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

Francisco J. Barrera,¹,²,³* Skand Shekhar,⁴,⁵* Rachel Wurth,⁴ Pablo J. Moreno-Pena,² Oscar J. Ponce,³,⁶ Michelle Hajdenberg,⁷ Neri A. Alvarez-Villalobos,¹,²,³,⁸ Janet E. Hall,⁵ Ernesto L. Schiffrin,⁹ Graeme Eisenhofer,¹⁰ Forbes Porter,¹¹ Juan P. Brito,³ Stefan R. Bornstein,¹²,¹³,¹⁴ Constantine A. Stratakis,⁴ José Gerardo González-González,¹,²,³,⁸ René Rodríguez-Gutiérrez,¹,²,³,⁸† Fady Hannah-Shmouni⁴†

*Authors share equal credit
† Corresponding authors

1. Endocrinology Division, Internal Medicine Department, University Hospital “Dr. Jose E. Gonzalez”, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico.

2. Plataforma INVEST-KER Unit Mayo Clinic (KER Unit Mexico), School of Medicine, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico.

3. Knowledge and Evaluation Research, Mayo Clinic, Rochester, Minnesota, USA.

4. Section on Endocrinology & Genetics (SEGEN), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Bethesda, Maryland, USA.

5. Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health (NIH), Research Triangle Park, North Carolina, USA.

Published by Oxford University Press on behalf of the Endocrine Society 2020. This work is written by (a) US Government employee(s) and is in the public domain in the US. js.2020-00197. See endocrine.org/publications for Accepted Manuscript disclaimer and additional information. This Open Access article contains public sector information licensed under the Open Government Licence v2.0 (http://www.nationalarchives.gov.uk/doc/open-government-licence/version/2/).
6. Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Perú.

7. College of Arts and Sciences at Washington University in St. Louis, Saint Louis, Missouri, USA.

8. Research Unit, School of Medicine and University Hospital “Dr. Jose E. Gonzalez”, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico.

9. Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, Quebec, Canada.

10. Institute of Clinical Chemistry and Laboratory Medicine, and Department of Medicine III, University Hospital Carl Gustav Carus, TechnischeUniversität Dresden, Germany.

11. Division of Translational Medicine, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (NIH), Bethesda, Maryland, USA.

12. Department of Medicine III, University Hospital Carl Gustav Carus, Dresden, Germany.

13. Department of Diabetes, School of Life Course Science & Medicine, King’s College London, London, UK.

14. Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, University Hospital, Zürich, Switzerland.
Corresponding authors:

Fady Hannah-Shmouni, MD, DABIM, FRCPC
Internal Medicine-Endocrinology, Hypertension & Metabolic Genetics
Principal Investigator, Endocrine Genetics & Hypertension
Director, Graduate Medical Education, Office of Education
Section on Endocrinology & Genetics
NICHD, National Institutes of Health
10 Center Drive, Room 1-3150
Bethesda, MD, USA, 20892
T:+1-301-827-2693
C:+1-240-328-0014
F:+1-301-402-0574
E: fady.hannah-shmouni@nih.gov
René Rodríguez-Gutiérrez, MD, MSc,
Professor of Medicine,
Division of Endocrinology, Internal Medicine Department,
School of Medicine and University Hospital “Dr. José E. González”,
Universidad Autonoma de Nuevo Leon,
Ave. Gonzalitos y Madero s/n 64460,
Monterrey, México.
Assistant Professor of Medicine,
Knowledge and Evaluation Research Unit,
Mayo Clinic,
201 W. Center St,
Rochester, Minnesota 55902, USA.
C: +52 8114749146
F: +52 83876185
E: rodriguezgutierrez.rene@mayo.edu

Conflict of interest declaration: The authors declare no conflict of interest
ABSTRACT

Covid-19 has impacted millions of people and may disproportionately affect those with hypertension and diabetes. Due to 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 language 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 using the. We included 65 (15,794 participants) observational studies at moderate-to-high risk of bias. Overall prevalence of diabetes and hypertension was 12% (95% CI 10-15%, n=12870, $I^2$: 89%), and 17% (95% CI 13-22%, n=12709, $I^2$: 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 ICU admission and mortality were 1.96 (95% CI 1.19-3.22, n=8,890, $I^2$: 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 1.18-7.99, 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 ICU admission and mortality for patients with diabetes or hypertension who developed Covid-19 is increased compared to those without these comorbidities.

Keywords: Covid-19, SARS-CoV-2, diabetes mellitus, hypertension, endocrinology

PROSPERO registration number: CRD42020176582.
INTRODUCTION

Coronavirus disease 2019 (Covid-19) is the worst pandemic in the last 100 years spanning more than 200 countries and affecting millions of individuals worldwide. 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 receptor. 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. 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.

A great risk of severe Covid-19 has been reported in patients with diabetes and hypertension. One study of 191 patients reported a mortality risk of 2.85-fold and 3.05-fold for those with diabetes and hypertension, respectively. Furthermore, the Chinese Center for Disease Control reported a higher case fatality rate for persons with diabetes compared to those without (7.3% vs. 2.3%, respectively). This risk may be explained by a dysregulated immune response, a higher comorbidity burden, and alterations of ACE2 cellular expression. 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, as well as other cardiovascular conditions that have been shown to enhance ACE2 expression.

Previous systematic reviews reported a prevalence of diabetes and hypertension in patients with Covid-19 ranging from 9.7-11.9% and 17.1-20%, respectively. The risks of severe Covid-
19 in patients with diabetes and hypertension were ~3 and ~2-fold, respectively.\textsuperscript{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.\textsuperscript{16,18-21} This has been listed by authors as a major limitation,\textsuperscript{20} and has raised major editorial concerns.\textsuperscript{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 (MOOSE) and Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA).\textsuperscript{25,26} Registration ID: CRD42020176582, available at: https://www.crd.york.ac.uk/prospero/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 population (age <18 years). We did not set a criterion
based on Covid-19 diagnosis definition, exposure ascertainment or outcome definition as these were expected to be different and/or with limited rigor.

**Search strategy**

An experienced librarian (NAV), with input from investigators, searched several databases for peer-reviewed manuscripts in English language 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. See **Supp. 1** (https://doi.org/10.6084/m9.figshare.12636428.v1).

**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 pre-piloted instructions in a round of title-and-abstract and one of full-text screening. In round one, disagreements were included; and in round two, disagreements were resolved by consensus or arbitration by a third investigator (FHS). To identify articles with high probability of patient repetition, studies that were included after full-text screening followed a preliminary data extraction conducted by two 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.\textsuperscript{27} Data extraction was also performed in an independent and duplicated manner using a standardized and pre-piloted.

**Risk of bias and confidence in the body of evidence**

For case series, we modified two tools and analyzed: selection, ascertainment of outcomes and exposures, causality, and reporting.\textsuperscript{28,29} For case control studies, the Newcastle-Ottawa Scale was used.\textsuperscript{30} The quality of evidence for each outcome was determined using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).\textsuperscript{31} Both risk of bias and overall quality of evidence assessment were performed independently and in duplicate. Disagreements were resolved by consensus between the two reviewers, or by arbitration by a third author (RRG).\textsuperscript{27} Full details are listed elsewhere.\textsuperscript{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 - GLMM).\textsuperscript{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.\textsuperscript{34} Meta-analysis of unadjusted and adjusted estimates were not combined. We were unable to calculate adjusted estimates due to 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.\textsuperscript{35} All statistical analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria).\textsuperscript{36}
Analysis of subgroups and sensitivity

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

RESULTS

Search strategy yielded 5,484 studies. After deduplication and screening, 122 studies fulfilled our selection criteria (Figure 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%). Ultimately, 65 (15,794 patients) were included in our analysis. Overall, 18 (28%) studies had low risk of bias, 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. We did not assess risk of publication bias through the funnel plot due to the limited number of studies.

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 reverse transcription-polymerase chain reaction (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 33-75 years. A total of five 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. 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% CI 10-15%; n=12870; I²: 89%) for diabetes, 17% (95% CI 13-22%; n=12709; I²: 95%) for hypertension, and 12% (95% CI 6-22%; n=54; I²: 0%) for coexisting diabetes and hypertension (Figure 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; I²: 74%, \( p=0.118 \)), ICU admission (1.96, 95% CI 1.19-3.22; n=8890; I²: 80%, \( p=0.007 \)), and mortality (2.78, 95% CI 1.39-5.58; n=2058 I²: 75%, \( p=0.004 \)). For patients with hypertension; Covid-19 severity (1.48, 95% CI 0.99-2.23; n=2023; I²: 69%, \( p=0.058 \)), ICU admission (2.95, 95% CI 2.18-3.99; n=1737; I²: 0%, \( p<0.001 \)), and mortality (2.39, 95% CI 1.54-3.73; n=3107; I²: 66%, \( p<0.001 \)). Furthermore, for patients with diabetes and hypertension, RR for Covid-19 severity was 10 (95% CI 0.94-105.92, n=22, I²: not applicable, \( p=0.056 \)).
Narrative synthesis

Adjusted and unadjusted estimates for mortality (hazard ratio, HR) in patients with diabetes were non-conclusive in two studies (0.75, 95% CI 0.38-1.50, n=416, \( p = .420 \)) and (1.09, 95% CI 0.57-2.08, n=339, \( p = .799 \)).\(^{42}\) 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 HR 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 Figure 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=12077/12870, \( I^2 = 93\% \), 22/31 studies) and hypertension (16.8%, 95% CI 11.5%-23.7%, n=11912/12709, \( I^2 = 96\% \), 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 .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).

After excluding single centered 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, \( I^2 = 33\% \), \( p = .009 \), 2/6 studies). In contrast, RR for ICU admission decreased (1.80, 95% CI 0.90-3.61, n=8752/8890, \( I^2 = 88\% \), \( p = .096 \), 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, \( I^2 = 0\% \), \( p = .0001 \), 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

As 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 or that of the novel coronavirus pneumonia prevention and control program (6th ed.). The RR resulted in similar estimates but decreased heterogeneity in diabetes (.97, 95% CI 1.65-1.46, n=335, I²: 0%, p=.886), and hypertension (1.03, 95% CI 1.67-1.57, n=345, I²: 38%, p=.909). The complete description of sensitivity analysis is provided separately.

Minimal sufficient adjustment sets

According to our DAG, conditioning age and obesity is necessary to analyze the effect of diabetes on mortality; while for hypertension, age, diabetes, and obesity.

DISCUSSION

Main findings

Our results suggest an overall prevalence of 12% and 17% for diabetes and hypertension (respectively) among non-pregnant, 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.
The body of evidence is comprised of 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 to 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 due to 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, due to 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, three 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 on the outcome assessed. 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 over-represented 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 10-11.9% 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 to 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 since 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, one study of 1,382 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 8,890 patients. However, the reported risk of Covid-19 mortality in diabetes was 2.85-3.21 fold, consistent with our findings.9,48 Other meta-analyses did not report ICU admission or mortality risk estimates.16,49 Comparatively, the severe acute respiratory syndrome (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 due to the disease itself and the employed treatment strategies.\textsuperscript{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.\textsuperscript{10,11,54-56} Given that obesity and diabetes often coexist,\textsuperscript{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.\textsuperscript{58} Furthermore, since diabetes is independently associated with comorbidities, COVID19 acts as an additional insult to pre-existing 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.\textsuperscript{6}

\textbf{Hypertension}

Initial reports indicated a 26-30\% prevalence of hypertension in Covid-19 patients.\textsuperscript{9,59} Published data from systematic reviews reported a 17.1-20\% prevalence of hypertension in Covid-19, comparable to our estimates of 17\% in our analysis of 12,709 patients.\textsuperscript{16,17} In the inpatient setting, our results suggest that hypertension prevalence could be up to 26\%, which is still lower compared to recent data from the United States of \textasciitilde 50\%.\textsuperscript{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.\textsuperscript{62}

We found a non-conclusive risk of severe Covid-19 in hypertension. Other reports suggest a higher risk of severe Covid-19 in hypertensives, of approximately 2.3-fold.\textsuperscript{17,49} However, after analyzing the important variation in the parameters used to define severity, we conclude that these
estimates, are non-interpretable. 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 2.4-3.0 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 over-adjustment of prognosticators. To date, the risk for severe Covid-19 faced by patients with diabetes and hypertension is unclear due to 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 to 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 to those without these comorbidities. However, the body of evidence are at high risk of bias and provide low confidence in the estimates.
Contributions:

Francisco J. Barrera: figures, study design, data collection, data analysis, data interpretation, writing.

Skand Shekhar: figures, study design, data collection, data analysis, data interpretation, writing.

Rachel Wurth: figures, data collection, data interpretation, writing.

Pablo J. Moreno-Pena: figures, data collection, data interpretation.

Oscar J. Ponce: figures, study design, data collection, data analysis, data interpretation.

Michelle Hajdenberg: data collection, data interpretation.

Neri A. Alvarez-Villalobos: literature search.

Janet E. Hall: study design, data interpretation, approval of final manuscript.

Ernesto Schiffrin: study design, data interpretation, approval of final manuscript.

Graeme Eisenhofer: study design, data interpretation, approval of final manuscript.

Forbes Porter: study design, data interpretation, approval of final manuscript.

Juan P. Brito: figures, study design, data collection, data analysis, data interpretation, approval of final manuscript.

Stefan R. Bornstein: study design, data interpretation, approval of final manuscript.

Constantine A. Stratakis: study design, data interpretation, approval of final manuscript.

Jose Gerardo González-González: study design, data interpretation, approval of final manuscript.

René Rodríguez Gutiérrez: study design, data collection, data analysis, data interpretation, approval of final manuscript.

Fady Hannah-Shmouni: study design, data collection, data analysis, data interpretation, approval of final manuscript.
**Funding:** This work was funded by the intramural research program of the National Institutes of Health.

**Competing Interests:** Nothing to disclose related to the work described in this article. Dr. Stratakis laboratory holds patents on the function of the PRKAR1A, PDE11A, and GPR101 molecules and has received research funding from Pfizer Inc. for work related to GPR101 and acromegaly/gigantism. The funders had no role in the design and conduct of this study, or the preparation of this manuscript.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.
References

1. Organization WH. Coronavirus disease (COVID-19) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Published 2020. Updated April 30, 2020. Accessed May 1, 2020.

2. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [press release]. 2020.

3. Li F, Li W, Farzan M, Harrison SC. Structure of SARS Coronavirus Spike Receptor-Binding Domain Complexed with Receptor. Science. 2005;309(5742):1864.

4. Guan W-j, Liang W-h, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J. 2020:2000547.

5. Fauci AS, Lane HC, Redfield RR. Covid-19 — Navigating the Uncharted. New England Journal of Medicine. 2020;382(13):1268-1269.

6. Ademolu AB. Whipple Triad Its Limitations in Diagnosis and Management of Hypoglycemia as a Co-morbidity in Covid-19 Diabetics and Diabetes Mellitus in General-A Review. International Journal of Diabetes and Endocrinology. 5(2):23-26.

7. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242.

8. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020:S2213-2600(2220)30116-30118.

9. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020.

10. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020.

11. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 2020.
12. Shekhar S, Wurth R, Kamilaris CDC, et al. Endocrine Conditions and COVID-19. *Horm Metab Res.* 2020.
13. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *New England Journal of Medicine.* 2020.
14. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol.* 2020.
15. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.* 2005;111(20):2605-2610.
16. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis.* 2020:101623.
17. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *Int J Infect Dis.* 2020;94:91-95.
18. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020;109(5):531-538.
19. Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *medRxiv.* 2020:2020.2004.20054361.
20. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr.* 2020;14(4):395-403.
21. Ioannidis JPA. Coronavirus disease 2019: the harms of exaggerated information and non-evidence-based measures. *Eur J Clin Invest.* 2020;n/a(n/a):e13222.
22. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA ed.: Cochrane; 2019: www.training.cochrane.org/handbook.
23. Bauchner H, Golub RM, Zylke J. Editorial Concern—Possible Reporting of the Same Patients With COVID-19 in Different Reports. *JAMA.* 2020.
24. Iverson C. Duplicate Publication. In: Oxford University Press; 2009.
25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008-2012.
26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.
27. Francisco B, Shekhar S, Ponce O, Rodríguez-Gutiérrez R, Hannah-Shmouni F. Prevalence and Impact of Diabetes and Hypertension on Patients with Covid-19. https://figshare.com/articles/online_resource/Prevalence_of_Diabetes_and_Hypertension_and_their_Associated_Risks_for_Poor_Outcomes_in_Covid-19_Patients/12636428 Published 2020. Accessed.
28. National Heart LaBl. *Study Quality Assessment Tools.*
29. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med.* 2018;23(2):60-63.
30. Wells G, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.
31. R Ryan SH. *How to GRADE the Quality of the Evidence.* London, UK: Cochrane Consumers and Communication Group. Cochrane; 2016.
32. Center TMCE-bP. Simulation-Based Comparison of Methods for Meta-Analysis of Proportions and Rates. In. Online2013.
33. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Research Synthesis Methods.* 2019;10(3):476-483.
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-188.
35. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557.
36. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing. https://www.r-project.org/. Published 2020. Accessed.
37. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol.* 2008;8(1):70.
38. Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. *Nephrology Dialysis Transplantation.* 2014;30(9):1418-1423.
39. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology (Cambridge, Mass).* 2004;15(5):615-625.
40. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology.* 2003;14(3):300-306.
41. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package ‘dagitty’. *Int J Epidemiol.* 2016;45(6):1887-1894.
42. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020.
43. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Critical Care.* 2020;24(1):108.
44. WHO. Clinical management of severe acute respiratory infection when COVID-19 disease is suspected Interim guidance. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Published 2020. Updated March 13, 2020. Accessed.
45. Commission CNH. Novel Coronavirus Pneumonia Prevention and Control Plan (6th ed.). (In Chinese). http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8af7c2.shtml. Published 2020. Accessed.
46. Hernán MA. A definition of causal effect for epidemiological research. *Journal of epidemiology and community health.* 2004;58(4):265-271.
47. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9<sup>th</sup> edition. *Diabetes Res Clin Pract.* 2019;157.
48. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol.* 2020;127:104354.
49. Chen Y, Gong X, Wang L, Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. *medRxiv.* 2020:2020.2003.2025.20043133.
50. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical Features and Short-term Outcomes of 144 Patients With SARS in the Greater Toronto Area. *JAMA.* 2003;289(21):2801-2809.
51. Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE2 Expression within Different Organs of the NOD Mouse. *Int J Mol Sci.* 2017;18(3).
52. Zhang W, Xu Y-Z, Liu B, et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *ScientificWorldJournal.* 2014;2014:603409-603409.
53. 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(7):e00127-00120.
54. Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol.* 1999;26(3-4):259-265.
55. Calvet HM, Yoshikawa TT. INFECTIONS IN DIABETES. *Infect Dis Clin North Am.* 2001;15(2):407-421.
56. Daryabor G, Kabelitz D, Kalantar K. An update on immune dysregulation in obesity-related insulin resistance. *Scand J Immunol.* 2019;89(4):e12747.
57. Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. *Diabetes Metab Syndr Obes.* 2013;6:327-338.
58. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. *Clin Infect Dis.* 2020.
59. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Internal Medicine.* 2020.
60. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020.
61. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020.
62. Mills KT, Bundy JD, Kelly TN, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation.* 2016;134(6):441-450.
63. Lippi G, Wong J, Henry BM. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. *Pol Arch Intern Med.* 2020.
64. Amador CA, Barrientos V, Pena J, et al. Spironolactone decreases DOCA-salt-induced organ damage by blocking the activation of T helper 17 and the downregulation of regulatory T lymphocytes. *Hypertension*. 2014;63(4):797-803.

65. Singh MV, Chapleau MW, Harwani SC, Abboud FM. The immune system and hypertension. *Immunol Res.* 2014;59(1-3):243-253.

66. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin–angiotensin system inhibition during the COVID-19 pandemic. *Nature Reviews Nephrology*. 2020.

67. Peiró C, Moncada S. Substituting Angiotensin-(1-7) to Prevent Lung Damage in SARS-CoV2 Infection? *Circulation*. 0(0).

68. Abboud FM, Harwani SC, Chapleau MW. Autonomic neural regulation of the immune system: implications for hypertension and cardiovascular disease. *Hypertension*. 2012;59(4):755-762.

69. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. *Am J Hypertens.* 2020.

70. Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. *JAMA Cardiology*. 2020.
Tables Legends

Table 1. Characteristics of the included studies. General selection criteria included hospitalized due to pneumonia caused by SARS-CoV-2.

Figure Legends

Figure 1. Flow chart of the selection process.

Figure 2. Prevalence of diabetes and hypertension, overall and by subgroups. Five studies in the diabetes, and three in the hypertension overall prevalence were not included in subgroups as they did not specify their setting. Non-survivor 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 inpatients.

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.
Table 1. Characteristics of the included studies. General selection criteria were patients hospitalized due to pneumonia caused by SARS-CoV-2.

| #  | ID  | Author                        | Publishing date | Country | Study design                        | Setting                     | Centers | Sample size | Male, s, n (%) | Age, mean ±SD | Molecular diagnosis |
|----|-----|-------------------------------|-----------------|---------|-------------------------------------|-----------------------------|---------|-------------|----------------|----------------|-------------------|
| 1  | 43  | Grasselli, et al.             | 4/6/20          | Italy   | Retrospective Case Series           | Severe (ICU)                | In-patient | 1043        | 100(82)        | 63±10         | RT-PCR            |
| 2  | 44  | Wang, et al., CMI.            | 4/3/20          | China   | Retrospective Case Series           | General                    | Outpatient | 1012        | 524(52)        | 50±14         | RT-PCR            |
| 3  | 48  | COVID-19 NRIST.               | 3/4/20          | Australia | Retrospective Case Series           | General                    | Community | 23          | 13(52)         | 48±18         | NA                |
| 4  | 14  | Fried, et al.                 | 4/3/20          | USA     | Retrospective Case Series           | General                    | In-patient | NR          | 4             | 54±12         | NA                |
| 5  | 79  | Zhang, et al., EJACI.         | 2/17/20         | China   | Retrospective Case Series           | General                    | In-patient | 140         | 71(51)        | 57±10         | RT-PCR            |
| 6  | 79  | Liu, et al., SCLS.            | 2/9/20          | China   | Retrospective Case Series           | General                    | In-patient | 12          | 8(67)         | 53±18         | RT-PCR            |
| 7  | 42  | Chan, et al., Lancet.         | 1/24/20         | China   | Retrospective Case Series           | General                    | In-patient | 6           | 3(50)         | 46±22         | RT-PCR            |
| 8  | 49  | Xu, et al., EJNMMI.           | 2/28/20         | China   | Retrospective Case Series           | General                    | In-patient | 90          | 39(43)        | 50±11         | RT-PCR            |
| 9  | 70  | Pung, et al.                  | 3/28/20         | Singapore | Retrospective Case Series           | General                    | Outpatient | 17          | 7(41)         | 40±11         | NA                |
| 10 | 49  | KSIID, et al., JKMS, b.       | 3/24/20         | South Korea | Retrospective Case Series          | Death patients             | Community | 54          | 33(61)        | 75±10         | NA                |
| 1  | 36  | Long, et al.                  | 3/15/20         | China   | Retrospective Case Series           | General                    | In-patient | 10          | 3(30)         | 54±27         | RT-PCR            |
| 1  | 64  | Qui, et al.                   | 4/2/20          | China   | Retrospective Case Series           | Severe (ICU)               | In-patient | 10          | 0(0)          | 65±9          | RT-PCR            |
| 1  | 80  | Wang, et al., AUN.            | 3/31/20         | China   | Retrospective Case Series           | General                    | In-patient | 116         | 67(58)        | 54±22         | RT-PCR            |
| 1  | 24  | Zhang, et al., Chest.         | 3/31/20         | China   | Retrospective Case Series           | Severe (Critical)          | In-patient | 4           | 2(50)         | 57±18         | RT-PCR            |
| 1  | 25  | Meng, et al.                  | 3/31/20         | China   | Retrospective Case Series           | General                    | In-patient | 42          | 24(57)        | 64±10         | RT-PCR            |
| # | 85 | Escalera, et al. | 4/2/20 | Bolivia | Retrospective Case Series | General | Both in- and outpatient | Multi center | 12 | 6(50) | 36±15 | RT-PCR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 86 | Kim, et al. | 4/6/20 | Republi c of Korea | Retrospective Case Series | General | In-patient | Multi center | 28 | 15(54) | 43±13 | RT-PCR |
| 1 | 86 | Lescure, et al. | 3/27/20 | France | Retrospective Case Series | General | In-patient | Multi center | 5 | 3(60) | 47±20 | RT-PCR |
| 1 | 86 | Wang, et al., JI. | 3/30/20 | China | Retrospective Case Series | General | In-patient | Single | 339 | 166(49) | 69±8 | RT-PCR |
| 2 | 86 | Mo, et al. | 3/16/20 | China | Retrospective Case Series | General | In-patient | Single | 155 | 86(55) | 54±18 | NA |
| 2 | 86 | Wang, et al., AJKD. | 3/31/20 | China | Retrospective Case Series | General | In-patient | Single | 5 | 3(60) | 61±8 | RT-PCR |
| 2 | 86 | Young, et al. | 3/30/20 | Singapore | Retrospective Case Series | General | In-patient | Multi center | 18 | 9(50) | 47±10 | RT-PCR |
| 2 | 86 | Shen, et al. | 3/27/20 | China | Prospective Case Series | Severe (ARDS) | In-patient | Single | 5 | 3(60) | 54±15 | RT-PCR |
| 2 | 86 | To, et al. | 3/23/20 | Hong Kong | Retrospective Case Series | General | In-patient | Multi center | 23 | 13(57) | 62±19 | RT-PCR |
| 2 | 86 | Yuan, et al. | 3/19/20 | China | Retrospective Case Series | General | In-patient | Single | 27 | 12(44) | 60±16 | RT-PCR |
| 2 | 86 | Fang, et al. | 3/21/20 | China | Retrospective Case Series | General | In-patient | Single | 32 | 16(50) | 41±15 | RT-PCR |
| 2 | 86 | Liu, et al., JID. | 3/12/20 | China | Retrospective Case Series | General | In-patient | Single | 10 | 4(40) | 43±10 | RT-PCR |
| 2 | 86 | Zhao, et al., CID. | 3/12/20 | China | Retrospective Case Series | General | In-patient | Multi center | 19 | 11(58) | 48±21 | RT-PCR |
| 2 | 86 | Lu, et al. | 3/17/20 | China | Retrospective Case Series | General | In-patient | Single | 5 | 1(20) | 52±9 | RT-PCR |
| 3 | 90 | Wang, et al., JAMA. | 2/7/20 | China | Retrospective Case Series | General | In-patient | Single | 138 | 75(54) | 56±19 | RT-PCR |
| 3 | 90 | Chen, et al., AIM. | 3/30/20 | China | Retrospective Case Series | General | In-patient | Single | 22 | 14(64) | 37±18 | RT-PCR |
| 3 | 90 | Ye, et al. | 4/2/20 | China | Retrospective Case Series | General | In-patient | Single | 5 | 3(60) | 40±14 | RT-PCR |
| 3 | 91 | Wang, et al., CR. | 3/23/20 | China | Retrospective Case Series | General | In-patient | Single | 114 | 58(51) | 53±9 | RT-PCR |
| 3 | 91 | Guo, et al., DMRR. | 3/31/20 | China | Retrospective Case Series | General | In-patient | Single | 174 | 20(11) | 61±9 | RT-PCR |
| 3 | 91 | Zhang, et al., IJD. | 3/20/20 | China | Retrospective Case Series | General | In-patient | Multi center | 645 | 328(51) | 41±15 | RT-PCR |
| 3 | 91 | Wang, et al., TERU. | 3/5/20 | China | Retrospective Case Series | General | In-patient | Single | 18 | 10(56) | 39±19 | RT-PCR |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |   |
| 3 | 91 | 51 | Zhu, et al. | 3/13/20 | China | Retrospective Case Series | General | In-patient | Multi center | 32 | NA | 46±13 | RT-PCR |
| 3 | 91 | 71 | Cai, et al., EJACI. | 4/2/20 | China | Retrospective Case Series | General | In-patient | Single | 298 | 145(48) | 48±21 | RT-PCR |
| 3 | 91 | 74 | Sun, et al. | 3/25/20 | Singapore | Case Control | General | In-patient | Single | 54 | 29(54) | 42±15 | RT-PCR |
| 4 | 91 | 75 | Cao, et al. | 4/2/20 | China | Retrospective Case Series | General | In-patient | Single | 102 | 53(52) | 54±22 | RT-PCR |
| 4 | 91 | 98 | Ren, et al. | 2/11/20 | China | Retrospective Case Series | Severe (ARDS) | In-patient | Single | 5 | 3(60) | 54±10 | RT-PCR |
| 4 | 93 | 07 | Guo, et al., J. C. | 3/27/20 | China | Retrospective Case Series | General | In-patient | Single | 187 | 91(49) | 59±15 | RT-PCR |
| 4 | 93 | 14 | Arentz, et al. | 3/19/20 | USA | Retrospective Case Series | Severe (ICU) | In-patient | Single | 21 | 11(52) | 70±12 | RT-PCR |
| 4 | 93 | 21 | Zhang, et al., AO. | 3/26/20 | China | Retrospective Case Series | General | In-patient | Multi center | 28 | 17(61) | 65±10 | RT-PCR |
| 4 | 93 | 32 | NCCE, et al. | 3/13/20 | Iran | Retrospective Case Series | Death patients | Community | Multi center | 514 | 6629(58) | 54±16 | RT-PCR |
| 4 | 93 | 39 | Ding, et al. | 3/20/20 | China | Retrospective Case Series | General | In-patient | Single | 5 | 2(40) | 50±10 | NA |
| 4 | 93 | 40 | Albarello, et al. | 2/26/20 | Italy | Retrospective Case Series | General | In-patient | Single | 2 | 1(50) | 66±1 | RT-PCR |
| 4 | 93 | 77 | Zhang, et al., ERJ. | 3/26/20 | China | Retrospective Case Series | General | In-patient | Single | 17 | 8(47) | 49±13 | RT-PCR |
| 4 | 94 | 00 | Wei, et al. | 2/28/20 | China | Retrospective Case Series | General | In-patient | Multi center | 78 | 39(50) | 33±18 | RT-PCR |
| 5 | 94 | 31 | Shi, et al. | 3/25/20 | China | Retrospective Case Series | General | In-patient | Single | 416 | 205(49) | 64±12 | RT-PCR |
| 5 | 94 | 46 | Wang, et al., AIC. | 3/30/20 | China | Retrospective Case Series | Severe (ARDS) | In-patient | Multi center | 17 | 7(41) | 65±14 | RT-PCR |
| 5 | 94 | 96 | Xin, et al. | 3/30/20 | China | Retrospective Case Series | General | In-patient | Single | 8 | 6(75) | 64±18 | NA |
| 5 | 96 | 08 | CDC COVID-19 RT, b. | 4/3/20 | USA | Retrospective Case Series | General | Inpatient, outpatient and community | Multi center | 7162 | NA | NA | RT-PCR |
| 5 | 96 | 09 | Iwasawa, et al. | 3/31/20 | Japan | Retrospective Case Series | General | In-patient | Single | 6 | 2(33) | 69±3 | RT-PCR |
| 5 | 96 | 22 | Liu, et al., Tj. | 3/27/20 | China | Retrospective Case Series | General | In-patient | Single | 56 | 31(55) | 58±13 | RT-PCR |
| 5 | 96 | 67 | Guan, et al., ERJ. | 3/26/20 | China | Retrospective Case Series | General | In-patient | Multi center | 1590 | 904(57) | 49±16 | RT-PCR |

Downloaded from https://academic.oup.com/jendso/article-abstract/doi/10.1210/jendso/bvaa102/5874109 by guest on 28 July 2020
|   | 596 | Wong, et al. | 3/27/20 | Hospital | Retrospective Case Series | General | In-patient | Multi center | 64 | 26(41) | 56±19 | RT-PCR |
|---|-----|-------------|---------|----------|---------------------------|---------|-------------|--------------|----|-------|-------|--------|
|   | 596 | Hu, et al.  | 3/4/20  | China    | Retrospective Case Series | General | In-patient | Singl e      | 79 | 44(56) | 60±13 | NA     |
|   | 97  | Xie, et al. | 4/2/20  | China    | Retrospective Case Series | General | In-patient | Singl e      | 79 | 44(56) | 60±13 | NA     |
| 50 | 97  | Xu, et al., IUId. | 3/13/20 | China    | Retrospective Case Series | General | In-patient | Singl e      | 51 | 25(49) | 42±20 | RT-PCR |
| 61 | 10  | Liu, et al., AJRCCM. | 3/23/20 | China    | Retrospective Case Series | General | In-patient | Singl e      | 8  | 7(88)  | 63±11 | RT-PCR |
| 62 | 10  | Gao, et al. | 3/17/20 | China    | Retrospective Case Series | General | In-patient | Singl e      | 43 | 26(60) | 44±12 | RT-PCR |
| 63 | 10  | McMichael, et al. | 3/27/20 | USA      | Retrospective Case Series | General | Both in- and out-patient | Multi center | 167 | 55(33) | 72±13 | RT-PCR |
| 63 | 10  | Bai, et al. | 3/10/20 | China    | Case Control | General | In-patient | Multi center | 219 | 119(54) | 45±15 | RT-PCR |
| 65 | 1   | CDC COVID-19 RT, a. | 4/8/20  | USA      | Retrospective Case Series | General | In-patient | Multi center | 159 | NA     | NA    | NA     |
Records identified through database searching (n = 5484)

Additional records identified through other sources (n = 1)

Records after duplicates removed (n = 3614)

Records screened (n = 3614)

Records excluded (n = 3124)

Full-text articles excluded, with reasons (n = 368)
- No population of interest = 175
- Other language = 72
- No original article/research = 67
- Does not evaluate patients = 25
- Others = 29

Others included: Protocols (14), Case reports (13), Unable to locate (1), Temporary removal (1)

Studies included before analysis for repeated patients (n = 122)

Studies included in qualitative and quantitative synthesis (n = 65)

Records at high risk of patient repetition (n = 57)
| Prevalence of Diabetes | N of studies | n/N          | I^2   | Prevalence (95% CI) |
|------------------------|--------------|--------------|-------|---------------------|
| Overall                | 31           | 1414 / 12870 | 89 %  | 0.12 95% CI (0.10 – 0.15) |
| Outpatient             | 1            | 27 / 1012    | na    | 0.03 95% CI (0.02 – 0.04) |
| Inpatient              | 25           | 488 / 4036   | 64 %  | 0.12 95% CI (0.10 – 0.15) |
| Severe COVID−19        | 5            | 194 / 1099   | 0 %   | 0.18 95% CI (0.16 – 0.20) |
| Non−survivors          | 1            | 16 / 54      | na    | 0.30 95% CI (0.19 – 0.43) |

| Prevalence of Hypertension | N of studies | n/N          | I^2   | Prevalence (95% CI) |
|----------------------------|--------------|--------------|-------|---------------------|
| Overall                    | 37           | 1416 / 12709 | 95 %  | 0.17 95% CI (0.13 – 0.22) |
| Outpatient                 | 2            | 47 / 1029    | 0 %   | 0.05 95% CI (0.03 – 0.06) |
| Inpatient                  | 32           | 1124 / 4082  | 84 %  | 0.21 95% CI (0.17 – 0.26) |
| Severe COVID−19            | 4            | 517 / 1078   | 63 %  | 0.32 95% CI (0.16 – 0.54) |

| Prevalence of Diabetes and Hypertension | N of studies | n/N          | I^2   | Prevalence (95% CI) |
|----------------------------------------|--------------|--------------|-------|---------------------|
| Overall                                 | 5            | 8 / 66       | 0 %   | 0.12 95% CI (0.06 – 0.22) |
| Severe COVID−19                         | 1            | 2 / 10       | na    | 0.20 95% CI (0.05 – 0.54) |
| Disease and outcome | Effect estimate | N of Studies | Total N | I^2  | Effect size (95%CI) | p value |
|--------------------|----------------|-------------|---------|------|---------------------|---------|
|                    |                |             |         |      |                     |         |
| Diabetes           |                |             |         |      |                     |         |
| Severe COVID–19    | Unadjusted (RR)| 6           | 1991    | 74 % | 1.50 (0.90 − 2.50)  | 0.119   |
| ICU admission      | Unadjusted (RR)| 3           | 8890    | 80 % | 1.96 (1.19 − 3.22)  | 0.008   |
| Mortality          | Unadjusted (RR)| 4           | 2058    | 75 % | 2.78 (1.39 − 5.58)  | 0.004   |
|                    | Adjusted (HR)* | 1           | 416     | na   | 0.75 (0.38 − 1.50)  | 0.420   |
|                    |                |             |         |      |                     |         |
| Hypertension       |                |             |         |      |                     |         |
| Severe COVID–19    | Unadjusted (RR)| 8           | 2023    | 69 % | 1.48 (0.99 − 2.23)  | 0.058   |
|                    | Adjusted (OR)**| 1           | 487     | na   | 2.71 (1.32 − 5.59)  | 0.007   |
| ICU admission      | Unadjusted (RR)| 4           | 1737    | 0 %  | 2.95 (2.18 − 3.99)  | <0.001  |
| Mortality          | Unadjusted (RR)| 8           | 3107    | 66 % | 2.39 (1.54 − 3.73)  | <0.001  |
|                    |                |             |         |      |                     |         |
| Diabetes and Hypertension | | | | | | |
| Severe COVID–19    | Unadjusted (RR)| 1           | 22      | na   | 10.00 (0.94 − 105.92)| 0.056   |