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Prevalence of Diabetes and Hypertension and Their Associated Risks for Poor Outcomes in Covid-19 Patients

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Abstract: Coronavirus disease 2019 (Covid-19) has affected millions of people and may disproportionately affect those with hypertension and diabetes. Because of inadequate methods in published systematic reviews, the prevalence of diabetes and hypertension and associated risks of poor outcomes in Covid-19 patients are unknown. We searched databases from December 1, 2019, to April 6, 2020, and selected observational peer-reviewed studies in English of patients with Covid-19. Independent reviewers extracted data on study participants, interventions, and outcomes and assessed risk of bias, and the certainty of evidence. We included 65 (15 794 participants) observational studies at moderate to high risk of bias. Overall prevalence of diabetes and hypertension was 12% (95% confidence interval [CI], 10-15; n = 12 870; I 2: 89%), and 17% (95% CI, 13-22; n = 12 709; I 2: 95%), respectively. In severe Covid-19, the prevalence of diabetes and hypertension were 18% (95% CI, 16-20; n = 1099; I 2: 0%) and 32% (95% CI, 16-54; n = 1078; I 2: 63%), respectively. Unadjusted relative risk for intensive care unit admission and mortality were 1.96 (95% CI, 1.19-3.22; n = 8890; I 2: 80%; P = .008) and 2.78 (95% CI, 1.39-5.58; n = 2058; I 2: 75%; P = .0004) for diabetics; and 2.95 (95% CI, 2.18-3.99; n = 1737; I 2: 0%; P < .001) and 2.39 (95% CI, 1.54-3.73; n = 3107; I 2: 66%; P < .001) for hypertensives. Neither diabetes (1.50; 95% CI, 0.90-2.50; n = 1991; I 2: 74%; P = .119) nor hypertension (1.48; 95% CI, 0.99-2.23; n = 2023; I 2: 69%; P = .058) was associated with severe Covid-19. In conclusion, the risk of intensive care unit admission and mortality for patients with diabetes or hypertension who developed Covid-19 is increased compared with those without these comorbidities.

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Prevalence of Diabetes and Hypertension and Their Associated Risks for Poor Outcomes in Covid-19 Patients

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Coronavirus disease 2019 (Covid-19) has affected millions of people and may disproportionately affect those with hypertension and diabetes. Because of inadequate methods in published systematic reviews, the prevalence of diabetes and hypertension and associated risks of poor outcomes in Covid-19 patients are unknown. We searched databases from December 1, 2019, to April 6, 2020, and selected observational peer-reviewed studies in English of patients with Covid-19. Independent reviewers extracted data on study participants, interventions, and outcomes and assessed risk of bias, and the certainty of evidence. We included 65 (15 794 participants) observational studies at moderate to high risk of bias. Overall prevalence of diabetes and hypertension was 12% (95% confidence interval [CI], 10-15; n = 12 870; I^2 : 89%), and 17% (95% CI, 13-22; n = 12 709; I^2 : 95%), respectively. In severe Covid-19, the prevalence of diabetes and hypertension were 18% (95% CI, 16-20; n = 1099; I^2 : 0%) and 32% (95% CI, 16-54; n = 1078; I^2 : 63%), respectively. Unadjusted relative risk for intensive care unit admission and mortality were 1.96 (95% CI, 1.19-3.22; n = 8890; I^2 : 80%; P = .008) and 2.78 (95% CI, 1.39-5.58; n = 2058; I^2 : 75%; P = .0004) for diabetics; and 2.95 (95% CI, 2.18-3.99; n = 1737; I^2 : 0%; P < .001) and 2.39 (95% CI, 1.54-3.73; n = 3107; I^2 : 66%; P < .001) for hypertensives. Neither diabetes (1.50; 95% CI, 0.90-2.50; n = 1991; I^2 : 74%; P = .119) nor hypertension (1.48; 95% CI, 0.99-2.23;

Abbreviations: ACE2, angiotensin-converting enzyme 2; CI, confidence interval; Covid-19, coronavirus disease 2019; DAG, directed acyclic graph; ICU, intensive care unit; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus

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$n = 2023$; $I^2: 69\%$; $P = .058$) was associated with severe Covid-19. In conclusion, the risk of intensive care unit admission and mortality for patients with diabetes or hypertension who developed Covid-19 is increased compared with those without these comorbidities.

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Freeform/Key Words: Covid-19, SARS-CoV-2, diabetes mellitus, hypertension, endocrinology

Coronavirus disease 2019 (Covid-19) is the worst pandemic in the past 100 years spanning more than 200 countries [1] and affecting millions of individuals worldwide [2]. The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) was identified as the causative agent of Covid-19, with angiotensin-converting enzyme 2 (ACE2) as one of its cellular receptors [3]. Covid-19 has a spectrum of clinical manifestations ranging from asymptomatic or mildly symptomatic in about 80% of those affected according to community surveys to an approximate 2% case fatality rate in the hospitalized populations [4-7]. Although the statistical estimations are changing daily, more than 11 million people have been affected by Covid-19, resulting in more than half a million deaths across the world by July 7, 2020 [1, 6].

A great risk of severe Covid-19 has been reported in patients with diabetes and hypertension [8]. One study of 191 patients reported a mortality risk of 2.85-fold and 3.05-fold for those with diabetes and hypertension, respectively [9]. Furthermore, the Chinese Center for Disease Control reported a higher case fatality rate for persons with diabetes compared with those without (7.3% vs 2.3%, respectively) [7]. This risk may be explained by a dysregulated immune response, a higher comorbidity burden, and alterations of ACE2 cellular expression [6, 10-12]. The latter has been the subject of intense scrutiny, given the lack of evidence against the use of renin-angiotensin system blocking agents and their known benefits in diabetes and hypertension [12-14], as well as other cardiovascular conditions that have been shown to enhance ACE2 expression [15].

Previous systematic reviews reported a prevalence of diabetes and hypertension in patients with Covid-19 ranging from 9.7% to 11.9% and 17.1% to 20%, respectively [16-19]. The risks of severe Covid-19 in patients with diabetes and hypertension were ~3 and ~2-fold, respectively [16-18, 20]. However, these reports failed to address the high probability of including repeated information and patient duplicates in the analysis and thus may lead to inaccurate effect sizes and misleading results [16, 18-21]. This has been listed by authors as a major limitation [20], and has raised major editorial concerns [22-24]. Ultimately, risk estimates remain uncertain. Therefore, we systematically assessed the prevalence of diabetes and hypertension in patients with Covid-19 after excluding repeated patients across studies and analyzed the associated risks for Covid-19 severity, intensive care unit (ICU) admission and mortality.

Methods

Protocol registration

This systematic review adheres to the standards set in the Meta-analysis of Observational Studies in Epidemiology and Preferred Reported Items for Systematic Reviews and Meta-Analysis [25, 26]. Registration ID is CRD42020176582 and is available at: https://www.crd.york.ac.uk/prospéro/display_record.php?RecordID=176582.

Eligibility criteria

For our first aim, we included observational and interventional studies that reported the frequency of diabetes and/or hypertension in adult population with Covid-19. For our second aim, we included studies that reported exposure-outcome association as univariate or multivariate analysis, with diabetes, hypertension being the exposure, and severe Covid-19 through ICU admissions or mortality being the outcome of interest. We excluded case reports ($n < 2$) and studies including pregnant women and pediatric populations (age < 18 years). We did not set a criterion based on Covid-19 diagnosis definition, exposure ascertainment, or outcome definition because these were expected to be different and/or with limited rigor.

Search strategy

An experienced librarian (N.A.V.), with input from investigators, searched several databases for peer-reviewed manuscripts in English published between December 1, 2019, and April 6, 2020, including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid Medline, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Manual screening of references from the included studies was performed [27]. All supplementary material and figures are located in a digital research materials repository [27].

Selection process and data extraction

Search results were uploaded into an online software program (DistillerSR; Evidence Partners, Ottawa, ON, Canada). Reviewers, working independently and in duplicate, screened studies for eligibility using standardized and prepiloted instructions in a round of title and abstract and one of full-text screening. In round 1, disagreements were included; and in round 2, disagreements were resolved by consensus or arbitration by a third investigator (F.H.S.). To identify articles with high probability of patient repetition, studies that were included after full-text screening followed a preliminary data extraction conducted by 2 pairs of investigators. We extracted the timeframes of each study, hospital(s), location(s), country of origin, and the list of authors. Next, the enrollment timeframes from the studies were plotted with the information of the hospital(s). Studies without overlap in the plot were included for all outcomes. If studies overlapped, we analyzed outcomes reported by each study. If outcomes were repeated in overlapping studies, we included the data for outcomes (or frequency of comorbidities) from the study with the largest sample [27]. Data extraction was also performed in an independent and duplicated manner using a standardized and prepiloted.

Risk of bias and confidence in the body of evidence

For case series, we modified 2 tools and analyzed: selection, ascertainment of outcomes and exposures, causality, and reporting [28, 29]. For case control studies, the Newcastle-Ottawa Scale was used [30]. The quality of evidence for each outcome was determined using the Grading of Recommendations Assessment, Development and Evaluation approach [31]. Both risk of bias and overall quality of evidence assessment were performed independently and in duplicate. Disagreements were resolved by consensus between the 2 reviewers, or by arbitration by a third author (R.R.G.) [27]. Full details are listed elsewhere [27].

Data synthesis

We estimated the full-text screening inter-rater reliability with the Cohen's kappa statistic. To estimate the prevalence, we used a binomial-normal model for meta-analysis of proportions (i.e., generalized linear mixed model) [32, 33]. We calculated the relative risk (RR) for each outcome and performed a meta-analysis results using a random-effect models

and the restricted maximum-likelihood estimator [34]. Meta-analysis of unadjusted and adjusted estimates was not combined. We were unable to calculate adjusted estimates because of scarcity of data. Inconsistency for each outcome, not attributable to chance, was assessed visually using forest plots and estimated using the percentage of variance in a meta-analysis that is attributable to study heterogeneity (I^2 statistic: $I^2 < 25\%$ and $> 75\%$ reflects low and high inconsistency, respectively [35]. All statistical analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) [36].

Analysis of subgroups and sensitivity

Details on all predefined and nonpredefined subgroup and sensitivity analyses are listed separately [27]. To identify confounders, we designed a directed acyclic graph (DAG) in R [27, 37-41].

Results

Search strategy yielded 5484 studies. After deduplication and screening, 122 studies fulfilled our selection criteria (Fig. 1). Full-text screening inter-observer agreements were substantial ($k = 0.77, 0.80,$ and 0.84 for each pair of reviewers). We identified 93 articles at high probability of repeating patients. From those, we fully excluded 57 (47%), and partially (some outcomes included) excluded some outcomes in 36 (30%) [27]. Ultimately, 65 (15 794 patients) were included in our analysis. Overall, 18 (28%) studies had low risk of bias,

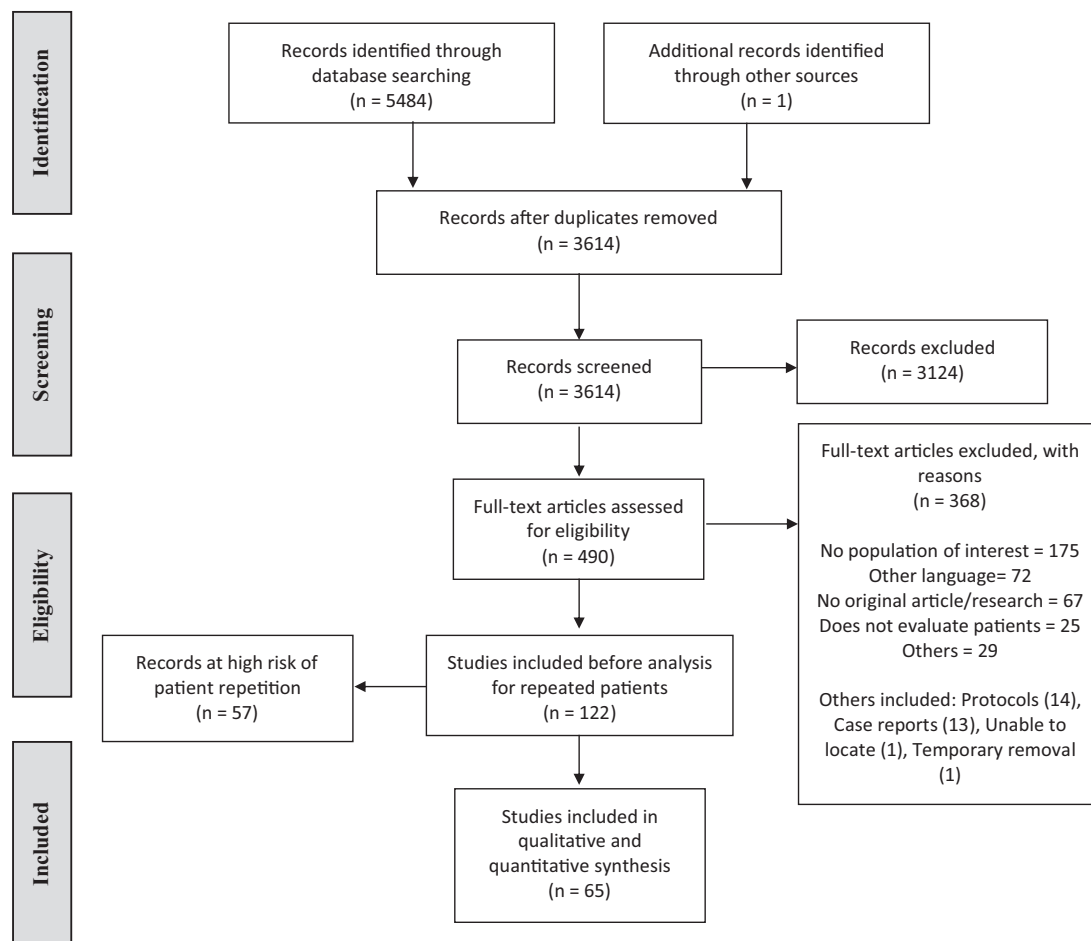


Figure 1. Flow chart of the selection process.

3 (4%) had some concerns, and 44 (68%) had high risk. For prevalence, 40 (62%) studies resulted at low risk of bias, 1 (1%) at some concerns, and 24 (37%) at high risk. Overall confidence in the body of evidence is graded as low [27]. We did not assess risk of publication bias through the funnel plot because of the limited number of studies [22].

Characteristics of included studies

Most studies were retrospective case series (97%) performed at a single center (63%) in China (71%), with inpatients (43%) diagnosed with Covid-19 using RT-PCR (Table 1) (97%). Most articles described treatments, which included standard of care (38%) and supplemental antiviral therapy (42%). Study length was reported in most studies (75%; 9-65 days). Percentage of males varied between 0 and 88, and the mean age ranged from 33 to 75 years. A total of 5 studies (8%) reported ethnicity.

Only 69% of studies reported their definition of severity. Among those that did report severity definitions, 78% of their definitions were derived from established guidelines [27]. Moreover, only 6 of the studies (9%) described the subtype of diabetes (type 2 diabetes), and 1 study (2%) defined the subtype of hypertension (primary hypertension). Finally, none of the included studies provided a definition for diabetes or hypertension.

Prevalence and risks of diabetes and hypertension

Quantitative synthesis. The overall prevalence was 12% (95% confidence interval [CI], 10-15; $n = 12\ 870$; I^2 : 89%) for diabetes, 17% (95% CI, 13-22; $n = 12\ 709$; I^2 : 95%) for hypertension, and 12% (95% CI, 6-22; $n = 54$; I^2 : 0%) for coexisting diabetes and hypertension (Fig. 2). The RR of patients with diabetes to develop our outcomes of interest were: Covid-19 severity (1.50; 95% CI, 0.90-2.50; $n = 1991$; I^2 : 74%; $P = .118$), ICU admission (1.96; 95% CI, 1.19-3.22; $n = 8890$; I^2 : 80%; $P = .007$), and mortality (2.78; 95% CI, 1.39-5.58; $n = 2058$; I^2 : 75%; $P = .004$). For patients with hypertension: Covid-19 severity (1.48; 95% CI, 0.99-2.23; $n = 2023$; I^2 : 69%; $P = .058$), ICU admission (2.95; 95% CI, 2.18-3.99; $n = 1737$; I^2 : 0%; $P < .001$), and mortality (2.39; 95% CI, 1.54-3.73; $n = 3107$; I^2 : 66%; $P < .001$). Furthermore, for patients with diabetes and hypertension, RR for Covid-19 severity was 10 (95% CI, 0.94-105.92; $n = 22$; I^2 : not applicable; $P = .056$).

Narrative synthesis. Adjusted and unadjusted estimates for mortality (hazard ratio) in patients with diabetes were nonconclusive in 2 studies (0.75; 95% CI, 0.38-1.50; $n = 416$; $P = .420$) [42] and (1.09; 95% CI, 0.57-2.08; $n = 339$; $P = .799$) [43]. Moreover, an adjusted odds ratio for severe Covid-19 in patients with hypertension reported by a study was 2.71 (95% CI, 1.32-5.59; $n = 487$; $P = .007$) [43]. Finally, another study reported an unadjusted hazard ratio that was inconclusive in determining the risk of severe Covid-19 associated with diabetes and hypertension (1.49; 95% CI, 0.92-2.44; $n = 339$; $P = .109$) [43]. Adjusted estimates are displayed along with our results for visual comparison in Fig. 3.

Sensitivity analyses

Predefined sensitivity analyses. After excluding studies at high risk of bias, the overall prevalence of diabetes (12.4%; 95% CI, 9.5-16; $n = 12\ 077/12\ 870$; I^2 : 93%; 22/31 studies) and hypertension (16.8%; 95% CI, 11.5-23.7; $n = 11\ 912/12\ 709$; I^2 : 96%; 25/37 studies) was similar. Moreover, in patients with hypertension, RR for severe Covid-19 remained the same but heterogeneity decreased (1.40; 95% CI, 0.65-3.00; $n = 53/2023$; I^2 : 0%; $P = .389$, 2/8 studies), whereas the risk for ICU admission decreased (2.62; 95% CI, 1.45-4.75; $n = 143/1733$; I^2 : 15%; $P = .001$; 2/3 studies), and mortality increased (3.24; 95% CI, 1.27-8.28; $n = 32/2063$; I^2 : 9%; $P = .014$; 2/5 studies).

Table 1. Characteristics of the Included Studies

No.	ID	Author	Publishing Date	Country	Study Design	Selection Criteria	Setting	Centers	Sample Males, n Size (%)	Age, Mean \pm SD	Molecular Diagnosis
1	43	Grasselli et al.	4/6/20	Italy	Retrospective case series	Severe (ICU)	Inpatient	Multicenter	1043 1304 (82)	63 \pm 10	RT-PCR
2	44	Wang et al.	4/3/20	China	Retrospective case series	General	Outpatient	Single	1012 524 (52)	50 \pm 14	RT-PCR
3	489	COVID-19 NIRST	3/4/20	Australia	Retrospective case series	General	Community	Multicenter	23 13 (52)	48 \pm 18	NA
4	1405	Fried et al.	4/3/20	USA	Retrospective case series	General	Inpatient	NR	4 2 (50)	54 \pm 12	NA
5	7916	Zhang et al.	2/17/20	China	Retrospective case series	General	Inpatient	Single	140 71 (51)	57 \pm 10	RT-PCR
6	7929	Liu et al.	2/9/20	China	Retrospective case series	General	Inpatient	Single	12 8 (67)	53 \pm 18	RT-PCR
7	7942	Chan et al.	1/24/20	China	Retrospective case series	General	Inpatient	Single	6 3 (50)	46 \pm 22	RT-PCR
8	7949	Xu et al.	2/28/20	China	Retrospective case series	General	Inpatient	Single	90 39 (43)	50 \pm 11	RT-PCR
9	8070	Pung et al.	3/28/20	Singapore	Retrospective case series	General	Outpatient	Multicenter	17 7 (41)	40 \pm 11	NA
10	8149	KSID et al.	3/24/20	Republic of Korea	Retrospective case series	Death patients	Community	Multicenter	54 33 (61)	75 \pm 10	NA
11	8236	Long et al.	3/15/20	China	Retrospective case series	General	Inpatient	Single	10 3 (30)	54 \pm 27	RT-PCR
12	8264	Qui et al.	4/2/20	China	Retrospective case series	Severe (ICU)	Inpatient	Single	10 0 (0)	65 \pm 9	RT-PCR
13	8405	Wang et al.	3/31/20	China	Retrospective case series	General	Inpatient	Single	116 67 (58)	54 \pm 22	RT-PCR
14	8424	Zhang et al.	3/31/20	China	Retrospective case series	Severe (critical)	Inpatient	Multicenter	4 2 (50)	57 \pm 18	RT-PCR
15	8525	Meng et al.	3/31/20	China	Retrospective case series	General	Inpatient	Single	42 24 (57)	64 \pm 10	RT-PCR
16	8542	Escalera et al.	4/2/20	Bolivia	Retrospective case series	General	Both in- and out-patient	Multicenter	12 6 (50)	36 \pm 15	RT-PCR
17	8581	Kim et al.	4/6/20	Republic of Korea	Retrospective case series	General	Inpatient	Multicenter	28 15 (54)	43 \pm 13	RT-PCR
18	8586	Lescure et al.	3/27/20	France	Retrospective case series	General	Inpatient	Multicenter	5 3 (60)	47 \pm 20	RT-PCR

Table 1. Continued

No.	ID	Author	Publishing Date	Country	Study Design	Selection Criteria	Setting	Centers	Sample Size	Males (%)	n	Age, Mean \pm SD	Molecular Diagnosis
19	8606	Wang et al.	3/30/20	China	Retrospective case series	General	Inpatient	Single	339	166 (49)	69 \pm 8	RT-PCR	
20	8609	Mo et al.	3/16/20	China	Retrospective case series	General	Inpatient	Single	155	86 (55)	54 \pm 18	NA	
21	8645	Wang et al.	3/31/20	China	Retrospective case series	General	Inpatient	Single	5	3 (60)	61 \pm 8	RT-PCR	
22	8680	Young et al.	3/3/20	Singapore	Retrospective case series	General	Inpatient	Multicenter	18	9 (50)	47 \pm 10	RT-PCR	
23	8691	Shen et al.	3/27/20	China	Prospective case series	Severe (ARDS)	Inpatient	Single	5	3 (60)	54 \pm 15	RT-PCR	
24	8816	To et al.	3/23/20	Hong Kong	Retrospective case series	General	Inpatient	Multicenter	23	13 (57)	62 \pm 19	RT-PCR	
25	8844	Yuan et al.	3/19/20	China	Retrospective case series	General	Inpatient	Single	27	12 (44)	60 \pm 16	RT-PCR	
26	8898	Fang et al.	3/21/20	China	Retrospective case series	General	Inpatient	Single	32	16 (50)	41 \pm 15	RT-PCR	
27	8920	Liu et al.	3/12/20	China	Retrospective case series	General	Inpatient	Single	10	4 (40)	43 \pm 10	RT-PCR	
28	8965	Zhao et al.	3/12/20	China	Retrospective case series	General	Inpatient	Multicenter	19	11 (58)	48 \pm 21	RT-PCR	
29	8969	Lu et al.	3/17/20	China	Retrospective case series	General	Inpatient	Single	5	1 (20)	52 \pm 9	RT-PCR	
30	9041	Wang et al.	2/7/20	China	Retrospective case series	General	Inpatient	Single	138	75 (54)	56 \pm 19	RT-PCR	
31	9056	Chen et al.	3/30/20	China	Retrospective case series	General	Inpatient	Single	22	14 (64)	37 \pm 18	RT-PCR	
32	9094	Ye et al.	4/2/20	China	Retrospective case series	General	Inpatient	Single	5	3 (60)	40 \pm 14	RT-PCR	
33	9113	Wang et al.	3/23/20	China	Retrospective case series	General	Inpatient	Single	114	58 (51)	53 \pm 9	RT-PCR	
34	9122	Guo et al.	3/31/20	China	Retrospective case series	General	Inpatient	Single	174	20 (11)	61 \pm 9	RT-PCR	
35	9123	Zhang et al.	3/20/20	China	Retrospective case series	General	Inpatient	Multicenter	645	328 (51)	41 \pm 15	RT-PCR	
36	9125	Wang et al.	3/5/20	China	Retrospective case series	General	Inpatient	Single	18	10 (56)	39 \pm 19	RT-PCR	

Table 1. Continued

No.	ID	Author	Publishing Date	Country	Study Design	Selection Criteria	Setting	Centers	Sample Size	Males (%)	n	Age, Mean \pm SD	Molecular Diagnosis
37	9151	Zhu et al.	3/13/20	China	Retrospective case series	General	Inpatient	Multicenter	32	NA	46	46 \pm 13	RT-PCR
38	9171	Cai et al.	4/2/20	China	Retrospective case series	General	Inpatient	Single	298	145 (48)	48	48 \pm 21	RT-PCR
39	9174	Sun et al.	3/25/20	Singapore	Case control	General	Inpatient	Single	54	29 (54)	42	42 \pm 15	RT-PCR
40	9175	Cao et al.	4/2/20	China	Retrospective case series	General	Inpatient	Single	102	53 (52)	54	54 \pm 22	RT-PCR
41	9198	Ren et al.	2/11/20	China	Retrospective case series	Severe (ARDS)	Inpatient	Single	5	3 (60)	54	54 \pm 10	RT-PCR
42	9307	Guo et al.	3/27/20	China	Retrospective case series	General	Inpatient	Single	187	91 (49)	59	59 \pm 15	RT-PCR
43	9314	Arentz et al.	3/19/20	USA	Retrospective case series	Severe (ICU)	Inpatient	Single	21	11 (52)	70	70 \pm 12	RT-PCR
44	9321	Zhang et al.	3/26/20	China	Retrospective case series	General	Inpatient	Multicenter	28	17 (61)	65	65 \pm 10	RT-PCR
45	9332	NCCE et al.	3/13/20	Iran	Retrospective case series	Death patients	Community	Multicenter	514	6629 (58)	54	54 \pm 16	RT-PCR
46	9339	Ding et al.	3/20/20	China	Retrospective case series	General	Inpatient	Single	5	2 (40)	50	50 \pm 10	NA
47	9340	Albarello et al.	2/26/20	Italy	Retrospective case series	General	Inpatient	Single	2	1 (50)	66	66 \pm 1	RT-PCR
48	9377	Zhang et al.	3/26/20	China	Retrospective case series	General	Inpatient	Single	17	8 (47)	49	49 \pm 13	RT-PCR
49	9400	Wei et al.	2/28/20	China	Retrospective case series	General	Inpatient	Multicenter	78	39 (50)	33	33 \pm 18	RT-PCR
50	9431	Shi et al.	3/25/20	China	Retrospective case series	General	Inpatient	Single	416	205 (49)	64	64 \pm 12	RT-PCR
51	9446	Wang et al.	3/30/20	China	Retrospective case series	Severe (ARDS)	Inpatient	Multicenter	17	7 (41)	65	65 \pm 14	RT-PCR
52	9496	Xin et al.	3/30/20	China	Retrospective case series	General	Inpatient	Single	8	6 (75)	64	64 \pm 18	NA
53	9608	CDC COVID-19 RT	4/3/20	USA	Retrospective case series	General	Inpatient, outpatient, and community	Multicenter	7162	NA	NA	NA	RT-PCR
54	9609	Iwasawa et al.	3/31/20	Japan	Retrospective case series	General	Inpatient	Single	6	2 (33)	69	69 \pm 3	RT-PCR

Table 1. Continued

No.	ID	Author	Publishing Date	Country	Study Design	Selection Criteria	Setting	Centers	Sample Size	Males, n (%)	Age, Mean \pm SD	Molecular Diagnosis
55	9622	Liu et al.	3/27/20	China	Retrospective case series	General	Inpatient	Single	56	31 (55)	58 \pm 13	RT-PCR
56	9667	Guan et al.	3/26/20	China	Retrospective case series	General	Inpatient	Multicenter	1590	904 (57)	49 \pm 16	RT-PCR
57	9679	Wong et al.	3/27/20	Hong Kong	Retrospective case series	General	Inpatient	Multicenter	64	26 (41)	56 \pm 19	RT-PCR
58	9695	Hu et al.	3/4/20	China	Retrospective case series	General	Inpatient	Single	24	8 (33)	33 \pm 28	RT-PCR
59	9702	Xie et al.	4/2/20	China	Retrospective case series	General	Inpatient	Single	79	44 (56)	60 \pm 13	NA
60	9764	Xu et al.	3/13/20	China	Retrospective case series	General	Inpatient	Single	51	25 (49)	42 \pm 20	RT-PCR
61	10641	Liu et al.	3/23/20	China	Retrospective case series	Severe (ICU)	Inpatient	Single	8	7 (88)	63 \pm 11	RT-PCR
62	10782	Gao et al.	3/17/20	China	Retrospective case series	General	Inpatient	Single	43	26 (60)	44 \pm 12	RT-PCR
63	10860	McMichael et al.	3/27/20	USA	Retrospective case series	General	Both in- and outpatient	Multicenter	167	55 (33)	72 \pm 13	RT-PCR
64	10861	Bai et al.	3/10/20	China	Case control	General	Inpatient	Multicenter	219	119 (54)	45 \pm 15	RT-PCR
65	1	CDC COVID-19 RT	4/8/20	USA	Retrospective case series	General	Inpatient	Multicenter	159	NA	NA	NA

General selection criteria were patients hospitalized because of pneumonia caused by SARS-CoV-2. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; NA, not available; NR, not reported.

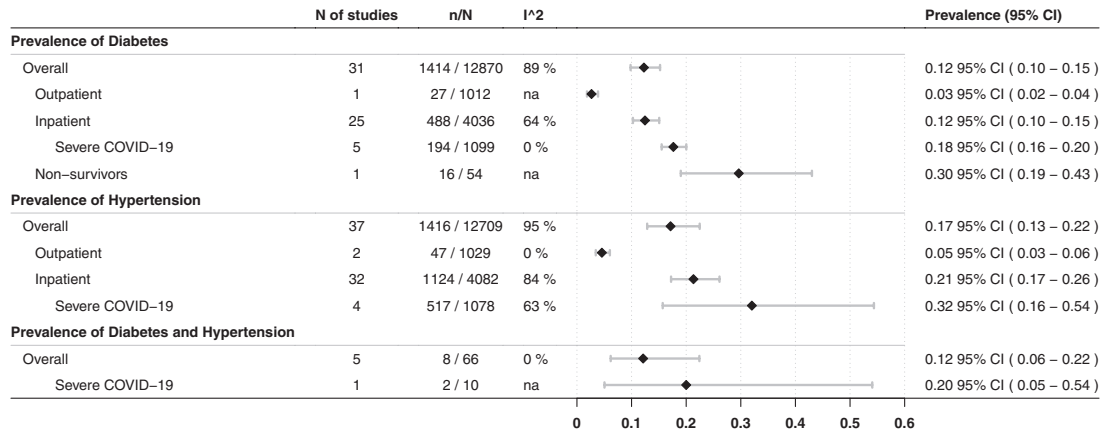


Figure 2. Prevalence of diabetes and hypertension, overall and by subgroups. Five studies in the diabetes, and 3 in the hypertension overall prevalence were not included in subgroups as they did not specify their setting. Nonsurvivor patients in diabetes were not included in the overall prevalence. Severe Covid-19 patients are also included in the inpatient subgroup prevalence; these patients were those from studies that included only severe, critical, or ICU patients, with or without acute respiratory distress syndrome. All patients included in the overall prevalence for the diabetes and hypertension population were in-patients. Covid-19, coronavirus disease 2019; ICU, intensive care unit.

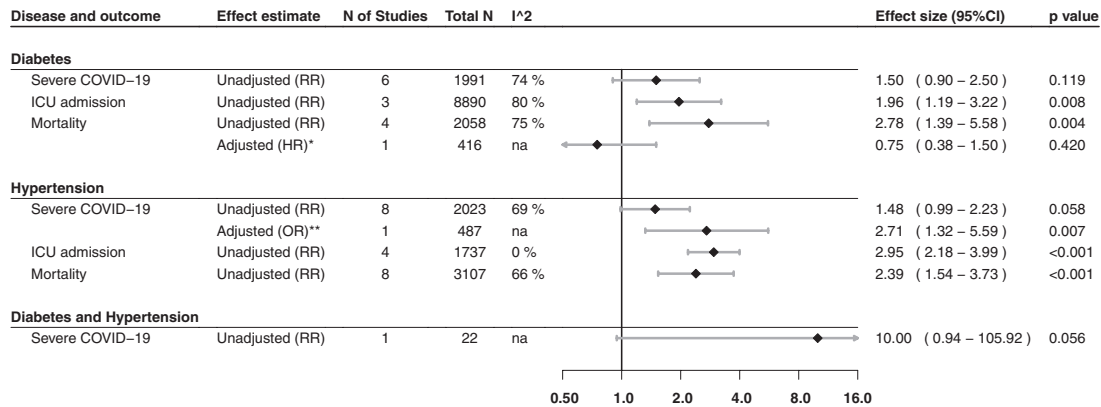


Figure 3. Risk estimates for severe Covid-19, intensive care unit admission, and mortality. RR = relative risk. HR = hazard ratio. *Adjusted for age, preexisting cardiovascular disease (hypertension, coronary heart disease, and chronic heart failure), cerebrovascular disease, chronic obstructive pulmonary disease, renal failure, cancer, acute respiratory distress syndrome, creatine levels, NT-proB-type natriuretic peptide levels, and cardiac injury. **Adjusted for time to admission.

After excluding single-center studies from the analysis, RR for severe Covid-19 among patients with diabetes increased (2.1; 95% CI, 1.20-3.66; n = 1613/1991; I²: 33%; P = .009; 2/6 studies). In contrast, RR for ICU admission decreased (1.80; 95% CI, 0.90-3.61; n = 8752/8890; I²: 88%; P = .096; 2/3 studies). Additionally, in patients with hypertension, RR for severe Covid-19 increased (2.55; 95% CI, 2.06-3.16; n = 1613/2023; I²: 0%; P < .0001; 2/8 studies); for ICU admission decreased (2.70; 95% CI, 1.58-4.60; n = 1595/1733; I²: 20%; P = .0002; 2/3 studies); and, for mortality increased (3.32; 95% CI, 1.36-8.10; n = 1595/2063; I²: 13%; P = .008; 2/5 studies).

Non-predefined sensitivity analyses

Because there was high variability in the definition of severe Covid-19 used by authors, we analyzed the risk for severe Covid-19 after including only those studies that defined severity according to the World Health Organization definition [44] or that of the novel coronavirus

pneumonia prevention and control program (6th ed.) [27, 45]. The RR resulted in similar estimates but decreased heterogeneity in diabetes (0.97; 95% CI, 0.65-1.46; $n = 335$; I^2 : 0%; $P = .886$), and hypertension (1.03; 95% CI, 0.67-1.57; $n = 345$; I^2 : 38%; $P = .909$). The complete description of sensitivity analysis is provided separately [27].

Minimal sufficient adjustment sets

According to our DAG, conditioning age and obesity is necessary to analyze the effect of diabetes on mortality, whereas for hypertension, age, diabetes, and obesity are necessary [27].

Discussion

Main findings

Our results suggest an overall prevalence of 12% and 17% for diabetes and hypertension (respectively) among nonpregnant, adult patients with Covid-19, respectively. Additionally, these comorbidities were associated with an increased risk for ICU admission and mortality. We found an overwhelming proportion of studies at high risk of data repetition, which indicates a high risk of misrepresentation of estimates in previous systematic reviews that did not address this issue [16, 18-20]. The body of evidence comprises observational studies at moderate to high risk of bias yielding low confidence in the estimates.

Strengths and limitations

We developed a methodology to identify publications at high risk of patient repetition, which, compared with previous systematic reviews, provides a major strength to the current analysis [16, 18-20]. Moreover, we also analyzed and grouped the various definitions used for severe Covid-19. From this, we conclude that this outcome lacks interpretability and therefore clinical significance because of the large heterogeneity in the definitions used. Hence, previous systematic reviews that have analyzed this outcome individually or as part of a composite, suffer from this limitation [16, 18-20]. Furthermore, although we could not perform a thorough isolation of the effect of comorbidities, we identified major confounders of our estimates using DAG [46].

Our study has several limitations. The effects of diabetes and hypertension in univariate analysis cannot be attributed only to these exposures because, aside from possible confounders, patients may have had other comorbidities. To overcome this limitation, we extracted data from reported multivariate analyses. However, because their scarcity, we could not synthesize adjusted estimates. Second, most published studies are sourced from China and may be less generalizable to populations in other parts of the world. Moreover, 3 of the included studies provided data on demographic or biochemical parameters such as blood pressure values, glycemic control markers, duration of disease, or smoking; however, we could not perform an adjusted analysis because these studies did not coincide with the assessed outcomes. Finally, auxiliary reasons for the observed risks could be a higher prevalence of obesity, cardiovascular, and renal disease in these patients. Additionally, elderly individuals are overrepresented among Covid-19 patients requiring hospital admission and critical care, where diabetes and hypertension is highest. Thus, the risks attributed to these comorbidities in relation to Covid-19 might be confounded, as our DAG suggests [27].

Comparison with previous studies

Diabetes. Two smaller reviews noted a prevalence of diabetes between 10% and 11.9% in Covid-19, comparable to our estimates [16, 17]. However, our estimates are lower than those reported by Shi et al. of 14.3% [43]. Furthermore, compared with the 9.3% global community prevalence of diabetes [47], our study found a 12% prevalence, suggesting a higher figure. In

contrast to author-defined severe Covid-19, dichotomous outcomes of disease severity such as ICU admission and mortality were significantly elevated (~2- and ~3-fold, respectively) in diabetes. This is of particular interest because Huang et al. noted an increased risk of a composite poor outcome in patients with diabetes, which included severe Covid-19 as one of the outcomes. However, our analysis suggests that severe Covid-19 is a largely heterogeneous outcome that lacks interpretability and may not accurately reflect the outcomes of interest [20].

Additionally, 1 study of 1382 Covid-19 patients with diabetes found a 2.79-fold risk of admission to the ICU [48], higher than our findings of 1.96-fold in 8890 patients. However, the reported risk of Covid-19 mortality in diabetes was 2.85- to 3.21-fold, consistent with our findings [9, 48]. Other meta-analyses did not report ICU admission or mortality risk estimates [16, 49]. Comparatively, the SARS epidemic in 2003, also caused by a betacoronavirus, was associated with a 3-fold risk of poor outcomes in the presence of diabetes, the highest among all comorbidities [50].

The heightened Covid-19 risks in diabetes are multifactorial. Diabetes may facilitate the entry of SARS-CoV-2 by increased expression of ACE2 surface receptors because of the disease itself and the treatment strategies used [10, 11, 51-53]. Furthermore, diabetes leads to dysregulation of immune responses by cytokines such as IL-6 and attenuating anti-inflammatory signaling leading to increased end-organ injury [10, 11, 54-56]. Given that obesity and diabetes often coexist [57], at least part of the heightened Covid-19 risks in diabetes could be attributed to comorbid obesity, an emerging independent risk factor for severe Covid-19 [58]. Furthermore, because diabetes is independently associated with comorbidities, Covid-19 acts as an additional insult to preexisting comorbidities. For instance, hypoglycemia, a comorbidity of diabetes, may be masked by hypoglycemia unawareness in asymptomatic Covid-19 carriers with diabetes mellitus with serious clinical consequences [6].

Hypertension. Initial reports indicated a 26% to 30% prevalence of hypertension in Covid-19 patients [9, 59]. Published data from systematic reviews reported a 17.1% to 20% prevalence of hypertension in Covid-19, comparable to our estimates of 17% in our analysis of 12 709 patients [16, 17]. In the inpatient setting, our results suggest that hypertension prevalence could be up to 26%, which is still lower compared with recent data from the United States of ~50% [60, 61]. Moreover, our estimates were lower than the 31.1% global prevalence of hypertension, which could suggest an average (or below average) risk of Covid-19 [62].

We found a nonconclusive risk of severe Covid-19 in hypertension. Other reports suggest a higher risk of severe Covid-19 in hypertensives, of approximately 2.3-fold [17, 49]. However, after analyzing the important variation in the parameters used to define severity, we conclude that these estimates are noninterpretable. In contrast, the risk of ICU admission, which we consider a more reliable proxy of Covid-19 severity, was elevated in our analysis. Finally, we found an elevated risk of Covid-19 mortality associated with hypertension that was not described in other meta-analyses but is comparable to the 2.4- to 3.0-fold risk reported in primary studies [9, 63].

The observed risk of Covid-19 in patients with hypertension is likely multifactorial. The underlying immune dysregulation, with a higher propensity for an exaggerated immune response to viral exposure, resulting in a cytokine storm and end-organ injury could be a major contributor to this risk [64, 65]. Additional contributors may include a higher sympathetic drive, hyperactivity of T-helper cells, increased ACE2 expression, and an enhanced angiotensin II/angiotensin 1-7 ratio reducing anti-inflammatory effects of the latter, and increased pro-inflammatory action of angiotensin II [66-70].

Implications for future research and clinical practice

Future studies of Covid-19 patients with diabetes or hypertension should report on patient characteristics, subtype of hypertension or diabetes, duration of disease, medications used,

and disease control markers. This information would not only be valuable for future systematic reviews but also assist frontline clinicians in individualizing the Covid-19 risks faced by their patients. Furthermore, future studies reporting multivariate analyses should consider our proposed minimal sufficient adjustment sets to avoid unnecessary or overadjustment of prognosticators. To date, the risk for severe Covid-19 faced by patients with diabetes and hypertension is unclear because of the large heterogeneity in the author definitions of Covid-19 severity. Until a universal definition of Covid-19 severity is adopted, we propose using the ICU admission rate as a more objective way to define severity.

Conclusion

Compared with previous reviews, our results suggest a lower prevalence of diabetes and hypertension in hospitalized Covid-19 patients. These patients face a higher risk of poor outcomes compared with those without these comorbidities. However, the body of evidence are at high risk of bias and provide low confidence in the estimates.

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