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SYSTEMATIC REVIEWS AND META-ANALYSES

Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies

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Abstract Aims: To estimate the prevalence of established diabetes and its association with the clinical severity and in-hospital mortality associated with COVID-19.
Data synthesis: We systematically searched PubMed, Scopus and Web of Science, from 1st January 2020 to 15th May 2020, for observational studies of patients admitted to hospital with COVID-19. Meta-analysis was performed using random-effects modeling. A total of 83 eligible studies with 78,874 hospitalized patients with laboratory-confirmed COVID-19 were included. The pooled prevalence of established diabetes was 14.34% (95% CI 12.62–16.06%). However, the prevalence of diabetes was higher in non-Asian vs. Asian countries (23.34% [95% CI 16.40–30.28] vs. 11.06% [95% CI 9.73–12.39]), and in patients aged ≥60 years vs. those aged <60 years (23.30% [95% CI 19.65–26.94] vs. 8.79% [95% CI 7.56–10.02]). Pre-existing diabetes was associated with an approximate twofold higher risk of having severe/critical COVID-19 illness (n = 22 studies; random-effects odds ratio 2.10, 95% CI 1.71–2.57; I² = 41.5%) and threefold increased risk of in-hospital mortality (n = 15 studies; random-effects odds ratio 2.68, 95% CI 2.09–3.44; I² = 46.7%). Funnel plots and Egger’s tests did not reveal any significant publication bias.
Conclusions: Pre-existing diabetes is significantly associated with greater risk of severe/critical illness and in-hospital mortality in patients admitted to hospital with COVID-19.
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Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been recently declared a pandemic by the World Health Organization, and the disease has spread to nearly all countries worldwide [1]. It is known that people with diabetes have a higher overall risk of infection(s) resulting from multiple perturbations of innate immunity [2–4]. Whether people with diabetes are also at greater susceptibility to COVID-19 is currently uncertain, but there is a perception that the risk is higher; both of infection, and of greater severity of illness [5,6].

We have therefore carried out an updated and comprehensive systematic review and meta-analysis of observational studies that have estimated the global prevalence of pre-existing diabetes in patients admitted to hospital with laboratory-confirmed SARS-CoV-2 infection. We also examined whether there is an association between presence of pre-existing diabetes and severity of COVID-19 illness or risk of in-hospital mortality amongst infected patients.

Materials and methods

Data sources and searches

We conducted a literature search from 1st January 2020 to 15th May 2020 (date last searched) of PubMed, Scopus and Web of Science databases for non-randomized observational studies examining the main clinical and biochemical characteristics of hospitalized patients with laboratory-confirmed COVID-19. We also searched preprint manuscripts available at https://www.medrxiv.org/collection/endocrinology-including-diabetes-mellitus-and-metabolic-disease. The search free text terms were “coronavirus disease 2019” (OR “COVID19” OR “COVID-19 disease” OR “SARS-CoV-2”). We also searched for MeSH (Medical Subject Headings) terms. Searches were restricted to human studies. Non-English-language articles were excluded. Additionally, we reviewed references from relevant original papers and review articles for identifying further eligible studies not covered by the original database searches.

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org). Additionally, because the included studies were observational in design, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis of these studies [7].

Study selection

Original studies were included if they met the following inclusion criteria: (1) observational studies examining the clinical and biochemical characteristics of hospitalized patients with laboratory-confirmed COVID-19; and (2) all studies that reported data on presence of established diabetes among hospitalized patients with COVID-19. Study participants included in the meta-analysis were adult individuals (aged ≥18 years) of either sex without any restriction in terms of age, race, ethnicity or comorbidities.

Criteria for exclusion of selected studies from our meta-analysis were as follows: (1) congress abstracts, case reports, review articles, practice guidelines, commentaries or editorials; (2) studies in which information on presence of pre-existing diabetes was not specifically reported; (3) pre-print manuscripts that have yet to be reviewed; and (4) studies performed in pediatric population (aged <18 years).

Two investigators (AM and GT) independently examined all titles and abstracts, and obtained full texts of potentially relevant papers. Working independently and in duplicate the papers were read by both investigators (AM and GT), and whether they met inclusion criteria was then assessed. Discrepancies were resolved by consensus, referring back to the original article, in consultation with a third author.

Quality assessment of eligible studies was also performed by two investigators (AM and GT), using the Newcastle-Ottawa Quality Assessment Scale (NOS), which is a validated scale for non-randomized observational studies in meta-analyses [8]. A NOS scale adapted for cross-sectional studies was specifically used [9]. The NOS scale uses a star system to assess the quality of a study in three domains: selection, comparability and outcome/exposure. The NOS assigns a maximum of five stars for selection, two stars for comparability, and three stars for outcome/exposure. Studies achieving a score of at least eight stars were classified as being at low risk of bias (i.e., thus reflecting the highest quality).

Data extraction and quality assessment

For all eligible studies, we extracted information on study country, study size, patients’ characteristics, including demographics and percentage of individuals with established diabetes (i.e., defined as self-reported history of diabetes and/or use of any glucose-lowering medication), and other outcome measures of interest. In the case of multiple publications, we included the most up-to-date or comprehensive information.

Data synthesis and analysis

The primary outcome measures of the meta-analysis were the proportion of established diabetes amongst patients with COVID-19 at hospital admission, as well as the risk of patients with established diabetes of having severe/critical illness or increased in-hospital mortality associated with COVID-10. The severity of COVID-19 illness was assessed during hospitalization and classified as non-severe and severe/critical [10].

The pooled prevalence of established diabetes and the odds of having severe/critical COVID-19 illness or in-
hospital mortality were considered as the effect size for all eligible studies, and an overall estimate of effect size was calculated using a random-effects model, as this methodology takes into account any differences between studies even if there is no statistically significant heterogeneity [8,11]. The 95% confidence intervals for the eligible studies that were used for estimating the pooled prevalence of established diabetes amongst hospitalized patients with COVID-19 were computed by the Wilson’s score method [12].

Visual inspection of the forest plots was used to examine the possibility of statistical heterogeneity. The statistical heterogeneity among studies was assessed by the \( I^2 \)-statistics, which provides an estimate of percentage of variability across studies that is due to heterogeneity rather than chance alone. According to Higgins and Thompson [13], a rough guide to interpretation is as follows: \( I^2 \) values of approximately 25% represent low heterogeneity; approximately 50% represent medium heterogeneity; and approximately 75% represent high heterogeneity.

The possibility of publication bias was evaluated using the funnel plot and the Egger’s regression asymmetry test [14]. To examine the possible sources of (expected) high heterogeneity among the pooled studies and to test the robustness of the associations, we conducted some subgroup analyses. In particular, based on the data from eligible studies, the pooled prevalence of established diabetes was assessed stratifying the studies according to study country (Asian vs. non-Asian countries), age (<60 vs. ≥60 years), COVID-19 severity of illness (non-severe vs. severe/critical), or discharge vital status (dead or alive). Additionally, we tested for possible excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies at a time. We also performed univariable meta-regression analyses in order to examine the effect of age and sex on the association between established diabetes and risk of both COVID-19 severity and in-hospital mortality in the eligible studies.

\( p \)-values for chi-square tests are reported in all forest plots. A chi-square test \( p \)-value <0.10 was used to determine statistical significance considered for heterogeneity. The proportion of heterogeneity accounted for between-study variability was also estimated using the \( I^2 \)-statistics and adjudicated to be significant if \( I^2 \) value was >50%. We used STATA® 14.2 (StataCorp, College Station, Texas) for all statistical analyses. Specifically, the STATA metaprop command was used for statistical analyses.

**Results**

Fig. 1 summarizes the PRISMA flow diagram of the literature search and study selection. After excluding duplicates, based on titles and abstracts of 13,684 citations (in accordance with the aforementioned exclusion criteria of the meta-analysis), we initially identified 95 potentially eligible studies from PubMed, Web of Science and Scopus databases that were published until 15th May 2020 (last date searched) [15–109]. After examining the full text of these 95 articles, we further excluded 12 studies, because of unsatisfactory inclusion criteria [15] or being a pre-print manuscript that has yet to be reviewed [16–26], as specified in the PRISMA flow diagram.

In total, 83 observational studies were eligible for inclusion in our meta-analysis and were assessed for quality [27–109]. The main characteristics of these studies are summarized in Supplementary Table 1. Overall, in the 83 studies included in the meta-analysis there were 78,874 confirmed COVID-19 cases (52.1% men; median age 54 years [inter-quartile range: 49–62 years]). Sixty-two studies were conducted in Asian countries, mostly in China (involving a total of 65,946 COVID-19 patients with a median age of 52 years), and 21 studies were conducted in the Europe (Italy, France and United Kingdom), Australia and United States (involving a total of 12,928 COVID-19 patients with a median age of 63 years). In eligible studies, the diagnosis of diabetes was mainly based on the self-reported history of disease and/or use of glucose-lowering medications. Data on severity of COVID-19 illness at hospital admission were available for 22 eligible studies performed in China, France and United States (involving a total of 14,017 patients: 11,831 with non-severe COVID-19 and 2186 with severe/critical COVID-19). Data on total in-hospital deaths for the meta-analysis were available in 15 eligible studies, most of which were performed in China (involving a total of 56,057 COVID-19 patients with 1832 in-hospital deaths). As also shown in Supplementary Table 1, all the eligible studies received five or six stars on the NOS indicating that those studies had a high risk of bias.

As shown in Fig. 2, the pooled prevalence of established diabetes in the overall population of confirmed COVID-19 cases (n = 83 studies included) was 14.34% (95% confidence intervals [CI] 12.62–16.06%). The high heterogeneity observed in the overall primary analysis of these studies (\( I^2 = 97.8\% \)) likely reflects differences in the characteristics of study populations (mostly age and country). Indeed, the pooled prevalence of pre-existing diabetes was remarkably greater amongst COVID-19 patients aged ≥60 years than amongst those aged <60 years (23.30% [95% CI 19.65–26.94] vs. 8.79% [95% CI 7.56–10.02]; p < 0.001 – Fig. 2). Furthermore, the pooled prevalence of diabetes was also significantly greater in non-Asian countries than in Asian countries (23.34% [95% CI 16.40–30.28] vs. 11.06% [95% CI 9.73–12.39]; p = 0.001 – Fig. 3), possibly reflecting the marked differences in median age values of the study populations between the two countries.

The distribution of studies by estimate of the association between diabetes and risk of having severe/critical COVID-19 illness at hospital admission is plotted in Fig. 4. Patients with established diabetes had an approximate twofold greater risk of severe/critical COVID-19 illness compared to their counterparts without diabetes (n = 22 studies included; random-effects odds ratio 2.10, 95% CI 1.71–2.57; \( I^2 = 41.5\% \)).

Fig. 5 summarized the distribution of studies by estimate of the association between diabetes and risk of in-
hospital mortality associated with COVID-19. Pre-existing diabetes was significantly associated with a ~three-fold greater risk of in-hospital mortality associated with COVID-19 (n = 15 studies included; random-effects odds ratio 2.68, 95%CI 2.09–3.44; I² = 46.7%).

We also tested for the possibility of excessive influence of individual studies using an influence test that eliminated each of the included studies one at a time. Eliminating each of the eligible studies from the aforementioned analyses had no significant effect on the diabetes-related risk on both COVID-19 severity and in-hospital mortality (data not shown).

Fig. 6 shows the results of univariable meta-regression analyses showing the effect of age and sex on the association between pre-existing diabetes and risk of severity of illness and in-hospital mortality (data not shown).

This analysis supports an adverse effect of pre-existing diabetes on these two clinical outcomes, irrespective of sex. There was a clearer effect of increasing age (p = 0.05) on the association between pre-existing diabetes and severity of COVID-19. Conversely, age did not appear to exert any significant effect on the association between pre-existing diabetes and risk of in-hospital mortality.

Finally, as shown in Supplementary Fig. 1, the Egger's regression test did not show statistically significant asymmetry of the funnel plots (except for a borderline significance for the eligible studies with available data for in-hospital mortality analysis), thus suggesting that publication bias for the main clinical outcomes of interest (panels A to C) was unlikely.

Discussion

In this updated and comprehensive systematic review and meta-analysis of 83 non-randomized observational studies from Asia (mostly China), Europe and United States (involving a total of nearly 79,000 adult individuals), we found that the pooled prevalence of established diabetes at hospital admission was 14.34% (95%CI 12.62–16.06) in patients with laboratory-confirmed COVID-19. However, the prevalence of established diabetes was markedly higher in non-Asian vs. Asian countries (23.34% [95%CI 16.40–30.28] vs. 11.06% [95%CI 9.73–12.39]), as well as in patients aged ≥60 years than in those aged <60 years (23.30% [95%CI 19.65–26.94] vs. 8.79% [95%CI 7.56–10.02]). In addition and most importantly, our results show that COVID-19 patients with established diabetes had an approximate twofold higher risk of having severe/critical illness requiring Intensive Care Unit care (n = 22 studies; random-effects odds ratio 2.10, 95%CI 1.71–2.57; I² = 41.5%) and ~threefold increased risk of in-hospital
mortality associated with COVID-19 (n = 15 studies; random-effects odds ratio 2.68, 95%CI 2.09–3.44; I² = 46.7%). Based on our meta-regression analyses, the association between established diabetes and risk of these two clinical outcomes (especially for in-hospital mortality) appeared to be independent of age and sex.

Figure 2  Forest plot and pooled prevalence of established diabetes among patients with laboratory-confirmed COVID-19, stratified by age (n = 83 studies included).

Our results corroborate and extend the recent findings of some smaller meta-analyses performed in Chinese patients with laboratory-confirmed COVID-19. In a meta-analysis of 12 studies including 2108 Chinese hospitalized patients with COVID-19, Fadini et al. reported that the pooled prevalence of established diabetes was 10%, and
that patients with diabetes had a twofold higher risk of having severe COVID-19 (random-effects odds ratio 2.26, 95% CI 1.47–3.49) [110]. Similar results were also reported by Jang et al. in a meta-analysis of 7 studies that included a total of 1576 Chinese patients with COVID-19 [111], and by Huang et al. in a meta-analysis of 30 studies (most of which were preprint manuscripts that have yet to be reviewed) involving 6450 Chinese patients with COVID-19 [112]. Lastly, in a meta-analysis of 43 studies (that also included pre-print manuscripts) involving 3600 Chinese patients, Fu et al. reported that the overall prevalence of pre-existing diabetes amongst patients with COVID-19 was

Figure 3 Forest plot and pooled prevalence of established diabetes among patients with laboratory-confirmed COVID-19, stratified by study country (n = 83 studies included).
10.1% in the 26 studies where this information was available [113].

Overall, therefore, our findings corroborate on a much larger sample size and number of published studies (83 observational studies involving a total of 78,874 individuals) the results that have been previously reported by the aforementioned four meta-analyses in Chinese inpatients with laboratory-confirmed COVID-19, but extend these results also to patients hospitalized for COVID-19 in non-Asian countries, such as United States, Europe (Italy, France and United Kingdom) and Australia. Most importantly, our meta-analysis is the first to analyze the pooled effect of the association between pre-existing diabetes at admission and the risk of in-hospital mortality among patients with COVID-19.

To date, the pathophysiological and virologic mechanisms underpinning the strong association between pre-existing diabetes and risk of having severe/critical illness or increased in-hospital mortality with COVID-19 are poorly elucidated. It is reasonable to hypothesize that more severe COVID-19 illness in patients with established diabetes may be the consequence of underlying metabolic changes, chronic inflammation and/or attenuation of innate and adaptive immune responses (e.g., impaired phagocytosis by leukocytes, impaired neutrophil chemotaxis and bactericidal activity, and impaired innate cell-mediated immunity), thereby predisposing people with diabetes to infectious events of varying severity [2,3]. Additionally, patients with diabetes could also have an increased expression of the angiotensin-converting enzyme 2 (ACE-2), thereby facilitating viral uptake and increasing the risk of severe infection [114,115]. Finally, it is also possible to speculate that the altered microenvironment associated with diabetes might support the emergence of pathogenic SARS-CoV-2 variants capable of causing greater disease severity of COVID-19 illness.

Whilst our meta-analysis provides the most comprehensive assessment to date on the prevalence of pre-existing diabetes and its role as a risk factor for severe/critical COVID-19 illness and increased in-hospital mortality, some important limitations that are strictly inherent to the studies included in the meta-analysis should be mentioned. First, the observational design of the eligible studies does not allow for proving causality. Second,
although we found a medium level of heterogeneity for the pooled primary analysis of studies examining the impact of pre-existing diabetes on severity of illness ($I^2 = 41.5\%$) and in-hospital mortality ($I^2 = 46.7\%$) associated with COVID-19, the overall quality of these studies was relatively low, suggesting a high risk of bias according to the Newcastle-Ottawa scale (e.g., only few of the eligible studies examining the impact of pre-existing diabetes on COVID-19 severity or in-hospital mortality have adjusted the results for age, sex, obesity and other comorbidities; so the possibility of residual confounding cannot be excluded). That said, the few eligible studies that adjusted the results for age, sex, obesity and other relevant comorbidities showed that pre-existing diabetes was independently associated with poorer in-hospital outcomes, and that diabetic patients with better controlled blood glucose had a less severe COVID-19 illness and lower mortality rate compared to those with poorly controlled blood glucose during hospitalization [95,96]. Third, the majority of patients (i.e., ~85% of total) included in the meta-analysis were of Asian ancestry (mostly Chinese population), and it was not possible to test for ethnic-specific differences in risk of COVID-19 severity and COVID-19 linked death, because of the limited number of studies in non-Asian individuals.

Fourth, since the diagnosis of diabetes was not always consistent among the included studies, some inaccuracy in the estimated prevalence of diabetes and in the identification of diabetic sub-types may not be excluded, although the vast majority of diabetic cases were likely to be type 2. Fifth, none of the eligible studies did provide detailed information on hemoglobin A1c level or use of specific classes of glucose-lowering medications. Finally, although a selective reporting bias of eligible studies could be not definitely excluded, we believe that our comprehensive search has made it unlikely that any published reports were missed and visual inspection of funnel plots and formal tests demonstrated no statistical evidence of any publication bias. However, further studies, especially in European and American populations, are needed to confirm these findings, and future mechanistic studies are also required to better understand the link between diabetes and risk of severe disease and in-hospital mortality associated with COVID-19.

In conclusion, health care professionals caring for patients with COVID-19 need to be aware that pre-existing diabetes (in most cases type 2 diabetes mellitus) is significantly associated with a two to three times greater risk of severe/critical illness and in-hospital mortality.
associated with COVID-19. These findings highlight the urgent need of a multidisciplinary team-based approach to the management of this patient population.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.05.014.

Declaration of Competing Interest

None declared.

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All authors contributed to the manuscript for important intellectual contents and approved the final submission.

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