury related to SARS-CoV infection in animal model [45]. It is unfortunate that all of the included studies in this systematic review did not provide report on diabetic or hypertensive medications. Furthermore, the link between those specific variables could be in line with the hypothesis of AlGhatrif et al. [46] Older hypertensive individuals have lower ACE2 levels but a higher RAS signalling, this difference is further expressed in COVID-19 patients in which ACE2 developed into a critically low levels and RAS signalling is exaggerated even more. Such disturbance result in a potentially decreased susceptibility to the disease, but a greater severity. In contrast, younger people without hypertension have higher ACE2 levels and lower RAS signalling, which transforms into a modestly low ACE2 levels and modestly increased RAS signalling due to COVID-19 infection. This results in a possibly increased susceptibility to the disease, but a lesser severity. Our meta-regression result may support the aforementioned hypothesis. The use of ACEI/ARB is expected in patients with both DM and HTN; and we observe that the age and HTN were in parallel, studies with older subjects having higher prevalence of hypertension. Hence, the clinical significance of DM in the older patients may be attenuated by the risk of hypertension and ACEI/ ARB use (which was hypothesized to increase severity in older patients).

Dysfunctional pro-inflammatory cytokine responses in diabetic patients might also be the underlying cause of severe COVID-19 [37,47,48]. Diabetic patients have been shown to have an elevated pro-inflammatory cytokine level, in particular IL-1, IL-6 and tumor necrosis factor (TNF)- α [48]. Different markers, including C-reactive protein, fibrinogen and D-dimer were also found to be elevated in diabetic patients who contracted COVID-19 [47]. Thus, this condition may further exaggerate the cytokine storms in COVID-19 leading to a more severe disease [37,48,49].

4.1. Implications for clinical practice

DM was shown to be associated with poor outcome in patients with COVID-19 and was influenced by age and hypertension. The association was stronger in younger patients and should alert physician even though the patient only presented with one comorbidity. This indicates that DM is a potential prognostic marker that should be explored in triage. We encourage researchers to include DM in studies investigating prognostic model for patients with COVID-19. Moreover, this finding adds the needs of further studies concerning the use of ACEI/ARB in COVID-19.

4.2. Limitations

Data on diabetic/hypertensive medications were lacking in the included studies, hence, cannot be analysed. Since ACEI/ARB is often used in DM, it may have influence on prognosis. Most of the articles included in this meta-analysis were preprints; nevertheless the authors have made exhaustive efforts to ensure that only sound studies were included. Most of the reports were from China, hence, the samples might overlap across the reports. The included studies were retrospective in design.

5. Conclusion

DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19. The association was weaker in the older and hypertensive patients.





Harbord's modified test for small-study effects: Regress Z/sqrt(V) on sqrt(V) where Z is efficient score and V is score variance

Number of stud	lies = 30	Root MSE	= 1.464			
Z/sqrt(V)	Coef.	Std. Err.	t	P> t	[95% Conf.	Interval]
sqrt(V)	.1056748	.3326084	0.32	0.753	5756427	.7869923
bias	2.05084	.6540622	3.14	0.004	.7110541	3.390625

Test of H0: no small-study effects P = 0.004

Fig. 4. Publication Bias Analysis. The Begg's funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot for the association between diabetes mellitus and composite poor outcome [A]. Regression-based Harbord's test showed indication of small-study effects for hypertension and composite poor outcome.

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None.

Data availability

The data used to support the findings of this study are included within the article.

Funding statement

None.

Declaration of competing interest

None.

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IH and RP conceived and designed the study. IH, RP, and MAL acquired the data. IH and MAL drafted the manuscript. IH and RP performed data extraction and interpreted the data. IH and MAL performed extensive research on the topic. RP reviewed and performed extensive editing of the manuscript. All authors contributed to the writing of the manuscript. IH and RP performed the statistical analysis.

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