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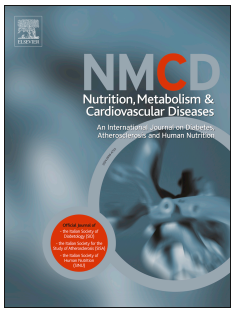

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Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies

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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; I^2=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; I^2=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.

Keywords: diabetes; COVID-19; coronavirus disease 2019; SARS-CoV-2; meta-analysis

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 were 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

156 random-effects model, as this methodology takes into account any differences
157 between studies even if there is no statistically significant heterogeneity [8,11]. The
158 95% confidence intervals for the eligible studies that were used for estimating the
159 pooled prevalence of established diabetes amongst hospitalized patients with
160 COVID-19 were computed by the Wilson's score method [12].
161
162 Visual inspection of the forest plots was used to examine the possibility of statistical
163 heterogeneity. The statistical heterogeneity among studies was assessed by the
164 I^2-statistics, which provides an estimate of percentage of variability across studies
165 that is due to heterogeneity rather than chance alone. According to Higgins and
166 Thompson [13], a rough guide to interpretation is as follows: I^2 values of
167 approximately 25% represent low heterogeneity; approximately 50% represent
168 medium heterogeneity; and approximately 75% represent high heterogeneity.
169
170 The possibility of publication bias was evaluated using the funnel plot and the Egger's
171 regression asymmetry test [14].
172
173 To examine the possible sources of (expected) high heterogeneity among the pooled
174 studies and to test the robustness of the associations, we conducted some subgroup
175 analyses. In particular, based on the data from eligible studies, the pooled prevalence
176 of established diabetes was assessed stratifying the studies according to study
177 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 possibly 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 by 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

Figure 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)

200 [15-109]. After examining the full text of these 95 articles, we further excluded 12
201 studies, because of unsatisfactory inclusion criteria [15] or being a pre-print
202 manuscript that has yet to be reviewed [16-26], as specified in the PRISMA flow
203 diagram.
204
205 In total, 83 observational studies were eligible for inclusion in our meta-analysis and
206 were assessed for quality [27-109]. The main characteristics of these studies are
207 summarized in **Supplementary Table 1**. Overall, in the 83 studies included in the
208 meta-analysis there were 78,874 confirmed COVID-19 cases (52.1% men; median age
209 54 years [inter-quartile range: 49-62 years]). Sixty-two studies were conducted in
210 Asian countries, mostly in China (involving a total of 65,946 COVID-19 patients with a
211 median age of 52 years), and 21 studies were conducted in the Europe (Italy, France
212 and United Kingdom), Australia and United States (involving a total of 12,928
213 COVID-19 patients with a median age of 63 years). In eligible studies, the diagnosis of
214 diabetes was mainly based on the self-reported history of disease and/or use of
215 glucose-lowering medications. Data on severity of COVID-19 illness at hospital
216 admission were available for 22 eligible studies performed in China, France and
217 United States (involving a total of 14,017 patients: 11,831 with non-severe COVID-19
218 and 2,186 with severe/critical COVID-19). Data on total in-hospital deaths for the
219 meta-analysis were available in 15 eligible studies, most of which were performed in
220 China (involving a total of 56,057 COVID-19 patients with 1,832 in-hospital deaths).
221 As also shown in **Supplementary Table 1**, all the eligible studies received five or six

222 stars on the NOS indicating that those studies had a high risk of bias.

223

224 As shown in **Figure 2**, the pooled prevalence of established diabetes in the overall
225 population of confirmed COVID-19 cases (n=83 studies included) was 14.34% (95%
226 confidence intervals [CI] 12.62-16.06%). The high heterogeneity observed in the
227 overall primary analysis of these studies (I^2=97.8%) likely reflects differences in the
228 characteristics of study populations (mostly age and country). Indeed, the pooled
229 prevalence of pre-existing diabetes was remarkably greater amongst COVID-19
230 patients aged ≥60 years than amongst those aged <60 years (23.30% [95%CI
231 19.65-26.94] vs. 8.79% [95%CI 7.56-10.02]; p<0.0001 – **Figure 2**). Furthermore, the
232 pooled prevalence of diabetes was also significantly greater in non-Asian countries
233 than in Asian countries (23.34% [95%CI 16.40-30.28] vs. 11.06% [95%CI 9.73-12.39];
234 p=0.001 - **Figure 3**), possibly reflecting the marked differences in median age values
235 of the study populations between the two countries.

236

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

242

243 **Figure 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; I^2=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).

Figure 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 associated with COVID-19. 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 Figure 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; I^2=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; I^2=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.

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 2,108 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 1,576 Chinese patients with COVID-19 [111], and by Huang *et al.* in a meta-analysis of 30 studies (most of which were preprint studies that have yet to be reviewed) involving 6,450 Chinese patients with COVID-19 [112]. Lastly, in a meta-analysis of 43 studies (that also included pre-print manuscripts) involving 3,600 Chinese patients, Fu *et al.* reported that the overall prevalence of pre-existing diabetes amongst patients with COVID-19 was 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 in-patients 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.

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AUTHORS CONTRIBUTIONS

Study concept and design: Alessandro Mantovani, Giovanni Targher
Acquisition of data: Alessandro Mantovani, Giovanni Targher
Analysis and interpretation of data: Alessandro Mantovani, Giovanni Targher

Drafting of the manuscript: Giovanni Targher
Critical revision of the manuscript for important intellectual contents: Christopher D. Byrne, Ming-Hua Zheng
All authors contributed to the manuscript for important intellectual contents and approved the final submission.

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871 **FIGURE LEGENDS**

872

873 **Figure 1**. The PRISMA flow diagram of the meta-analysis.

874

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

877

878 **Figure 3.** Forest plot and pooled prevalence of established diabetes among patients
879 with laboratory-confirmed COVID-19, stratified by study country (n=83 studies
880 included).

881

882 **Figure 4.** Forest plot and pooled risk of having severe/critical COVID-19 among
883 patients with and without established diabetes (n=22 studies included). Note: *in the
884 study of Targher *et al.* [96] the odds ratio for severe/critical COVID-19 was adjusted
885 for age, sex, smoking history, obesity and hypertension.

886

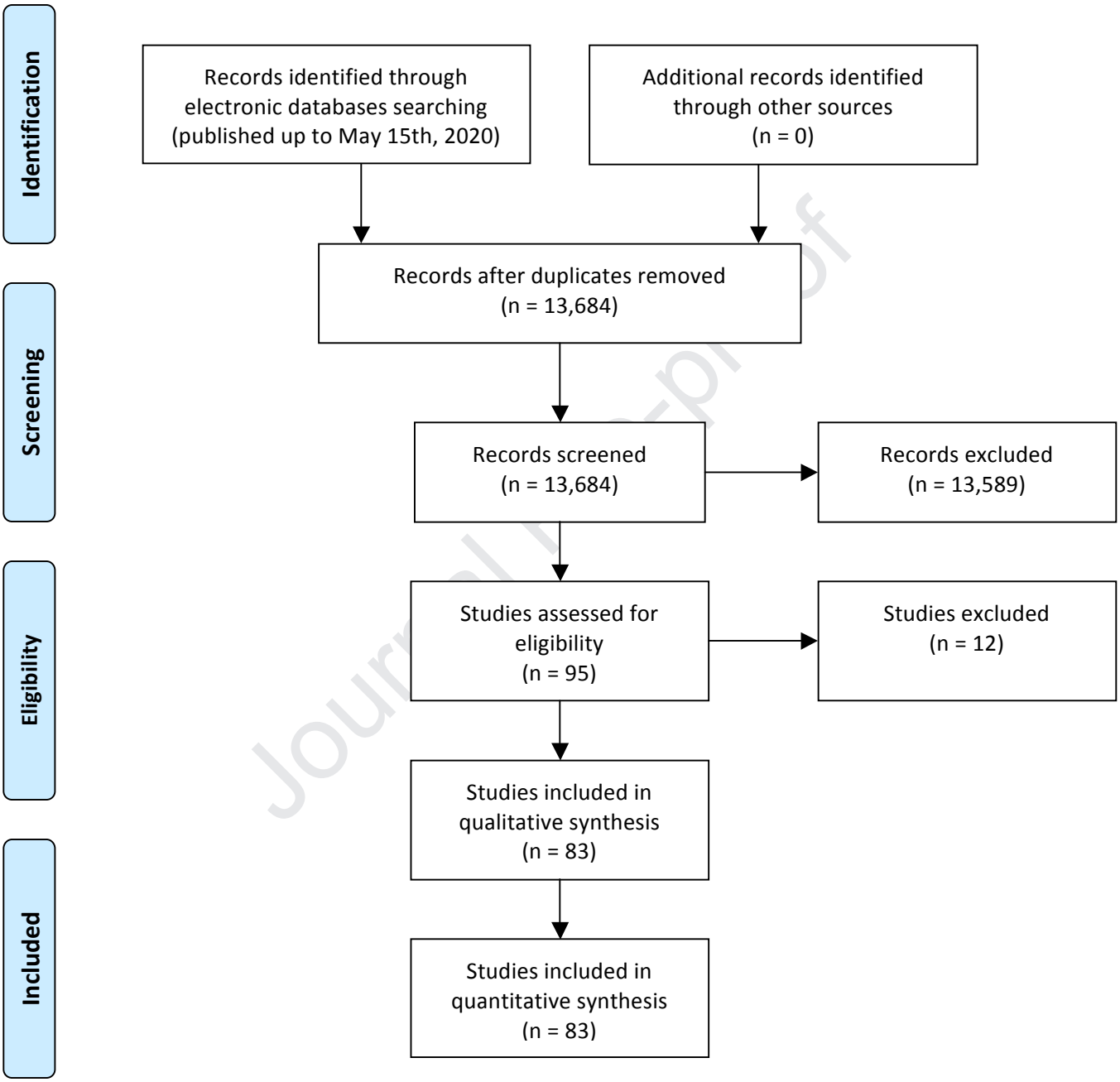
887 **Figure 5.** Forest plot and pooled risk of COVID-19-related in-hospital mortality among
888 patients with and without established diabetes (n=15 studies included). Note: *in a
889 subsequent study conducted on the same database (Crit Care. 2020 Apr 28;24:179),
890 Deng G *et al*. reported that the fatality rate of COVID-19 patients with diabetes was
891 higher than that of patients without diabetes.

892

893 **Figure 6.** Univariable linear meta-regression analyses. A meta-analysis of the

894 association of either age (panels A and C) or sex (panels B and D) with the
895 diabetes-related risk of COVID-19 severity or in-hospital mortality.
896
897 **Supplementary Figure 1**. Funnel plots of standard error by logit-transformed
898 prevalence rate of established diabetes (panel A, n=83 eligible studies); by log-odds
899 ratio for risk of severe COVID-19 (panel B, n=22 studies); and by log-odds ratio for risk
900 of in-hospital mortality (panel C, n=15 studies) among confirmed COVID-19 cases
901 with and without established diabetes.

PRISMA Flow Diagram



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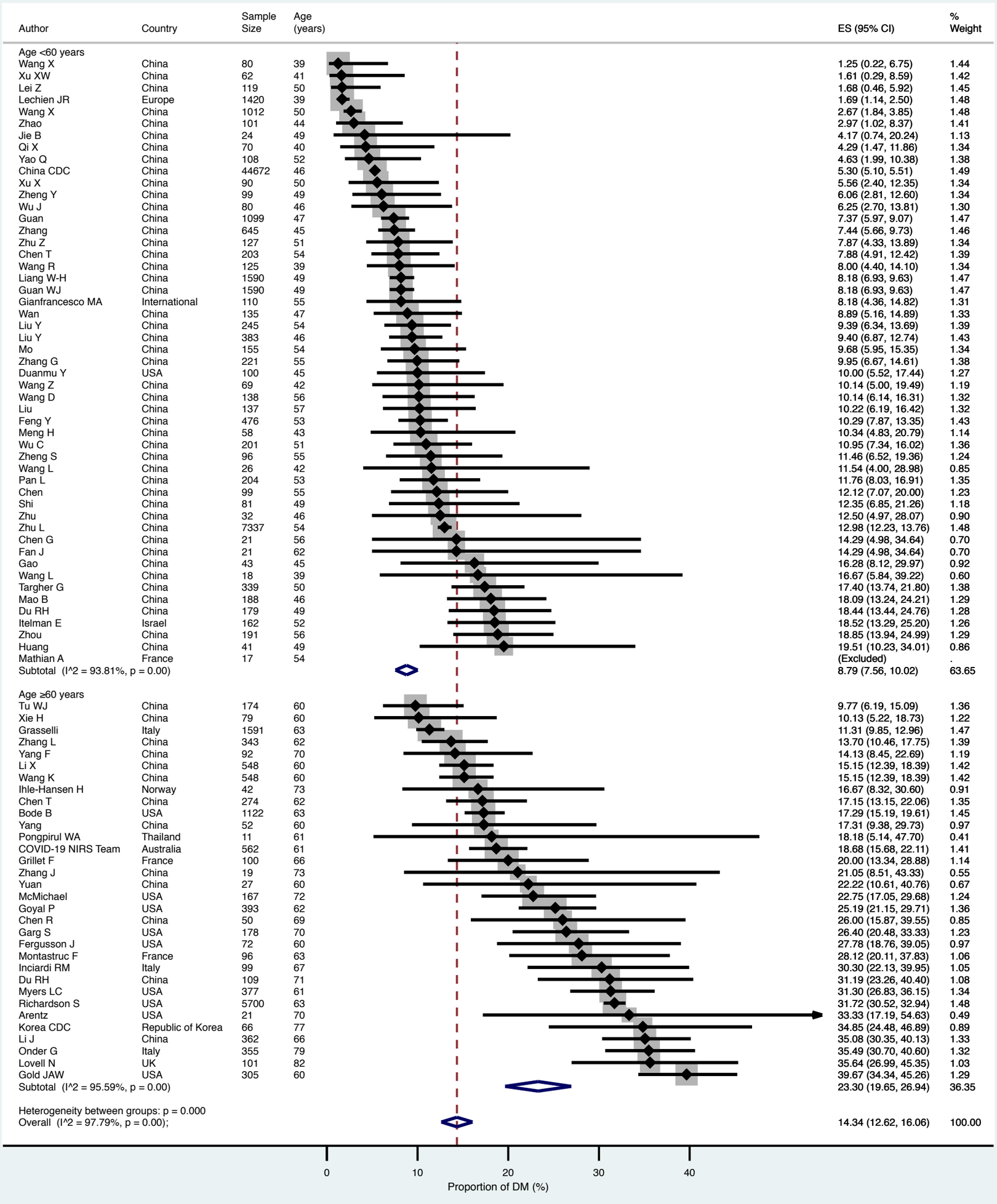
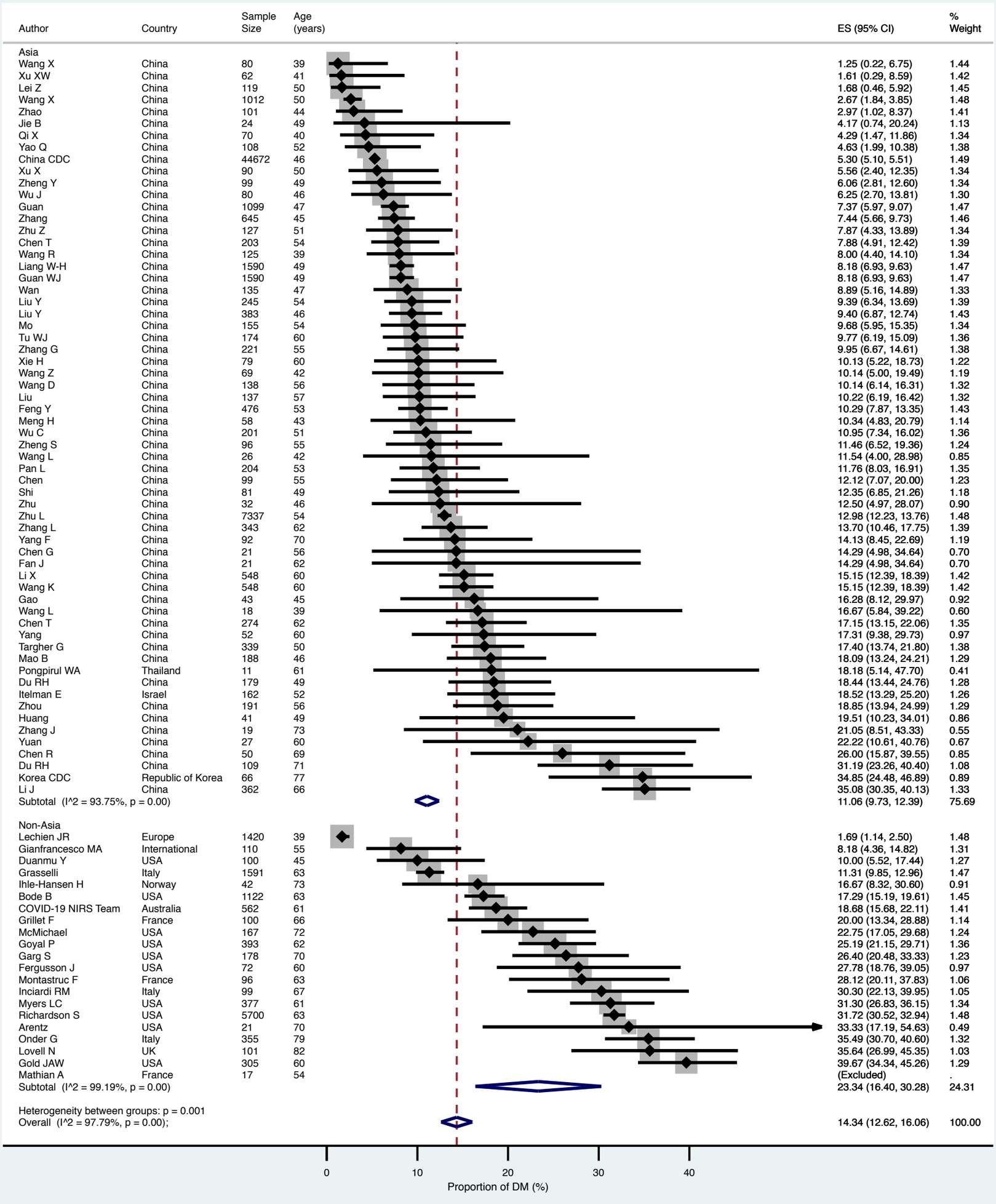

Author
Country
Sample Size
Age (years)
ES (95% CI)
% Weight
Age <60 years
Wang X China 80 39 1.25 (0.22, 6.75) 1.44
Xu XW China 62 41 1.61 (0.29, 8.59) 1.42
Lei Z China 119 50 1.68 (0.46, 5.92) 1.45
Lechien JR Europe 1420 39 1.69 (1.14, 2.50) 1.48
Wang X China 1012 50 2.67 (1.84, 3.85) 1.48
Zhao China 101 44 2.97 (1.02, 8.37) 1.41
Jie B China 24 49 4.17 (0.74, 20.24) 1.13
Qi X China 70 40 4.29 (1.47, 11.86) 1.34
Yao Q China 108 52 4.63 (1.99, 10.38) 1.38
China CDC China 44672 46 5.30 (5.10, 5.51) 1.49
Xu X China 90 50 5.56 (2.40, 12.35) 1.34
Zheng Y China 99 49 6.06 (2.81, 12.60) 1.34
Wu J China 80 46 6.25 (2.70, 13.81) 1.30
Guan China 1099 47 7.37 (5.97, 9.07) 1.47
Zhang China 645 45 7.44 (5.66, 9.73) 1.46
Zhu Z China 127 51 7.87 (4.33, 13.89) 1.34
Chen T China 203 54 7.88 (4.91, 12.42) 1.39
Wang R China 125 39 8.00 (4.40, 14.10) 1.34
Liang W-H China 1590 49 8.18 (6.93, 9.63) 1.47
Guan WJ China 1590 49 8.18 (6.93, 9.63) 1.47
Gianfrancesco MA International 110 55 8.18 (4.36, 14.82) 1.31
Wan China 135 47 8.89 (5.16, 14.89) 1.33
Liu Y China 245 54 9.39 (6.34, 13.69) 1.39
Liu Y China 383 46 9.40 (6.87, 12.74) 1.43
Mo China 155 54 9.68 (5.95, 15.35) 1.34
Zhang G China 221 55 9.95 (6.67, 14.61) 1.38
Duanmu Y USA 100 45 10.00 (5.52, 17.44) 1.27
Wang Z China 69 42 10.14 (5.00, 19.49) 1.19
Wang D China 138 56 10.14 (6.14, 16.31) 1.32
Liu China 137 57 10.22 (6.19, 16.42) 1.32
Feng Y China 476 53 10.29 (7.87, 13.35) 1.43
Meng H China 58 43 10.34 (4.83, 20.79) 1.14
Wu C China 201 51 10.95 (7.34, 16.02) 1.36
Zheng S China 96 55 11.46 (6.52, 19.36) 1.24
Wang L China 26 42 11.54 (4.00, 28.98) 0.85
Pan L China 204 53 11.76 (8.03, 16.91) 1.35
Chen China 99 55 12.12 (7.07, 20.00) 1.23
Shi China 81 49 12.35 (6.85, 21.26) 1.18
Zhu China 32 46 12.50 (4.97, 28.07) 0.90
Zhu L China 7337 54 12.98 (12.23, 13.76) 1.48
Chen G China 21 56 14.29 (4.98, 34.64) 0.70
Fan J China 21 62 14.29 (4.98, 34.64) 0.70
Gao China 43 45 16.28 (8.12, 29.97) 0.92
Wang L China 18 39 16.67 (5.84, 39.22) 0.60
Targher G China 339 50 17.40 (13.74, 21.80) 1.38
Mao B China 188 46 18.09 (13.24, 24.21) 1.29
Du RH China 179 49 18.44 (13.44, 24.76) 1.28
Itelman E Israel 162 52 18.52 (13.29, 25.20) 1.26
Zhou China 191 56 18.85 (13.94, 24.99) 1.29
Huang China 41 49 19.51 (10.23, 34.01) 0.86
Mathian A France 17 54 (Excluded) .
Subtotal (I^2 = 93.81%, p = 0.00) 8.79 (7.56, 10.02) 63.65
Age ≥60 years
Tu WJ China 174 60 9.77 (6.19, 15.09) 1.36
Xie H China 79 60 10.13 (5.22, 18.73) 1.22
Grasselli Italy 1591 63 11.31 (9.85, 12.96) 1.47
Zhang L China 343 62 13.70 (10.46, 17.75) 1.39
Yang F China 92 70 14.13 (8.45, 22.69) 1.19
Li X China 548 60 15.15 (12.39, 18.39) 1.42
Wang K China 548 60 15.15 (12.39, 18.39) 1.42
Ihle-Hansen H Norway 42 73 16.67 (8.32, 30.60) 0.91
Chen T China 274 62 17.15 (13.15, 22.06) 1.35
Bode B USA 1122 63 17.29 (15.19, 19.61) 1.45
Yang China 52 60 17.31 (9.38, 29.73) 0.97
Pongpirul WA Thailand 11 61 18.18 (5.14, 47.70) 0.41
COVID-19 NIRS Team Australia 562 61 18.68 (15.68, 22.11) 1.41
Grillet F France 100 66 20.00 (13.34, 28.88) 1.14
Zhang J China 19 73 21.05 (8.51, 43.33) 0.55
Yuan China 27 60 22.22 (10.61, 40.76) 0.67
McMichael USA 167 72 22.75 (17.05, 29.68) 1.24
Goyal P USA 393 62 25.19 (21.15, 29.71) 1.36
Chen R China 50 69 26.00 (15.87, 39.55) 0.85
Garg S USA 178 70 26.40 (20.48, 33.33) 1.23
Fergusson J USA 72 60 27.78 (18.76, 39.05) 0.97
Montastruc F France 96 63 28.12 (20.11, 37.83) 1.06
Inciardi RM Italy 99 67 30.30 (22.13, 39.95) 1.05
Du RH China 109 71 31.19 (23.26, 40.40) 1.08
Myers LC USA 377 61 31.30 (26.83, 36.15) 1.34
Richardson S USA 5700 63 31.72 (30.52, 32.94) 1.48
Arentz USA 21 70 33.33 (17.19, 54.63) 0.49
Korea CDC Republic of Korea 66 77 34.85 (24.48, 46.89) 0.89
Li J China 362 66 35.08 (30.35, 40.13) 1.33
Onder G Italy 355 79 35.49 (30.70, 40.60) 1.32
Lovell N UK 101 82 35.64 (26.99, 45.35) 1.03
Gold JAW USA 305 60 39.67 (34.34, 45.26) 1.29
Subtotal (I^2 = 95.59%, p = 0.00) 23.30 (19.65, 26.94) 36.35
Heterogeneity between groups: p = 0.000
Overall (I^2 = 97.79%, p = 0.00); 14.34 (12.62, 16.06) 100.00
0
10
20
30
40
Proportion of DM (%)


Author
Country
Sample Size
Age (years)
ES (95% CI)
% Weight
Asia
Wang X China 80 39 1.25 (0.22, 6.75) 1.44
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China CDC China 44672 46 5.30 (5.10, 5.51) 1.49
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Liu China 137 57 10.22 (6.19, 16.42) 1.32
Feng Y China 476 53 10.29 (7.87, 13.35) 1.43
Meng H China 58 43 10.34 (4.83, 20.79) 1.14
Wu C China 201 51 10.95 (7.34, 16.02) 1.36
Zheng S China 96 55 11.46 (6.52, 19.36) 1.24
Wang L China 26 42 11.54 (4.00, 28.98) 0.85
Pan L China 204 53 11.76 (8.03, 16.91) 1.35
Chen China 99 55 12.12 (7.07, 20.00) 1.23
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Zhu China 32 46 12.50 (4.97, 28.07) 0.90
Zhu L China 7337 54 12.98 (12.23, 13.76) 1.48
Zhang L China 343 62 13.70 (10.46, 17.75) 1.39
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Fan J China 21 62 14.29 (4.98, 34.64) 0.70
Li X China 548 60 15.15 (12.39, 18.39) 1.42
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Gao China 43 45 16.28 (8.12, 29.97) 0.92
Wang L China 18 39 16.67 (5.84, 39.22) 0.60
Chen T China 274 62 17.15 (13.15, 22.06) 1.35
Yang China 52 60 17.31 (9.38, 29.73) 0.97
Targher G China 339 50 17.40 (13.74, 21.80) 1.38
Mao B China 188 46 18.09 (13.24, 24.21) 1.29
Pongpirul WA Thailand 11 61 18.18 (5.14, 47.70) 0.41
Du RH China 179 49 18.44 (13.44, 24.76) 1.28
Itelman E Israel 162 52 18.52 (13.29, 25.20) 1.26
Zhou China 191 56 18.85 (13.94, 24.99) 1.29
Huang China 41 49 19.51 (10.23, 34.01) 0.86
Zhang J China 19 73 21.05 (8.51, 43.33) 0.55
Yuan China 27 60 22.22 (10.61, 40.76) 0.67
Chen R China 50 69 26.00 (15.87, 39.55) 0.85
Du RH China 109 71 31.19 (23.26, 40.40) 1.08
Korea CDC Republic of Korea 66 77 34.85 (24.48, 46.89) 0.89
Li J China 362 66 35.08 (30.35, 40.13) 1.33
Subtotal (I^2 = 93.75%, p = 0.00) 11.06 (9.73, 12.39) 75.69
Non-Asia
Lechien JR Europe 1420 39 1.69 (1.14, 2.50) 1.48
Gianfrancesco MA International 110 55 8.18 (4.36, 14.82) 1.31
Duanmu Y USA 100 45 10.00 (5.52, 17.44) 1.27
Grasselli Italy 1591 63 11.31 (9.85, 12.96) 1.47
Ihle-Hansen H Norway 42 73 16.67 (8.32, 30.60) 0.91
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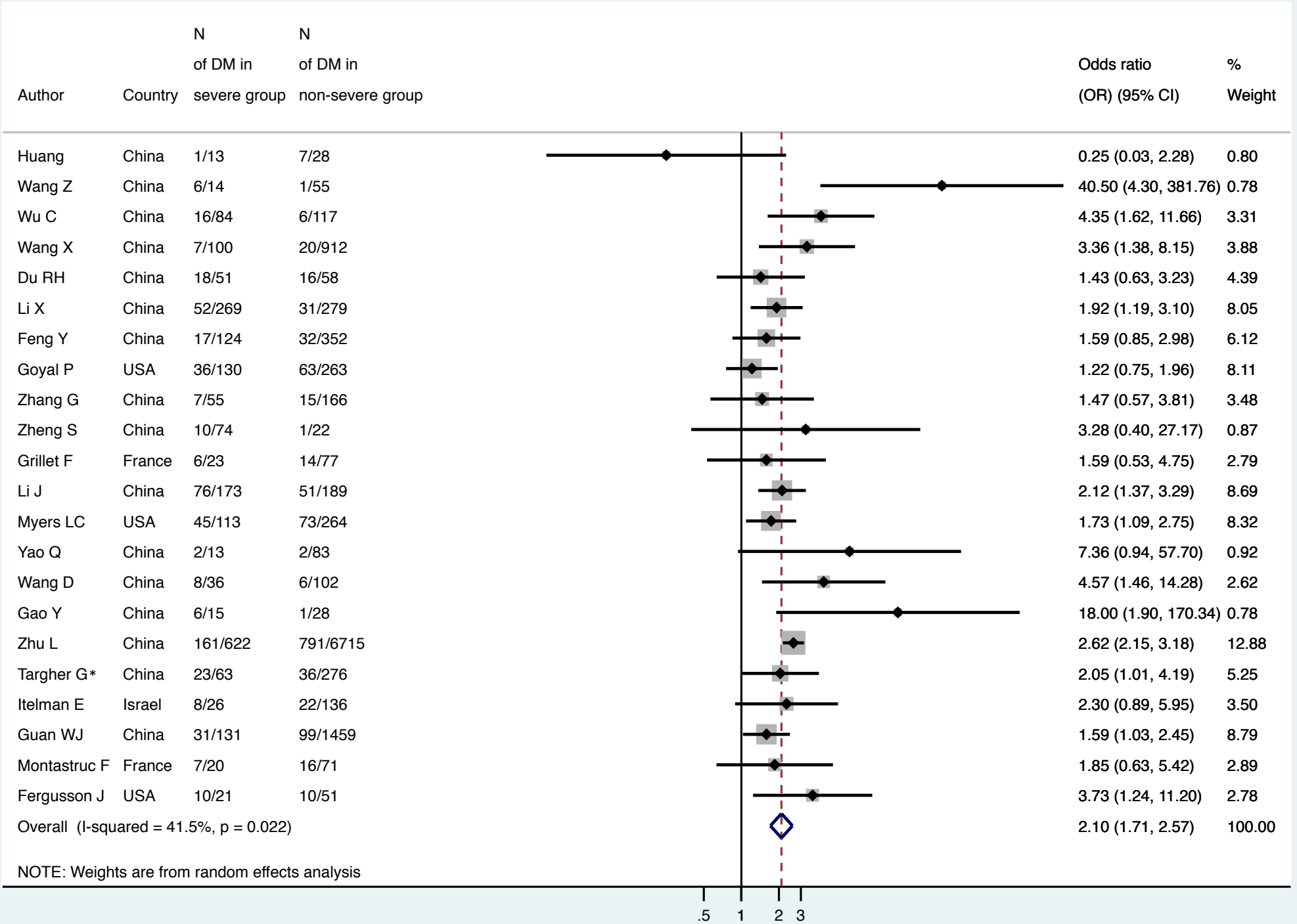
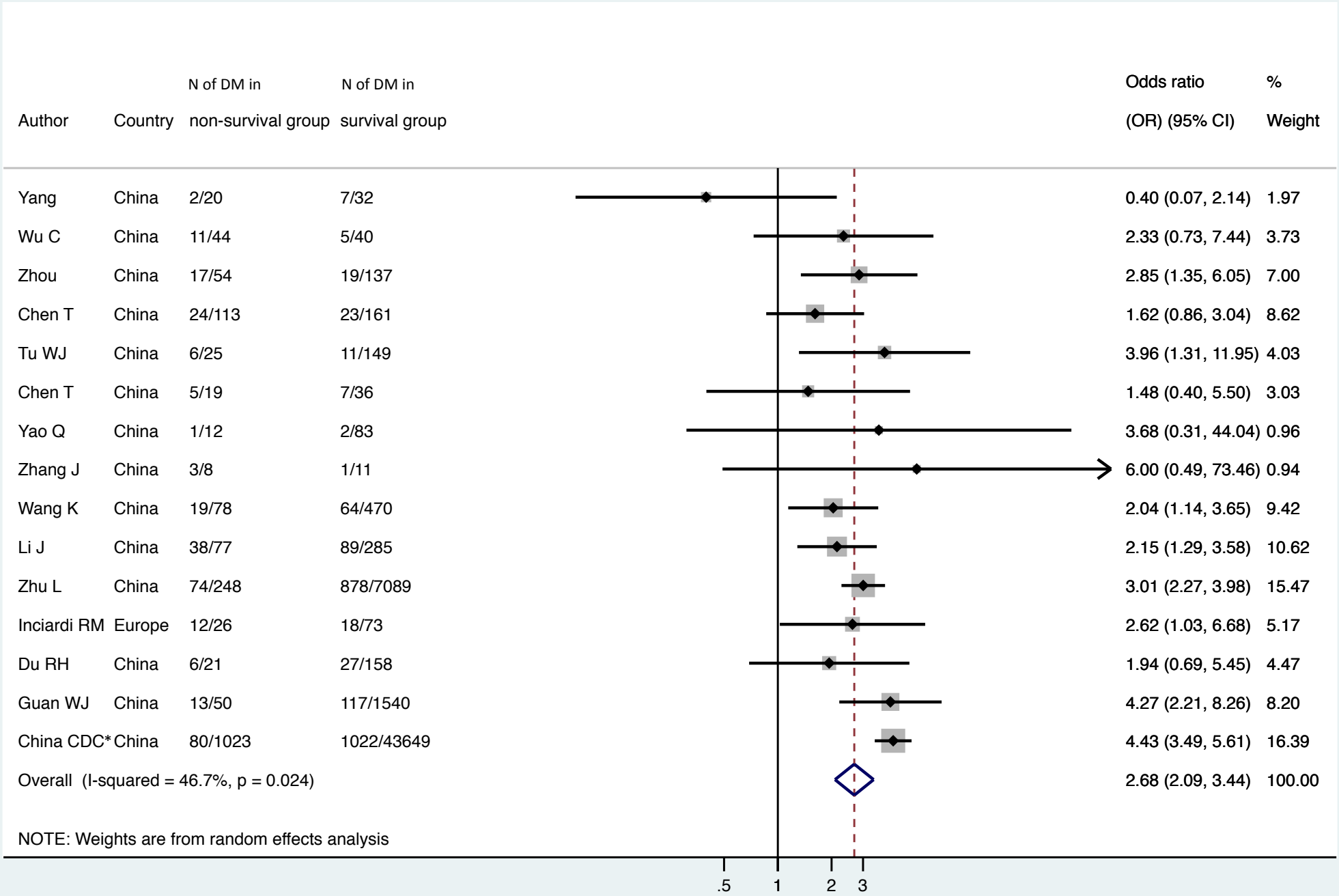
COVID-19 NIRS Team Australia 562 61 18.68 (15.68, 22.11) 1.41
Grillet F France 100 66 20.00 (13.34, 28.88) 1.14
McMichael USA 167 72 22.75 (17.05, 29.68) 1.24
Goyal P USA 393 62 25.19 (21.15, 29.71) 1.36
Garg S USA 178 70 26.40 (20.48, 33.33) 1.23
Fergusson J USA 72 60 27.78 (18.76, 39.05) 0.97
Montastruc F France 96 63 28.12 (20.11, 37.83) 1.06
Inciardi RM Italy 99 67 30.30 (22.13, 39.95) 1.05
Myers LC USA 377 61 31.30 (26.83, 36.15) 1.34
Richardson S USA 5700 63 31.72 (30.52, 32.94) 1.48
Arentz USA 21 70 33.33 (17.19, 54.63) 0.49
Onder G Italy 355 79 35.49 (30.70, 40.60) 1.32
Lovell N UK 101 82 35.64 (26.99, 45.35) 1.03
Gold JAW USA 305 60 39.67 (34.34, 45.26) 1.29
Mathian A France 17 54 (Excluded) .
Subtotal (I^2 = 99.19%, p = 0.00) 23.34 (16.40, 30.28) 24.31
Heterogeneity between groups: p = 0.001
Overall (I^2 = 97.79%, p = 0.00); 14.34 (12.62, 16.06) 100.00
0
10
20
30
40
Proportion of DM (%)

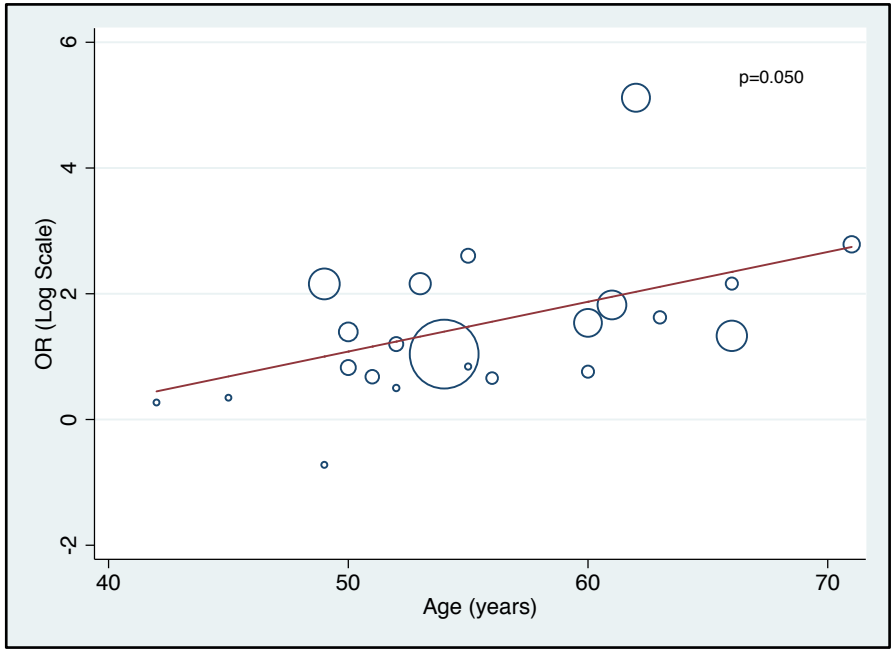

Author
Country
N of DM in severe group
N of DM in non-severe group
Odds ratio (OR) (95% CI)
% Weight
Huang China 1/13 7/28 0.25 (0.03, 2.28) 0.80
Wang Z China 6/14 1/55 40.50 (4.30, 381.76) 0.78
Wu C China 16/84 6/117 4.35 (1.62, 11.66) 3.31
Wang X China 7/100 20/912 3.36 (1.38, 8.15) 3.88
Du RH China 18/51 16/58 1.43 (0.63, 3.23) 4.39
Li X China 52/269 31/279 1.92 (1.19, 3.10) 8.05
Feng Y China 17/124 32/352 1.59 (0.85, 2.98) 6.12
Goyal P USA 36/130 63/263 1.22 (0.75, 1.96) 8.11
Zhang G China 7/55 15/166 1.47 (0.57, 3.81) 3.48
Zheng S China 10/74 1/22 3.28 (0.40, 27.17) 0.87
Grillet F France 6/23 14/77 1.59 (0.53, 4.75) 2.79
Li J China 76/173 51/189 2.12 (1.37, 3.29) 8.69
Myers LC USA 45/113 73/264 1.73 (1.09, 2.75) 8.32
Yao Q China 2/13 2/83 7.36 (0.94, 57.70) 0.92
Wang D China 8/36 6/102 4.57 (1.46, 14.28) 2.62
Gao Y China 6/15 1/28 18.00 (1.90, 170.34) 0.78
Zhu L China 161/622 791/6715 2.62 (2.15, 3.18) 12.88
Targher G* China 23/63 36/276 2.05 (1.01, 4.19) 5.25
Itelman E Israel 8/26 22/136 2.30 (0.89, 5.95) 3.50
Guan WJ China 31/131 99/1459 1.59 (1.03, 2.45) 8.79
Montastruc F France 7/20 16/71 1.85 (0.63, 5.42) 2.89
Fergusson J USA 10/21 10/51 3.73 (1.24, 11.20) 2.78
Overall (I-squared = 41.5%, p = 0.022) 2.10 (1.71, 2.57) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
3


Author
Country
N of DM in non-survival group
N of DM in survival group
Odds ratio (OR) (95% CI)
% Weight
Yang China 2/20 7/32 0.40 (0.07, 2.14) 1.97
Wu C China 11/44 5/40 2.33 (0.73, 7.44) 3.73
Zhou China 17/54 19/137 2.85 (1.35, 6.05) 7.00
Chen T China 24/113 23/161 1.62 (0.86, 3.04) 8.62
Tu WJ China 6/25 11/149 3.96 (1.31, 11.95) 4.03
Chen T China 5/19 7/36 1.48 (0.40, 5.50) 3.03
Yao Q China 1/12 2/83 3.68 (0.31, 44.04) 0.96
Zhang J China 3/8 1/11 6.00 (0.49, 73.46) 0.94
Wang K China 19/78 64/470 2.04 (1.14, 3.65) 9.42
Li J China 38/77 89/285 2.15 (1.29, 3.58) 10.62
Zhu L China 74/248 878/7089 3.01 (2.27, 3.98) 15.47
Inciardi RM Europe 12/26 18/73 2.62 (1.03, 6.68) 5.17
Du RH China 6/21 27/158 1.94 (0.69, 5.45) 4.47
Guan WJ China 13/50 117/1540 4.27 (2.21, 8.26) 8.20
China CDC* China 80/1023 1022/43649 4.43 (3.49, 5.61) 16.39
Overall (I-squared = 46.7%, p = 0.024) 2.68 (2.09, 3.44) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
3

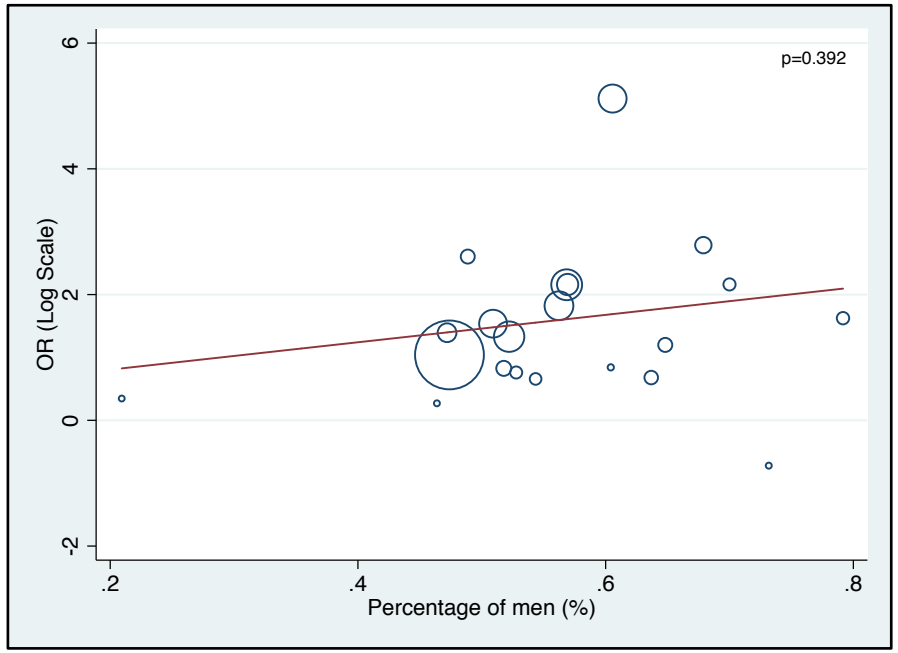
Severe COVID-19

In-hospital death

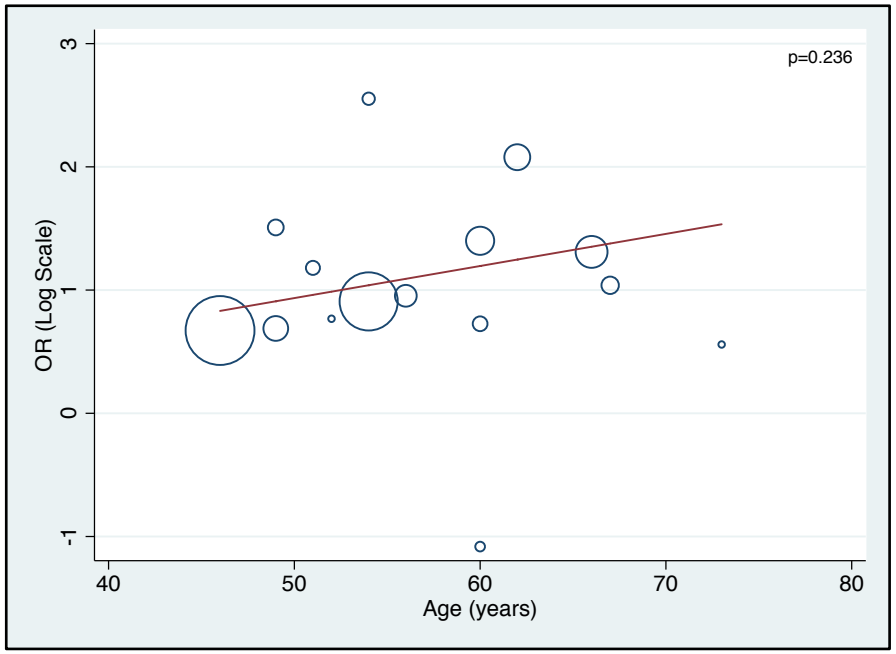
Panel A



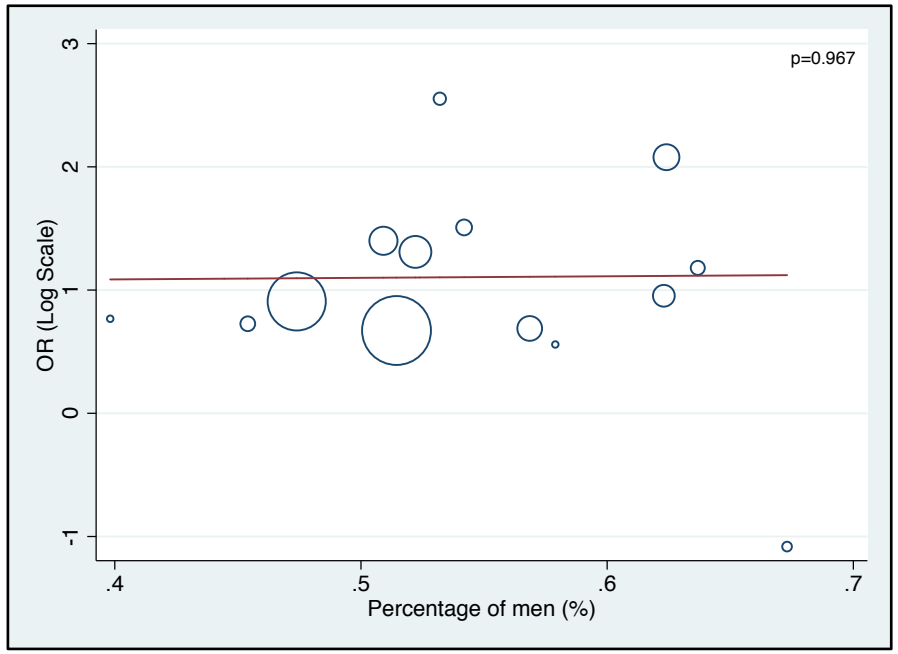
Panel B



Panel C



Panel D



HIGHLIGHTS

- Little is known about the association of diabetes with the clinical severity and in-hospital mortality associated with COVID-19.
- We meta-analyzed 83 observational studies for a total of 78,874 in-patients with COVID-19.
- Pre-existing diabetes was associated with a two to three times greater risk of severe/critical illness and in-hospital mortality associated with COVID-19.