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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☆

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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 ≥55 years-old (RR 1.92) compared to <55 years-old (RR 3.48), and in prevalence of hypertension ≥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.

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 2020	Observational Retrospective	440 (13/427)	56.4 (61.5 vs 56.2)	48	7.9 (15.3 vs 7.7)	5.7 (15.3 v 5.4)	7.5 (30.8 vs 6.8)	N/A	Mortality
Bai T 2020	Observational Retrospective	127 (36/91)	63 (77.8 vs 57.1)	55 (67 vs 50)	28.3 (41.7 vs 23.1)	2.4 (5.6 vs 1.1) (CVD)	11.8 (13.9 vs 11.0)	N/A	Mortality
Cao J 2020	Observational Retrospective	102 (17/85)	52 (76.5 vs 47.1)	54 (72 vs 53)	27.5 (64.7 vs 20)	4.9 (17.6 vs 2.4)	10.8 (35.3 vs 5.9)	9.8 (23.5 vs7.1)	Mortality
Chen 2020	Observational Retrospective	123 (31/92)	49 (71 vs 42)	56 (72 vs 53)	33.3 (48.4 vs 38.3)	12.2 (25.8 vs 7.6)	11.4 (19.4 vs 8.7)	4.9 (9.7 vs 3.3)	Mortality
Chen T 2020	Observational Retrospective	274 (113/161)	62 (73 vs 55)	62 (68.0 vs 51.0)	34 (48 vs 24)	8 (14 vs 4) (CVD)	17 (21 vs 14)	7 (10 vs 4) (CLD)	Mortality
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 2020	Observational Retrospective	403 (100/303)	47.9 (57 vs 44.9)	56 (71 vs 49)	28 (60 vs 17.5)	8.9 (16 vs 6.6)	14.1 (25 vs 10.6)	6.9 (17 vs 3.6)	Mortality
Yuan M 2020	Observational 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 (173/926)	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 L 2020	Observational Retrospective	323 (172/151)	51.4 (52.9 vs 49.7)	61 (65 vs 56)	32.5 (38.3 vs 25.8)	12.7 (19.2 vs 5.3) (CVD)	14.6 (19.2 vs 9.3)	1.9 (3.5 vs 0)	Severe COVID-19
Li Q 2020	Observational Retrospective	325 (26/299)	51.4 (76.9 vs 49.2)	51 (65 vs 49)	24 (46.2 vs 22.1)	5.5 (19.2 vs 4.3)	9.2 (19.2 vs 8.4)	1.2 (7.7 vs 0.6)	Severe COVID-19
Liu J 2020	Prospective Cohort	61 (17/44)	50.8 (58.8 vs 47.7)	40 (56 vs 41)	19.7 (35.3 vs 13.6)	1.6 (5.9 vs 0) (CVD)	8.2 (1.6 vs 4.5)	8.2 (1.6 vs 4.5)	Severe COVID-19
Liu Lei 2020	Observational Retrospective	51 (7/44)	62.7 (57.1 vs 63.7)	45 (52 vs 44)	7.8 (14.3 vs 6.8)	N/A	7.8 (57.1 vs 0)	N/A	Severe COVID-19
Ma LK 2020	Observational Retrospective	84 (20/64)	57.1 (60 vs 56.3)	48 (58 vs 46.5)	14.3 (20.0 vs 12.5)	6 (10 vs 4.7)	11.9 (35 vs 4.7)	6.0 (10.0 vs 4.7) (CLD)	Severe COVID-19
Qin 2020	Observational Retrospective	452 (286/166)	52.0 (54.2 vs 48.2)	58 (61 vs 53)	29.5 (36.7 vs 18.1)	5.9 (8.4 vs 1.8) (CVD)	16.4 (18.5 vs 13.3)	2.6 (3.1 vs 1.8)	Severe COVID-19
Wan 2020	Observational Retrospective	135 (40/135)	53.3 (52.5 vs 54.7)	47 (56 vs 44)	9.6 (10 vs 9.4)	5.2 (15 vs 1) (CVD)	8.9 (22.5 vs 3.1)	0.7 (2.5 vs 0) (CLD)	Severe COVID-19
Wang Dan 2020	Observational Retrospective	143 (71/72)	51 (62 vs 40.3)	58 (65 vs 44)	25.2 (43.7 vs 6.9)	11.2 (16.9 vs 5.6)	9.1 (12.7 vs 5.6)	7.0 (9.9 vs 4.2)	Severe COVID-19
Wang Y 2020	Observational Retrospective	110 (38/72)	43 (63.2 vs 33.3)	≤40 (53%), 41–60 (21%), >60 (36%) ≤40 (7.9 vs 69.4), 41–60 (21.0 vs 18.1), >60 (71.0 vs 12.5)	20.9 (39.5 v 11.1)	N/A	13.7 (21.0 v 9.7)	5.4 (10.5 v 2.8)	Severe 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 Guqin 2020	Observational Retrospective	221 (55/166)	48.9 (63.6 vs 44.0)	55 (62 vs 51)	24.4 (47.3 vs 16.9)	10 (23.6 vs 5.4)	10 (12.7 vs 9.0)	2.7 (7.3 vs 1.2)	Severe COVID-19
Zhang J 2020	Observational Retrospective	140 (58 vs 82)	50.7 (56.9 vs 46.3)	<30 (1.7 vs 4.9), 30–49 (15.5 vs 34.1), 50–69 (48.3 vs 50), ≥70 (34.5 vs 11.0)	30 (37.9 vs 24.4)	5 (6.9 vs 3.7)	12.1 (13.8 vs 11.0)	1.4 (3.4 vs 0)	Severe 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 Retrospective	41 (13/28)	73 (85 vs 68)	49.0 (49.0 vs 49.0)	14.6 (15 vs 14)	14.6 (23 vs 11) (CVD)	19.5 (8 vs 25)	2.4 (8 vs 0)	ICU Care
Wang, Dawei 2020	Observational Retrospective	138 (36 vs 102)	54.3 (61.1 vs 52.0)	56 (66 vs 51)	31.2 (58.3 vs 21.6)	14.5 (25 vs 10.8)	10.1 (22.2 vs 5.9)	2.9 (8.3 vs 1.0)	ICU Care
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 (CIs) for dichotomous variables, respectively. P-value was two-tailed, 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], $p < 0.001$; I^2: 10%, $p = 0.35$) showed a lower RR for composite poor outcome compared to <55 years-old (RR 3.48 [2.55, 4.77], $p < 0.001$; I^2: 21%, $p = 0.22$).

Subgroup analysis for studies with prevalence of hypertension $\geq$25% (RR 1.93 [1.48, 2.52], $p < 0.001$; I^2: 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], $p < 0.001$; I^2: 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].

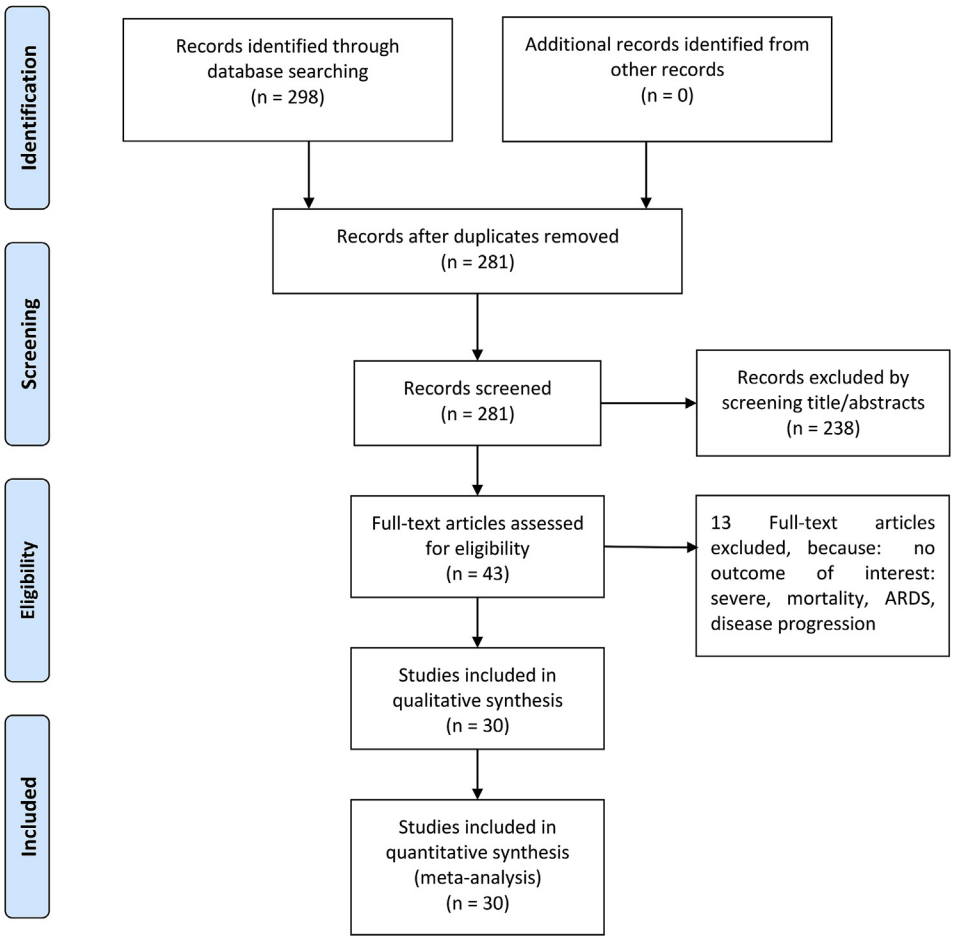


Fig. 1. Prisma flowchart.

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

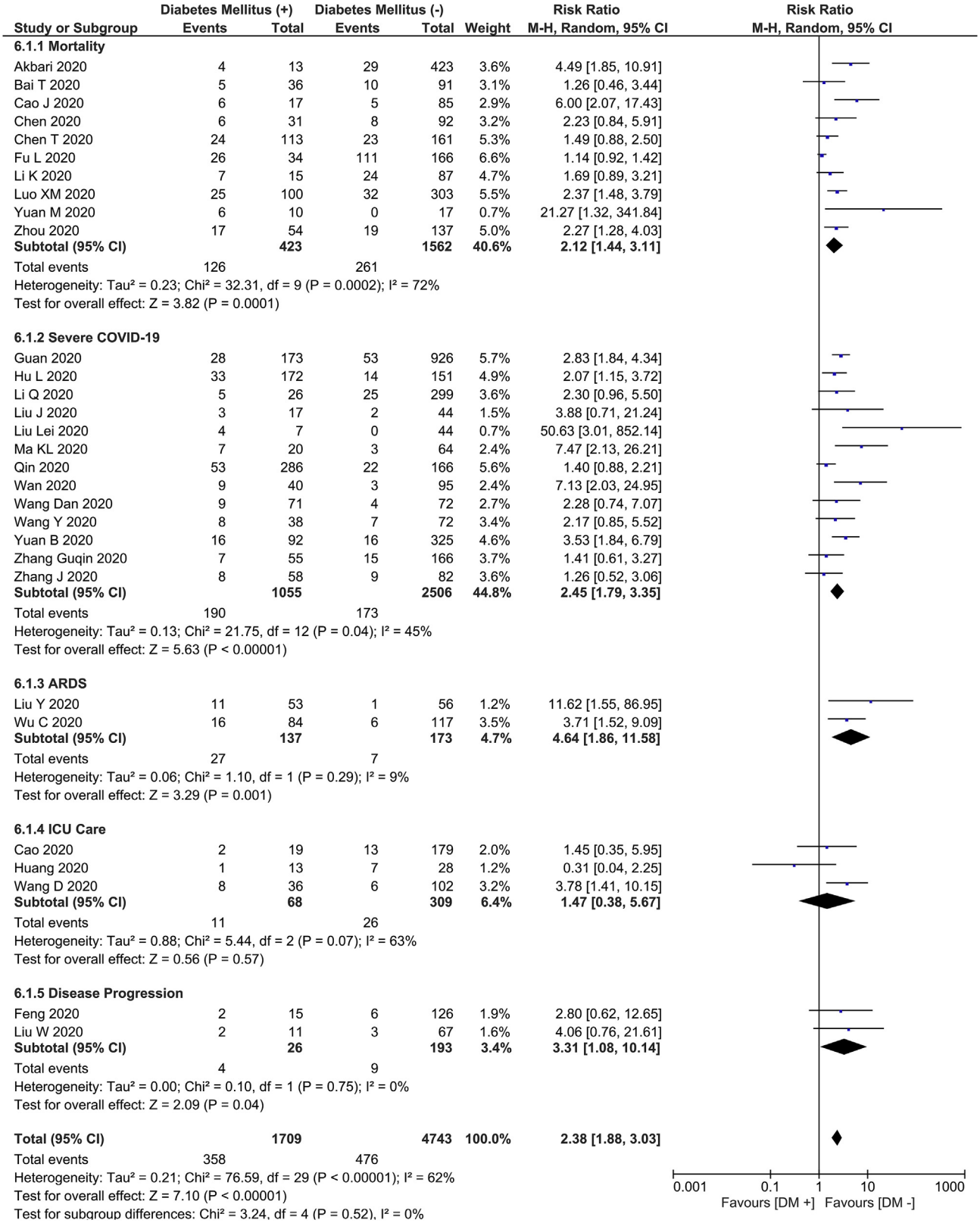


Fig. 2. Diabetes Mellitus and Poor Outcome. Forest-plot shows that diabetes mellitus was associated with increased composite poor outcome and its subgroup which comprises of mortality, severe COVID-19, ARDS, need for ICU care, and disease progression in patients with COVID-19. ARDS: Acute Respiratory Distress Syndrome, COVID-19: Coronavirus Disease 2019, ICU: Intensive Care Unit.

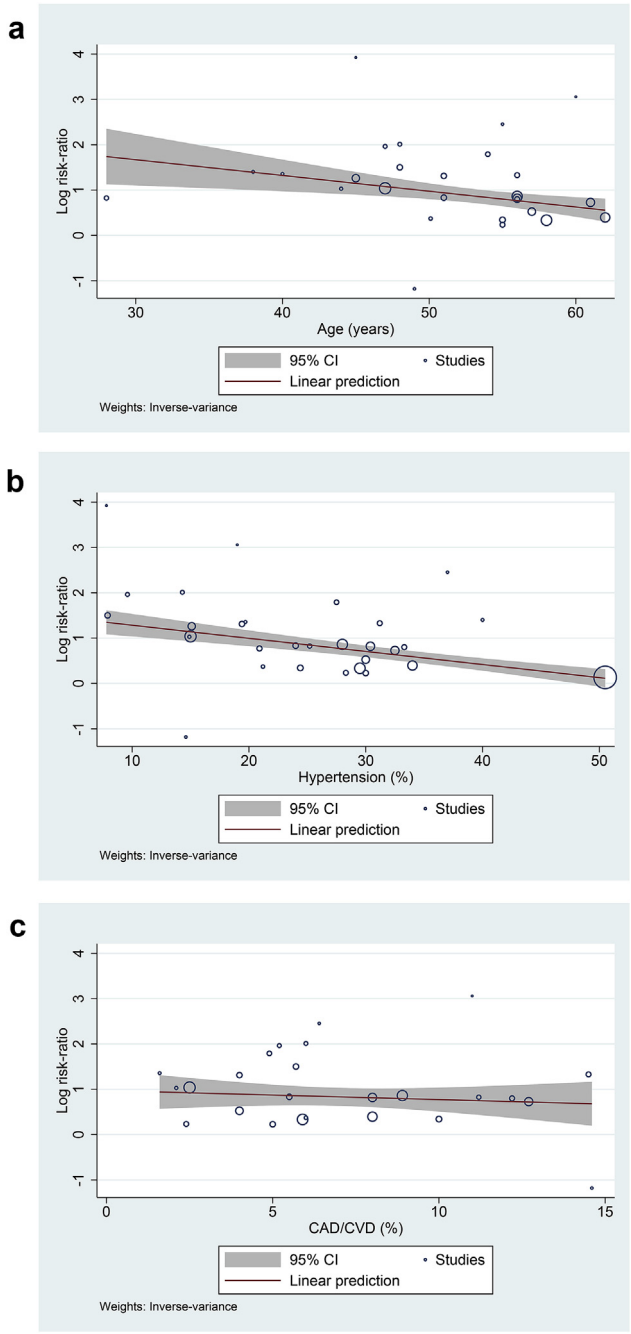


Fig. 3. Bubble-plot for Meta-regression. Meta-regression analysis showed that the association between diabetes mellitus and composite poor outcome was affected by age [A] and hypertension [B], but not by cardiovascular diseases [C].

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

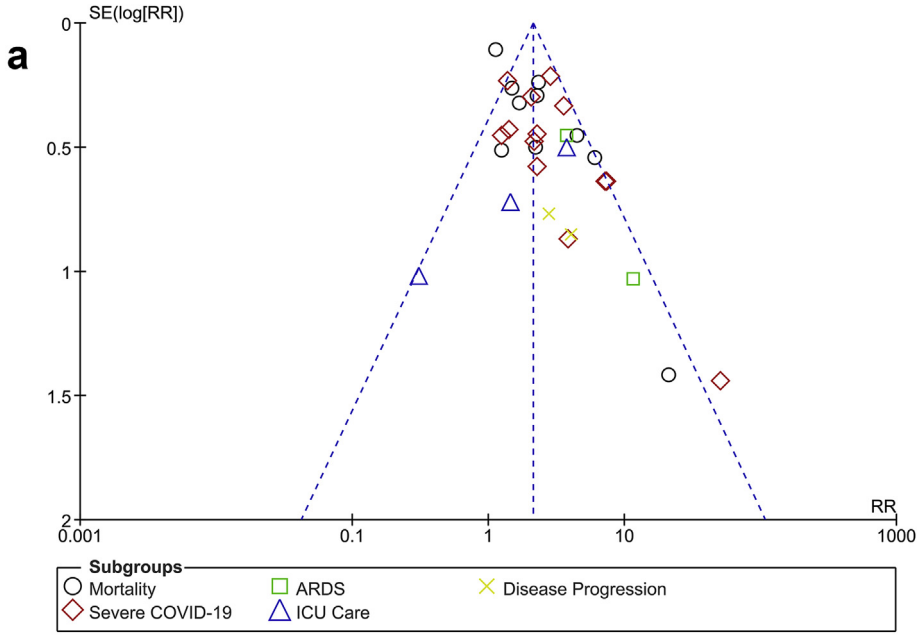
DM was shown to be associated with poor outcome in patients with COVID-19 and was influenced by age and hypertension. The association was stronger in younger patients and should alert physician even though the patient only presented with one comorbidity. This indicates that DM is a potential prognostic 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.

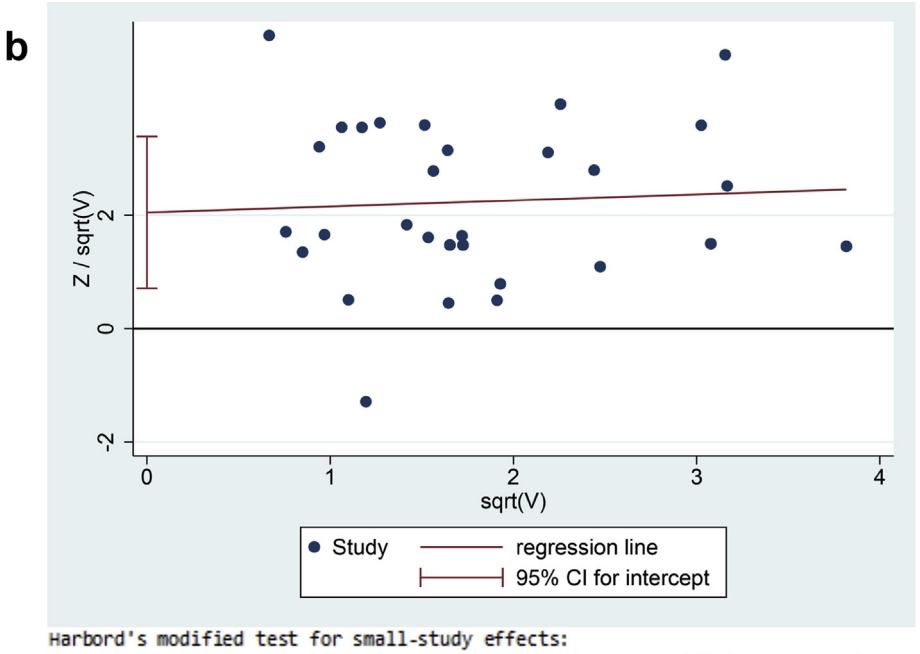
4.2. Limitations

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 studies = 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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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.

Acknowledgement

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.

References

[1] World Health Organization. Coronavirus disease 2019 (COVID-19) situation report – 78. 2020.
[2] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843. https://doi.org/10.1016/j.diabres.2019.107843.
[3] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;6736:1–9. https://doi.org/10.1016/S0140-6736(20)30566-3.
[4] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020:e3319. https://doi.org/10.1002/dmrr.3319.
[5] Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet Med 2020. https://doi.org/10.1111/dme.14300.
[6] World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2020. p. 1–21.
[7] World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 COVID-19 report. vol. vol. 2019. n.d.
[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
[9] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;2600:1–7. https://doi.org/10.1016/S2213-2600(20)30079-5.
[10] Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. MedRxiv 2020. https://doi.org/10.1101/2020.03.02.20030452. 2020.03.02.20030452.
[11] Zhang J jin, Dong X, Cao Y yuan, Yuan Y dong, Yang Y bin, qin Yan Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy Eur J Allergy Clin Immunol 2020:1–12. https://doi.org/10.1111/all.14238.
[12] Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in Northeast Chongqing. J Med Virol 2020:1. https://doi.org/10.1002/jmv.25783.
[13] Qu R, Ling Y, Zhang Y-H, Wei L-Y, Chen X, Li X, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with Corona Virus Disease-19. J Med Virol 2020:3. https://doi.org/10.1002/jmv.25767.
[14] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;53:1689–99. https://doi.org/10.1093/cid/ciaa248.
[15] Wang Y, Zhou Y, Yang Z, Xia D, Geng S. Clinical characteristics of patients with severe pneumonia caused by the 2019 novel coronavirus in Wuhan, China. MedRxiv 2020:1–15. https://doi.org/10.1101/2020.03.02.20029306.
[16] Feng Z, Yu Q, Yao S, Luo L, Duan J, Yan Z, et al. Early prediction of disease progression in 2019 novel coronavirus pneumonia patients outside Wuhan with CT and clinical characteristics. MedRxiv 2020. https://doi.org/10.1101/2020.02.19.20025296. 2020.02.19.20025296.
[17] Lei L, Jian-ya G, Hu W, Zhang X, Gua L, Liu C, et al. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing,China. MedRxiv 2020. https://doi.org/10.1101/2020.02.20.20025536. 2020.02.20.20025536.
[18] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. MedRxiv 2020:2020. https://doi.org/10.1101/2020.02.16.20023671.
[19] Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases Hospital Outside Hubei Province,China. MedRxiv 2020. https://doi.org/10.1101/2020.02.17.20024018. 2020.02.17.20024018.
[20] Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-Lymphocyte ratio Predicts severe illness patients with 2019 novel coronavirus in the early stage. MedRxiv 2020. https://doi.org/10.1101/2020.02.10.20021584.
[21] Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, et al. Non-severe vs severe symptomatic COVID-19: 104 cases from the outbreak on the cruise ship "Diamond Princess" in Japan. MedRxiv 2020. https://doi.org/10.1101/2020.03.18.20038125.
[22] Chen M, Fan Y, Wu X, Zhang L, Guo T, Deng K, et al. Clinical characteristics and risk factors for fatal outcome in patients with 2019-coronavirus infected disease (COVID-19) in Wuhan, China. SSRN Electron J 2020. https://doi.org/10.2139/ssrn.3546069.
[23] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA, J Am Med Assoc 2020:1–9. https://doi.org/10.1001/jama.2020.1585.
[24] Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. MedRxiv 2020:2020. https://doi.org/10.1101/2020.03.04.20030395.
[25] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020:1–10. https://doi.org/10.1001/jamainternmed.2020.0994.
[26] Yanli L, Wenwu S, Jia L, Liangkai C, Yujun W, Lijuan Z, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. MedRxiv 2020:1–9. https://doi.org/10.1101/2020.02.17.20024166.
[27] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020:1–13. https://doi.org/10.1056/NEJMoa2002032.
[28] Liu W, Tao Z-W, Lei W, Ming-Li Y, Kui L, Ling Z, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020:1. https://doi.org/10.1097/cm9.0000000000000775.
[29] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020. https://doi.org/10.1007/s00134-020-05991-x.
[30] Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PloS One 2020;15:1–10. https://doi.org/10.1371/journal.pone.0230548.
[31] Li K, Chen D, Chen S, Feng Y, Chang C. Radiographic findings and other predictors in adults with Covid-19. MedRxiv 2020;2. https://doi.org/10.1101/2020.03.23.20041673.
[32] Fu L, Fei J, Xiang H-X, Xiang Y, Tan Z-X, Li M-D, et al. Analysis of death risk factors among 200 COVID-19 patients in Wuhan, China: a hospital-based case-cohort study. SSRN Electron J 2020;86. https://doi.org/10.2139/ssrn.3551430.
[33] Luo X, Xia H, Yang W, Wang B, Guo T, Xiong J, et al. Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan , China. MedRxiv 2020. https://doi.org/10.1101/2020.03.19.20033175.
[34] Li Q, Ling Y, Zhang J, Li W, Zhang X, Jin Y, et al. Clinical characteristics of SARS-CoV-2 infections involving 325 hospitalized patients outside Wuhan. Res Sq 2020:1–15. https://doi.org/10.21203/rs.3.rs-18699/v1.
[35] Yuan B, Chen Y, Wang J, Wang C, Song S, Liu H-Q. Epidemiological Characteristics of 417 patients infected with COVID-19 and 368 discharged cases among them in Shenzhen City , China CURRENT STATUS : under review. Res Sq 2020:1–14. https://doi.org/10.21203/rs.3.rs-19554/v1.
[36] Wang D, Li R, Wang J, Jiang Q, Gao C, Yang J, et al. Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. Res Sq n.d.:1–17. doi: 10.21203/rs.3.rs-19680/v1.
[37] Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract 2020;162:108132. https://doi.org/10.1016/j.diabres.2020.108132.
[38] Jafar N, Edriss H, Nugent K. The effect of Short-term hyperglycemia on the innate immune system. Am J Med Sci 2016;351:201–11. https://doi.org/10.1016/j.amjms.2015.11.011.
[39] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long Structural studies of SARS coronavirus. J Virol 2020;94:1–9. https://doi.org/10.1128/jvi.00127-20.
[40] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is Blocked by

a clinically proven protease inhibitor. Cell 2020. https://doi.org/10.1016/j.cell.2020.02.052.
[41] Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. Elife 2020;9. https://doi.org/10.7554/eLife.57278.
[42] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21. https://doi.org/10.1016/S2213-2600(20)30116-8.
[43] Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, Santisteban P, González-Matías LC, Vigo E, et al. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology 2015;156:3559–69. https://doi.org/10.1210/en.2014-1685.
[44] Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc). Diabetes Metab Syndr Clin Res Rev 2020;14:251–4. https://doi.org/10.1016/j.dsx.2020.03.012.
[45] Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112–6. https://doi.org/10.1038/nature03712.
[46] AlGhatrif M, Cingolani O, Lakatta EG. The dilemma of coronavirus disease 2019, aging, and cardiovascular disease: Insights from cardiovascular aging science. JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.1329.
[47] Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev 2020:e33213321. https://doi.org/10.1002/dmrr.3321.
[48] Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999;26:259–65. https://doi.org/10.1016/S0928-8244(99)00142-X.
[49] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.