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Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis

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ABSTRACT

Background: Many studies on COVID-19 have reported diabetes to be associated with severe disease and mortality, however, the data is conflicting. The objectives of this meta-analysis were to explore the relationship between diabetes and COVID-19 mortality and severity, and to determine the prevalence of diabetes in patients with COVID-19.

Methods: We searched the PubMed for case-control studies in English, published between Jan 1 and Apr 22, 2020, that had data on diabetes in patients with COVID-19. The frequency of diabetes was compared between patients with and without the composite endpoint of mortality or severity. Random effects model was used with odds ratio as the effect size. We also determined the pooled prevalence of diabetes in patients with COVID-19. Heterogeneity and publication bias were taken care by meta-regression, subgroup analyses, and trim and fill methods.

Results: We included 33 studies (16,003 patients) and found diabetes to be significantly associated with mortality of COVID-19 with a pooled odds ratio of 1.90 (95% CI: 1.37–2.64; p < 0.01). Diabetes was also associated with severe COVID-19 with a pooled odds ratio of 2.75 (95% CI: 2.09–3.62; p < 0.01). The combined corrected pooled odds ratio of mortality or severity was 2.16 (95% CI: 1.74–2.68; p < 0.01). The pooled prevalence of diabetes in patients with COVID-19 was 9.8% (95% CI: 8.7%–10.9%) (after adjusting for heterogeneity).

Conclusions: Diabetes in patients with COVID-19 is associated with a two-fold increase in mortality as well as severity of COVID-19, as compared to non-diabetics. Further studies on the pathogenic mechanisms and therapeutic implications need to be done.

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1. Introduction

Coronavirus Disease 2019 (COVID-19) is a new disease, which within four months of its origin in Wuhan, China, has now spread to more than two hundred countries around the world, affecting more than 2,818,000 people and has caused more than 196,000 deaths, as of April 25, 2020 [1]. On March 11, 2020, the World Health Organization (WHO) had declared COVID-19 a pandemic because of alarming levels of its spread, severity and inaction [2]. COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is sufficiently genetically divergent from the closely related Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), to be considered a new human-infecting betacoronavirus [3]. It mainly affects the respiratory tract and the illness ranges in severity from asymptomatic or mild to severe or critical disease. Although the current estimate of the case fatality rate of COVID-19 is < 5%, up to 15–18% of patients may become severe or critically ill, some of them requiring ICU care and mechanical ventilation [4].

Since COVID-19 is a new disease, knowledge about this disease is still incomplete and evolving. Many case-control studies have shown that patients of COVID-19, who have underlying diabetes mellitus, develop a severe clinical course, and also have increased mortality. However, most of these studies have small sample size,
and the data in them are heterogenous and conflicting. In addition, the data on prevalence of diabetes in patients with COVID-19 is also not clear.

Hence, this meta-analysis was conducted with the primary objective of exploring the relationship between underlying diabetes and severity and mortality of COVID-19 disease; and with the secondary objective of determining the prevalence of diabetes in patients with COVID-19.

2. Materials and methods

Since, this is a meta-analysis, therefore an institutional board or an ethics committee approval was not required. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines were consulted during the stages of design, analysis, and reporting of this meta-analysis [5–7]. The protocol of this meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPERO) vide registration number CRD42020181756 and is available in full on the NIHR (National Institute for Health Research) website (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=181756).

2.1. Search strategy and study selection

Three authors (AK, SAA and SK) independently searched, screened and selected the studies according to the search, inclusion and exclusion criteria. PubMed database was searched for papers in English language using the following keywords: ‘2019-nCoV’, ‘nCoV-2019’, “novel Coronavirus 2019”, “SARS-CoV-2”, “COVID-19”, “coronavirus”, “coronavirus covid-19”, and “corona virus”. Since the first report of COVID-19 disease was published on December 31, 2019 [8], we limited our search to articles published since January 01, 2020, and the last search was performed on April 22, 2020. Since there is a high likelihood of duplicate publications on COVID-19 [9], especially, same set of patients being reported in English as well as Chinese or other languages, hence we restricted our search to papers published in English language only. For the same reason we restricted our search to PubMed database only and did not search other databases. In addition, each included study was carefully evaluated for study setting and author list to exclude any duplicate publication.

The inclusion and exclusion criteria of studies were as follows:

(1) The studies should be in English language in the PubMed database.
(2) The study design should be case-control and should have categorized the patients into two or more groups depending on the severity, clinical course, or mortality of the patients with COVID-19 (i.e. composite endpoint). Studies without this categorization were not included. The study should have data of diabetes mellitus in each group.
(3) The study should be observational (retrospective or prospective). Interventional studies such as controlled or uncontrolled drug trials were excluded.
(4) The study should have included at least 100 patients of COVID-19.
(5) The participants should be adult patients with COVID-19. Studies describing exclusively pediatric population were excluded, however, studies which had both adult and pedi- atric patients were included. Studies describing exclusively pregnant women were also excluded.

2.2. Data extraction

The following data were extracted from each study: date of online publication, PMID number, study setting, total number of patients, their demographic data, number of patients with composite endpoint, and number of patients with diabetes mellitus among patients with or without the composite endpoint. For studies with missing data, the corresponding authors of those studies were contacted with a request to provide the missing data.

2.3. Study outcome

The primary outcome of interest was the occurrence of composite endpoint which for the purpose of our study was labelled as ‘severe clinical course’ and defined as occurrence of one of the two endpoints depending on each study’s individual endpoint:

1. For studies comparing survival and mortality — mortality of COVID-19 patients was taken as the composite endpoint;
2. For studies not having mortality as the endpoint, one of the following were chosen as the composite endpoint of ‘severe disease’, depending on study’s individual endpoint: a. Patients requiring invasive ventilation; or b. Patients requiring ICU care; or c. Patients having progressive disease; or d. Patients having refractory disease; or e. Patients categorized as severe/critical according to one of the standard predefined criteria:
   i. WHO criteria [10]; or ii. National Health Commission of the People’s Republic of China (version 3–5) criteria [11,12]; or iii. American Thoracic Society guidelines [13].

Patients not having any of the above features of ‘severe clinical course’ were categorized into ‘good clinical course’.

The secondary outcome of interest was to study the prevalence of diabetes mellitus in patients with COVID-19.

2.4. Assessment of quality of studies

For the assessment of quality of studies, including the risk of bias, the National Institute of Health (NIH) tool for case-control studies was used. This tool has been developed jointly by the National Heart, Lung and Blood Institute (NHLBI) and the Research Triangle Institute International [14]. It uses a composite score of twelve domains, with each domain scored as ‘1’ or ‘0’ depending on the response ‘yes’ or ‘no’, respectively. The studies were categorized as good quality if they scored ≥8 points, fair quality if they scored 6–7 points, and poor quality if they scored <6 points.

2.5. Statistical analysis

The categorical data was displayed as n and % and continuous data as mean and SD. If the study had reported the data as median with IQR or range, the method described by Wan et al. was used to calculate the mean and SD [15].

To study the prevalence of diabetes mellitus in patients with COVID-19, pooled proportion and 95% confidence interval (CI) was taken as the effect size. First the raw proportion from each study was extracted and transformed with the Freeman-Tukey double arctine method to stabilize the variance [16], then the pooled proportion was obtained using the DerSimonian-Laird random effects model [17].

To study the association of diabetes mellitus with the composite endpoint (severe clinical course), pooled odds ratio (with 95% CI)
was taken as the effect size. We performed the meta-analysis using the generic inverse variance approach and DerSimonian-Laird random effects model [17]. A p value of <0.05 was used to show statistically significant association. The meta-analysis was sub-grouped according to the composite endpoint of severe disease and mortality.

To assess the heterogeneity among studies I^2 statistic was calculated. An I^2 value >50% indicated substantial heterogeneity. To take care of heterogeneity among the studies, and to calculate a more conservative result, the odds ratios were pooled using only the random effects model [17]. To explore the source of heterogeneity meta-regression analysis was done using age, type of composite endpoint (severity versus mortality), country of study (China versus others), number of patients, quality score, and quality type (good versus fair) as co-variates. In addition, if the heterogeneity among the studies was >50%, a sensitivity analysis was also performed after identifying and removing the outlier studies.

We evaluated the publication bias through visual inspection of funnel plot and Begg [18] and Egger [19] tests. When the funnel plot was symmetrical and the p value of Begg and Egger tests were >0.05, no significant publication bias was considered to exist in the meta-analysis. However, if publication bias was found, a trim and fill analysis of Duval and Tweedie [20] was used to evaluate the number of missing studies, and recalculation of the pooled odds ratio was done after addition of those missing hypothetical studies.

Review Manager software (version 5.3.5, The Nordic Cochrane Centre, Copenhagen, Denmark), OpenMetaAnalyst software (version 10.12) [21], JASP software (version 0.12.1, University of Amsterdam, The Netherlands), and Microsoft Excel (version 16.35) were employed for the meta-analysis and statistical analyses.

3. Results

3.1. Study selection and data collection

Using the keywords “2019-nCoV”, “nCoV-2019”, “novel Coronavirus 2019”, “SARS-CoV-2”, “COVID-19”, “coronavirus”, “corona virus” and “limiting the Entrez date from 01-Jan-2020 through 22-Apr-2020, initially 5834 publications in English language were retrieved from the PubMed database, which were screened for relevance (Fig. 1). After carefully going through the abstracts and full texts (if needed) of these publications, only 207 potentially relevant studies were selected and evaluated in detail for potential inclusion. Of these 174 studies were excluded because of the following reasons: (1) 144 studies did not have comparative data on COVID-19 patients with and without composite endpoint; (2) 22 studies were small with less than 100 participants; (3) 7 studies did not have diabetes as one of the comparative factors; and (4) 1 study was a duplicate publication. Hence, remaining 33 studies were included in the qualitative as well as quantitative synthesis meta-analysis (Fig. 1).

3.2. Characteristics and quality of the included studies

The study characteristics of the 33 included studies are given in Table 1. The online publication date of the studies in the PubMed database was from February 7, 2020 through April 17, 2020. Twenty out of 33 (61%) studies were from single centres, while remaining 13 (39%) were multi-centre studies. Most studies (30/33, 91%) were from mainland China, and of the remaining 3 studies, two (6%) were from USA and one (3%) from France. The total included patients were 16,003, and of them 8849 (55%) were reported from Mainland China, 7030 (44%) from USA, and 124 (1%) from France. The median number of patients included in the studies was 214 (IQR: 139–368).

Diabetes was present in 1724 patients out of total 16,003 patients of COVID-19. The pooled prevalence of diabetes was calculated to be 11.2% (95% CI: 9.5%–13.0%) by using the Freeman-Tukey double arcine transformation and DerSimonian-Laird random effects model (Fig. 2). However, the heterogeneity among the studies was substantial with an I^2 value of 92%. To explore the source of heterogeneity meta-regression analyses were done using age, type of composite endpoint (severity versus mortality), country of study (China versus others), number of patients, quality score, and quality type (good versus fair) as co-variates (Supplementary Table 1 and Supplementary Fig. 1). The results of meta-regression showed that proportion of diabetes in patients with COVID-19 was influenced by age (with studies with higher patient age having higher proportion of diabetes, p < 0.001), type of composite endpoint (with studies reporting mortality endpoint having higher proportion of diabetes, p = 0.004), and country of study (with studies outside of China having higher proportion of diabetes, p = 0.006). There was no influence of number of patients in studies or quality score of studies. A sub-group analysis revealed that proportion of diabetes mellitus in China was 10.5% (95% CI: 8.7%–12.3%) while in countries other than China (mainly USA) it was 19.3% (95% CI: 8.4%–30.3%), but with high heterogeneity (data not shown). A sensitivity analysis was also done by excluding 13 outlier studies, which revealed a pooled prevalence of diabetes to be 9.8% (95% CI: 8.7%–10.9%) in patients with COVID-19 with an acceptable I^2 value of 46% (Supplementary Fig. 2).

3.5. Association of diabetes mellitus with mortality or severity of COVID-19 (primary outcome)

Of the 33 included studies in this meta-analysis, 24 had used...
severity as the composite endpoint and 9 had used mortality as the composite endpoint. Presence of diabetes was found to be significantly associated with severe COVID-19 (pooled odds ratio 2.75 [95% CI: 2.09–3.62; p < 0.01]) as well as mortality due to COVID-19 (pooled odds ratio 1.90 [95% CI: 1.37–2.64; p < 0.01]). The combined pooled odds ratio for both the composite endpoints (labelled as severe clinical course) was 2.49 (95% CI: 1.98–3.14; p < 0.01) (Fig. 3).

For the mortality endpoint, the heterogeneity among the studies was low (I² = 32%), while for the severity endpoint the heterogeneity among the studies was substantial (I² = 63%). Thus the combined heterogeneity was also substantial (I² = 63%). To explore the source of heterogeneity meta-regression analyses were done using age, type of composite endpoint (severity versus mortality), country of study (China versus others), number of patients, quality score, and quality type (good versus fair) as co-variates (Supplementary Table 2 and Supplementary Fig. 3). The results of meta-regression showed that odds ratio was influenced by age (with studies with higher patients’ age having lower odds ratio, p < 0.001). In addition it was found that the CDC study from USA [22], which was of not good quality (being a registry data), significantly influenced the outcome of this meta-analysis and was mainly responsible for the significant

![PRISMA flow chart showing the flow of study selection.](image-url)
heterogeneity. Hence, a sensitivity analysis was performed after excluding this study, which again revealed a significant combined pooled odds ratio of 2.33 (95% CI: 1.90–2.83; \( p < 0.01 \)) and an \( I^2 \) value of 41\% (acceptable heterogeneity) (Supplementary Fig. 4).

### 3.6. Influence of publication bias

For the main outcome of this meta-analysis, i.e. association of diabetes mellitus with severe clinical course of COVID-19, publication bias was evaluated through the visual inspection of funnel plot and Begg and Egger tests [18,19]. The funnel plot (Fig. 4) was found to be mildly asymmetric and the Begg’s rank correlation test for funnel plot asymmetry (Kendall’s \( \tau = 0.439 \)) as well as Egger’s regression test for funnel plot asymmetry (\( 2 = 2.561 \)) were statistically significant (\( p < 0.05 \)). Hence, a trim and fill analysis of Duval and Tweedie [20] was used to evaluate the number of missing studies and we recalculated the pooled odds ratio with the addition of those missing hypothetical studies. The recalculated pooled odds ratio of association of diabetes mellitus with severe clinical course of COVID-19 was 2.26 (95% CI: 1.78–2.87; \( p < 0.01 \)) (Supplementary Fig. 5). The redrawn funnel plot after addition of four missing hypothetical studies was now symmetrical (Supplementary Fig. 6).

After adjusting for both, heterogeneity as well as publication bias, the corrected pooled odds ratio for diabetes mellitus being associated with severe clinical course of COVID-19 (i.e. both mortality and severity) was still significant (2.16 [95% CI: 1.74–2.68]; \( p < 0.01 \)) (Supplementary Fig. 7).

### 4. Discussion

To summarise the results of this meta-analysis of 33 studies (16,003 patients), we found diabetes mellitus to be significantly associated with mortality risk of COVID-19 with a pooled odds ratio of 1.90 (95% CI: 1.37–2.64; \( p < 0.01 \)) with low heterogeneity (\( I^2 = 32\% \)). In addition, diabetes mellitus was associated with severe COVID-19, including risk of ARDS, ICU requirement, and invasive ventilatory requirement, with a pooled odds ratio of 2.75 (95% CI: 2.09–3.62; \( p < 0.01 \)). The combined pooled odds ratio of diabetics developing severe COVID-19 or dying due to it (i.e. composite endpoint) was 2.49 (95% CI: 1.98–3.14; \( p < 0.01 \)). After adjusting for both, heterogeneity among the studies as well as publication bias, the corrected pooled odds ratio for diabetes being associated with severe clinical course of COVID-19 was still significantly high (2.16 [95% CI: 1.74–2.68]; \( p < 0.01 \)). As a secondary outcome, we also calculated the pooled prevalence of diabetes mellitus in patients with COVID-19, which was 11.2% (95% CI: 9.5%–13.0%) (uncorrected) and 9.8% (95% CI: 8.7%–10.9%) (after adjusting for heterogeneity). There are many strengths of this meta-analysis. First, to the best of our knowledge this is the first large meta-analysis on specific influence of diabetes on severity of COVID-19, as well as on its mortality. In addition, we also studied the prevalence of diabetes among COVID-19 patients. Second, we have included a large number of studies, with patient population above sixteen thousand, spanning three continents. Third, we have included only large studies, with more that 100 patients, thus each study contributed a robust data on diabetes–COVID19 association without increasing.

### Table 1

Characteristics and quality of studies included in the meta-analysis.

| Author | Date of publication | PMID | Setting | Remarks | Quality score |
|--------|---------------------|------|---------|---------|--------------|
| Wang D [55] | 07-Feb-20 | 32031570 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Zhang J [56] | 19-Feb-20 | 32077115 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Guan W [57] | 28-Feb-20 | 32109013 | 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China | | 9 |
| Ruan Q [58] | 03-Mar-20 | 32125452 | Two centres in Wuhan, Hubei Province, China | | 9 |
| Zhou F [59] | 11-Mar-20 | 32171076 | Two hospitals in Wuhan, Hubei Province, China | | 9 |
| Wu C [60] | 13-Mar-20 | 32167524 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Mo P [61] | 16-Mar-20 | 32173725 | Single centre in Wuhan, Hubei Province, China, 8 | | 8 |
| Shi Y [62] | 18-Mar-20 | 32188484 | Multi-centre in Zhejiang Province, China | | 8 |
| Zhang X [63] | 20-Mar-20 | 32205284 | Multi-centre in Zhejiang Province, China | | 9 |
| Deng Y [64] | 20-Mar-20 | 32209890 | Two tertiary hospitals in Wuhan, Hubei Province, China | | 8 |
| Wan S [65] | 21-Mar-20 | 32198776 | Multi-centre in Chongqing, China | | 9 |
| Chen T [66] | 26-Mar-20 | 32217556 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Wang L [67] | 30-Mar-20 | 32240670 | Single centre in Wuhan, Hubei Province, China | Only elderly >60 years patients | 9 |
| Wang L [68] | 31-Mar-20 | 32229732 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Cai Q [69] | 02-Apr-20 | 32239761 | Single centre in Shenzhen, Guangdong Province, China | | 9 |
| Cao J [70] | 02-Apr-20 | 32239127 | Single centre in Wuhan, Hubei Province, China | | 9 |
| CDC COVID-19 | 03-Apr-20 | 32240123 | Cases reported from all over US to CDC, USA Registry data | | 7 |
| Wang X [71] | 03-Apr-20 | 32251842 | Single centre in Wuhan, Hubei Province, China | Only non-critical patients | 9 |
| Wang Y [72] | 08-Apr-20 | 32267160 | Single centre in Wuhan, Hubei Province, China | Only ICU patients | 9 |
| Du RH [73] | 09-Apr-20 | 32311050 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Zheng F [75] | 09-Apr-20 | 32271459 | Single centre in Changsha, Hunan Province, China | | 8 |
| Simonnet A [76] | 09-Apr-20 | 32271993 | Single centre in Lille, France | Only ICU patients | 9 |
| Feng Y [77] | 10-Apr-20 | 32275452 | Three hospitals in China | | 9 |
| Yang Z [78] | 10-Apr-20 | 32275643 | Single centre in Shanghai, China | | 9 |
| Liu Y [79] | 10-Apr-20 | 32283162 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Mao L [80] | 10-Apr-20 | 32275288 | Multi-centre in Wuhan, Hubei Province, China | | 9 |
| Shen L [81] | 10-Apr-20 | 32283164 | Multi-centre in Xiangyang, Hubei Province, China | | 9 |
| Zhang R [82] | 11-Apr-20 | 32279115 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Li X [83] | 12-Apr-20 | 32294485 | Single centre in Wuhan, Hubei Province, China | | 9 |
| Wei YY [84] | 16-Apr-20 | 32209890 | Two tertiary hospitals in Wuhan, Hubei Province, China | | 8 |
| Wan S [85] | 16-Apr-20 | 32297671 | Single centre in Chongqing, China | | 9 |
| Goyal P [86] | 17-Apr-20 | 32302078 | Two hospitals in New York City, USA | | 8 |
heterogeneity. Fourth, we have avoided including any duplicate studies by limiting our search to single database, limiting search to English articles only, and carefully going through each included article's study setting and author list. Fifth, while synthesizing results we have taken care of both heterogeneity as well as publication bias by appropriate statistical tools.

First discussing about the secondary outcome of our meta-analysis, we determined the corrected pooled prevalence of diabetes mellitus in COVID-19 patients to be close to 10%, with a higher prevalence in USA than China. Our results on prevalence are similar to a large Chinese nationwide study of 1590 patients which had shown the prevalence of diabetes in COVID-19 patients to be 10.3%. Our study as well as these other studies indicate that the prevalence of diabetes in patients developing more adverse disease due to SARS-CoV-2 infection [24,28]. Another systematic review of 7 studies by Singh et al. also reported the prevalence of diabetes in COVID-19 patients as 10.3%. Our results are similar to two small meta-analyses, by Fadini et al. (6 studies, 1687 patients) and Wang et al. (6 studies, 1558 patients), which gave odds ratio of 2.26 and 2.47, respectively, for diabetic patients developing more adverse disease due to SARS-CoV-2 infection [24,28]. Another systematic review of 7 studies by Singh et al. also suggested that diabetes is a determinant of severity and mortality of COVID-19 patients [29]. However, our meta-analysis is the largest with 33 studies, and we have now conclusively shown the association of diabetes with COVID-19 mortality as well as severity.

Whether diabetes is an independent determinant of severity was studied by Guo et al. in their case-control study from China [30], in which they compared diabetic and non-diabetic COVID-19 patients, and found that even in absence of other comorbidities, diabetics were at higher risk of severe pneumonia, uncontrolled inflammatory storm that leads to worsening of COVID-19 [30]. Another large meta-analysis supported the previously held notion that the susceptibility of diabetic population to COVID-19 infection might not be increased but be similar to the non-diabetic population [27]. The primary and the more important outcome of our meta-analysis was to study the association of diabetes with mortality and severity of COVID-19 disease. We found that diabetic patients with COVID-19 are twice more likely to develop severe COVID-19 disease and twice more likely to die due to it (odds ratio close to 2 for severity as well as mortality). Thus patients with COVID-19 and diabetes are more likely to develop ARDS, need ICU care, need invasive ventilation, and are more vulnerable to succumb to it. Our results are similar to two small meta-analyses, by Fadini et al. (6 studies, 1687 patients) and Wang et al. (6 studies, 1558 patients), which gave odds ratio of 2.26 and 2.47, respectively, for diabetic patients developing more adverse disease due to SARS-CoV-2 infection [24,28]. Another systematic review of 7 studies by Singh et al. also suggested that diabetes is a determinant of severity and mortality of COVID-19 patients [29]. However, our meta-analysis is the largest with 33 studies, and we have now conclusively shown the association of diabetes with COVID-19 mortality as well as severity.

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Table 2
Characteristics of the included patients.

| Author       | Number of patients | Age (years) | Males | Patients with composite endpoint | Patients with diabetes |
|--------------|--------------------|-------------|-------|-----------------------------------|------------------------|
|              |                    | Mean SD     | n     | %                                 | n %                    |
| Total        | 16003              | 52.6 17.37  | 5068  | 54%                               | 2827 18%               | 1724 11%               |

Wang D [55] 138 55.3 19.50 75 54% 36 26% ICU 14 10%
Zhang JJ [56] 140 56.5 11.80 71 51% 58 41% Criteria 17 12%
Guan WJ [57] 1099 46.7 17.10 64 58% 173 16% Criteria 81 7%
Ruan Q [58] 150 57.7 12.50 102 68% 68 45% Died 25 17%
Zhao F [59] 191 56.3 15.70 119 62% 54 28% Died 36 19%
Wu C [60] 201 51.3 12.70 128 64% 84 42% ARDS 22 11%
Mo P [61] 155 54.0 18.00 86 55% 85 55% Refractory 15 10%
Shi Y [62] 487 46.0 19.00 259 53% 49 10% Criteria 29 6%
Zhang X [63] 597 45.3 14.34 328 55% 64 11% Criteria 48 8%
Deng Y [64] 225 55.4 19.04 124 55% 109 48% Died 26 12%
Wan S [65] 135 46.0 14.24 72 53% 40 30% Criteria 12 9%
Chen T [66] 274 58.7 19.38 171 62% 113 41% Died 47 17%
Wang L [67] 339 70.0 8.19 166 49% 65 19% Died 54 16%
Wang L [68] 116 53.7 23.27 67 58% 57 49% Criteria 18 6%
Cai Q [69] 298 47.2 20.86 145 49% 58 19% Criteria 18 6%
Cao J [70] 102 52.7 22.56 53 52% 17 17% Died 11 11%
CDC COVID-19 [22] 6637 No data No data No data No data 457 7% ICU 730 11%
Wang X [71] 1012 51.3 11.30 524 52% 100 10% Progression 27 3%
Wang Y [72] 344 62.7 14.89 179 52% 133 39% Died 64 19%
Du RH [73] 179 57.6 13.70 97 54% 21 12% Died 33 18%
Zhang G [74] 221 53.5 20.52 108 49% 55 25% Criteria 22 10%
Zheng F [75] 161 45.2 17.58 80 50% 30 19% Criteria 7 4%
Simonet A [76] 124 60.3 14.25 91 73% 85 69% Ventilation 28 23%
Feng Y [77] 476 52.3 17.85 271 57% 124 26% Criteria 49 10%
Yang Z [78] 273 49.1 13.75 134 49% 71 26% Progression 18 7%
Liu Y [79] 245 54.0 16.90 114 47% 33 13% Died 23 9%
Mao L [80] 214 52.7 15.50 87 41% 59 28% Criteria 30 14%
Shi Y [81] 487 46.0 19.00 259 53% 49 10% Criteria 29 6%
Zhang X [82] 597 45.3 14.34 328 55% 64 11% Criteria 48 8%
Shen L [83] 548 46.0 19.00 259 53% 49 10% Criteria 29 6%
Zhang R [84] 120 54.4 15.60 43 36% 30 25% Criteria 7 6%
Wu C [85] 123 46.2 15.15 66 54% 21 17% Criteria 8 7%
Wei YY [86] 167 42.3 15.29 95 57% 30 18% Criteria 11 7%
Goyal P [87] 393 61.5 18.68 238 61% 130 33% Ventilation 99 25%
resulted in increased severity and fatality in patients with diabetes mellitus [31–35]. All these previous outbreaks were also caused by other coronaviruses, namely SARS-CoV and MERS-CoV, respectively. To elucidate the mechanism of enhanced disease severity in diabetics following MERS-CoV infection, Kulcsar et al. [36] used an animal model in which mice were made susceptible to MERS-CoV infection by expressing human dipeptidyl peptidase 4 (DPP4), and type 2 diabetes was induced by administering a high-fat diet. Upon infection with MERS-CoV, diabetic mice had a prolonged phase of severe disease and delayed recovery that was independent of viral titres. Histological examination revealed that diabetic mice had delayed but prolonged systemic inflammation, fewer inflammatory monocyte/macrophages and CD4+ T cells, lower levels of chemokine ligand 2 and C-X-C motif chemokine 10 expression, lower levels of tumor necrosis factor alpha (TNFα), interleukin (IL) 6, IL 12β, and arginase 1 expression and higher levels of IL 17α expression. The data suggested that the increased disease severity observed in diabetes was likely due to a dysregulated immune response, which resulted in more severe and prolonged lung pathology [36]. Since patients with diabetes have multiple immune dysregulations such as phagocytic cell dysfunction, inhibition of neutrophil chemotaxis, impaired T-cell mediated immune response, altered cytokine production, and ineffective microbial clearance [37], these dysregulated immune responses may result into a cytokine profile resembling secondary haemophagocytic lymphohistiocytosis in patients with severe SARS-CoV-2 infection, characterised by increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemotactic protein 1, macrophage inflammatory protein 1-α, and TNFα [38,39]. In addition, type 2 diabetes mellitus and coronavirus infection also have shared pathogenic pathways, which has therapeutic implications [40]. Two of the coronavirus receptors, angiotensin converting enzyme 2 (ACE2) and DPP4 are also transducers of metabolic pathways regulating glucose homeostasis, renal and cardiovascular physiology, and inflammation. DPP4 inhibitors are widely used in subjects with type 2 diabetes because of their effect of lowering blood glucose levels. However, the effects of DPP4 inhibition on the immune response in patients with diabetes is still controversial and not completely understood [41]. Two recent meta-analyses had shown that DPP4 inhibitors increased the risk of various infections [42,43] while a third meta-analysis showed that there is no increased risk of infections with DPP4 inhibitors [44]. Whether DPP4 inhibitors increase the susceptibility or severity of SARS-CoV-2 infection needs to be studied in future trials.

The results our meta-analysis has three major implications during the current COVID-19 pandemic. First, since diabetes can lead to severe COVID-19, its prevention in diabetics is imperative. It should be the responsibility of the treating physicians to advice their diabetic patients to take extra-precautions of social distancing and hand hygiene to protect themselves from coronavirus infection [45]. Second, there should be an increased vigilance in the outpatient clinics of diabetes for COVID-19, and the threshold for testing for this infection in diabetic patients should be lowered [46]. Third, any patient with COVID-19, who has co-morbid diabetes, should be taken as potentially serious, even though he or she may show only mild or no symptoms at presentation. These patients will need extra monitoring, and their threshold for hospital and ICU...
admission also needs to be lowered.

The results of our meta-analysis has also implications for India, which is often called the ‘Diabetes Capital’ of the world. According to the 2019 estimate, the age standardised diabetes prevalence in South-East Asia, including India, among ages 20–79 years, was estimated to be 11.3% (95% CI: 8.0%–15.9%), with the actual number of people with diabetes in India being more than 77 million [25,47]. Drivers of type 2 diabetes in south Asia include genetic and epigenetic factors, intrauterine and early life factors, high carbohydrate dietary patterns, and increase in physical inactivity [48]. All these factors, not only increase the prevalence of diabetes, but are also major factors in the causation of obesity, hypertension, metabolic syndrome, fatty liver, cardiovascular and cerebrovascular diseases, with a resultant increase in morbidity and mortality. In fact, diabetes, along with cardiovascular disease and chronic kidney disease accounted for 4%, 27%, and 3% of deaths, respectively, in South Asia [49]. During the current COVID-19 pandemic, our meta-analysis, as well as multiple other studies have shown that COVID-19 is particularly more severe in patients with these comorbidities with increased hospitalization, ICU and ventilatory requirements [50,51]. With the huge population burden of diabetes in India, if urgent and strong measures are not taken to flatten the curve of COVID-19 pandemic in India, it will lead to disastrous consequences with overburdening of already stretched healthcare system of India. Especially, elderly population of India with comorbidities such as diabetes, hypertension, and cardiac diseases will need special protection as enumerated in the preceding paragraph. Their blood sugars need to be better controlled and their health condition need to be better monitored, even in the face of lockdown, through measures such as tele-consultation and tele-medicine [52].

4.1. Limitations

Our meta-analysis has two limitations. We have shown that diabetes is associated with COVID-19 severity and mortality; however, it cannot be said whether diabetes is acting as an independent factor responsible for this severity and mortality, or it is just a confounding factor. Many conditions such as elderly age, hypertension, cardiovascular disease, and obesity, often co-exist with diabetes, and each of these comorbidities have been shown to be associated with severe COVID-19 and its mortality. In spite of this limitation, the implication our meta-analysis will remain

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| Study or Subgroup | log(Odds Ratio) | SE | Odds Ratio IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|------------------|----------------|----|-------------------------------|-------------------------------|
| 1.1.1 Severe Disease |                |    |                               |                               |
| Gayal P          | 0.1954         | 0.2435 | 4.7%                         | 1.22 [0.75, 1.96]             |
| Zhang J          | 0.2607         | 0.5194 | 2.7%                         | 1.10 [0.47, 2.59]             |
| Wang L (31–Mar)  | 0.3048         | 0.5156 | 2.7%                         | 1.36 [0.49, 3.73]             |
| Zhang C          | 0.3839         | 0.4868 | 2.9%                         | 1.47 [0.57, 3.81]             |
| Mao L            | 0.4191         | 0.395 | 3.5%                         | 1.52 [0.70, 3.30]             |
| Feng Y           | 0.463          | 0.3202 | 4.1%                         | 1.59 [0.85, 2.98]             |
| Zheng F          | 0.5678         | 0.8624 | 1.4%                         | 1.80 [0.33, 9.76]             |
| Yang Z           | 0.6414         | 0.5946 | 2.8%                         | 1.90 [0.71, 5.11]             |
| Xu X             | 0.6508         | 0.2452 | 4.7%                         | 1.92 [1.19, 3.10]             |
| Zhang X          | 0.7975         | 0.3977 | 3.5%                         | 2.22 [1.02, 4.84]             |
| Simonseth A      | 0.9233         | 0.5376 | 2.6%                         | 2.52 [0.88, 7.24]             |
| Shi Y            | 1.1479         | 0.4612 | 3.1%                         | 3.15 [1.27, 7.81]             |
| Guan Wj          | 1.1571         | 0.2502 | 4.6%                         | 3.18 [1.95, 5.19]             |
| Wang X           | 1.211          | 0.4525 | 3.1%                         | 3.36 [1.38, 8.13]             |
| Mo F             | 1.3005         | 0.6675 | 2.0%                         | 1.67 [0.99, 13.58]            |
| Cai Q            | 1.3029         | 0.4993 | 2.8%                         | 3.68 [1.38, 9.79]             |
| Wu C             | 1.4709         | 0.5028 | 2.8%                         | 4.35 [2.62, 11.66]            |
| Shen L           | 1.4773         | 0.6484 | 2.1%                         | 4.48 [1.25, 15.61]            |
| Wang D           | 1.5198         | 0.5812 | 2.4%                         | 4.57 [1.46, 14.28]            |
| CDC USA          | 1.5276         | 0.109  | 5.6%                         | 4.61 [3.72, 5.70]             |
| Wan S (21–Mar)   | 2.1864         | 0.6983 | 1.9%                         | 8.90 [2.27, 34.99]            |
| Wei YY           | 2.3145         | 0.6662 | 2.0%                         | 10.12 [2.74, 37.35]           |
| Wan S (16–Apr)   | 2.3334         | 0.7784 | 1.6%                         | 10.31 [2.44, 47.42]           |
| Zhang R          | 4.0564         | 1.4784 | 0.6%                         | 57.77 [3.18, 1048.10]         |
| Subtotal (95% CI)| 70.3%          | 2.75  | 2.62 [1.29, 5.32]            |
| Heterogeneity: Tau² = 0.23; Chi² = 62.47, df = 23 (P < 0.0001); I² = 63% |
| Test for overall effect: Z = 7.24 (P < 0.0001) |

| 1.1.2 Mortality |                          |    |                               |                               |
|------------------|--------------------------|----|-------------------------------|-------------------------------|
| Wang L (30–Mar)  | 0.0901                   | 0.3702 | 3.7%                         | 1.09 [0.53, 2.26]             |
| Qian Q           | 0.1287                   | 0.4839 | 3.2%                         | 1.14 [0.48, 2.69]             |
| Wang Y           | 0.1563                   | 0.2795 | 4.4%                         | 1.52 [0.88, 2.62]             |
| Chen T           | 0.4812                   | 0.3219 | 4.1%                         | 1.62 [0.86, 3.04]             |
| Du RH            | 0.6631                   | 0.5273 | 2.7%                         | 1.94 [0.69, 5.34]             |
| Deng Y           | 0.767                    | 0.4361 | 3.2%                         | 2.20 [0.93, 5.10]             |
| Zhou F           | 1.0485                   | 0.3833 | 3.6%                         | 2.81 [1.35, 5.30]             |
| Liu Y            | 1.1389                   | 0.4987 | 2.8%                         | 3.30 [1.24, 8.77]             |
| Cai J            | 2.1665                   | 0.6858 | 1.9%                         | 8.73 [2.26, 33.40]            |
| Subtotal (95% CI)| 29.7%                    | 1.90  | 1.90 [1.37, 2.64]            |
| Heterogeneity: Tau² = 0.08; Chi² = 11.82, df = 8 (P = 0.10); I² = 32% |
| Test for overall effect: Z = 3.87 (P < 0.0001) |
| Total (95% CI)   |                          | 100%| 2.49 [1.98, 3.14]            |
| Heterogeneity: Tau² = 0.23; Chi² = 85.93, df = 12 (P < 0.0001); I² = 63% |
| Test for overall effect: Z = 7.81 (P < 0.0001) |
| Test for subgroup differences: Chi² = 2.38, df = 1 (P = 0.09); I² = 65.0% |

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![Fig. 3. Forest plot showing pooled odds ratio of diabetes mellitus associated with severe clinical course including mortality.](image-url)
unchanged that diabetic need to be protected from COVID-19, and they will need extra care if infected. The second limitation of this meta-analysis is that we have not been able to document the role of glycemic control on the severity or mortality of COVID-19. It has been shown previously that poor glycemic control, in terms of high HbA1c, was significantly associated with increased risk of various infections [53,54]. However, none of the included studies on COVID-19 in our meta-analysis had evaluated glycemic control as one of the factors associated with severity and/or mortality; and this needs to be explored in further trials.

In conclusion, we have shown in this meta-analysis that presence of underlying diabetes in patients with COVID-19 is associated with two-fold increased risk of mortality, as well as two-fold increased risk of severity of COVID-19. This necessitates enhanced prevention of COVID–19 in diabetics, increased vigilance in patients of diabetes for COVID–19, and a lower threshold for monitoring, hospitalization, and ICU care if diabetics develop this infection. Results of our meta-analysis emphasizes the need for further investigation on the pathogenic mechanism of relationship between diabetes and COVID-19, and to explore its therapeutic implications.

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Author contributions

AK designed the study. AK, SAA and SK searched, screened and selected the articles. AK, PS, NB and AS extracted the data from the articles. AK and PS performed data analysis and interpretation. AK drafted the manuscript. All authors contributed in writing and editing of the manuscript. AA supervised the study.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2020.04.044.

References

[1] Coronavirus update (live): 2,818,181 cases and 196,576 deaths from COVID-19 virus pandemic - worldometer. n.d, https://www.worldometers.info/coronavirus/ (accessed April 25, 2020).

[2] Mahase E. Covid-19: WHO declares pandemic because of “alarming levels” of spread, severity, and inaction. BMJ 2020;368:m1036. https://doi.org/10.1136/bmj.m1036.

[3] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74. https://doi.org/10.1016/S0140-6736(20)30251-8.

[4] Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis. J Med Virol 2020. https://doi.org/10.1002/jmv.25735.

[5] Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

[6] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100. https://doi.org/10.1371/journal.pmed.1000100.

[7] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. J Am Med Assoc 2000;283. https://doi.org/10.1001/jama.283.15.2008. 2000–12.

[8] Wuhan Municipal Health Commission. [Wuhan Municipal Health Commission on the current situation of pneumonia in our city]. n.d, http://wjw.wuhan.gov.cn/front/web/showDetail/2020010210010 (accessed April 27, 2020).

[9] Bauchner H, Golub RM, Zylke J. Editorial concern-possible reporting of the same patients with COVID-19 in different reports. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.3980.

[10] Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. n.d, https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed March 28, 2020).

[11] State Administration of Traditional Chinese Medicine. [Notice on the issuance...

Fig. 4. Funnel plot for evaluation of publication bias.

Subgroups
- Severe Disease
- Mortality

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of a new coronavirus infection pneumonia diagnosis and treatment plan (trial fifth version).” n.d., http://www.sctcm.gov.cn/gh/content?info_id=133426 (accessed April 27, 2020).

[12] National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19 (trial version 7).” n.d., http://en.cnki.com.cn/2020-03-02/9be07480978409.htm (accessed April 27, 2020).

[13] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[14] Study Quality Assessment Tools. National Heart, lung, and blood Institute (NHLBI).” n.d., https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed March 28, 2020).

[15] Wenzel S, Wang L, Wang T. Estimation of the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135. https://doi.org/10.1186/1471-2288-14-135.

[16] Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950;21:607-1...

[17] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis of randomised controlled trials. Lancet 1994;345:109-13. https://doi.org/10.1016/0140-6736(94)90974-X.

[18] Sulav S, Tweeide R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2007;63:565-71. https://doi.org/10.1111/j.1541-0420.2006.00751.x.

[19] Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the study registration gap: an overview of initiatives and recommendations. JAMA Intern Med 2020;180:1542-7. https://doi.org/10.1001/jamainternmed.2020.0994.

[20] Saeedi P, MacIntyre P, Wessely S, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[21] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[22] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[23] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[24] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[25] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[26] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[27] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[28] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[29] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[30] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[31] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.

[32] MacIntyre P, Wang L, Wang T, Beeching N, Wessely S, Green K, et al. Coronavirus: impact of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infection diseases society of America. Am J Respir Crit Care Med 2020;200:1044-61. https://doi.org/10.1164/rccm.202004-0758sl.
[63] Zhang X, Cai H, Hu J, Liu J, Gu J, Zhang S, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.040.

[64] Deng Y, Liu W, Liu K, Fang Y-Y, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J 2020. https://doi.org/10.1097/ CM910000000000000824.

[65] Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020. https://doi.org/10.1002/jmv.25783.

[66] Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020. https://doi.org/10.1111/all.14309.

[67] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020. https://doi.org/10.1002/jaci.202004.001.

[68] Wei Y-Y, Wang R-R, Zhang D-W, Tu Y-H, Chen C-S, Ji S, et al. Risk factors for severe COVID-19: evidence from 167 hospitalized patients in Anhui, China. J Infect 2020. https://doi.org/10.1016/j.jinf.2020.04.010.

[69] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of covid-19 in New York city. N Engl J Med 2020. https://doi.org/10.1056/NEJMc2014019.