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Burden of diabetes mellitus and its impact on COVID-19 patients: A meta-analysis of real-world evidence

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ABSTRACT

Background & aims: Coronavirus disease 2019 (COVID-19) spreads rapidly and within no time, it has been declared a pandemic by the World Health Organization. Evidence suggests diabetes to be a risk factor for the progression and poor prognosis of COVID-19. Therefore, we aimed to understand the pooled prevalence of diabetes in patients infected with COVID-19. We also aimed to compute the risk of mortality and ICU admissions in COVID-19 patients with and without diabetes.

Methods: A comprehensive literature search was performed in PubMed to identify the articles reporting the diabetes prevalence and risk of mortality or ICU admission in COVID-19 patients. The primary outcome was to compute the pooled prevalence of diabetes in COVID-19 patients. Secondary outcomes included risk of mortality and ICU admissions in COVID-19 patients with diabetes compared to patients without diabetes.

Results: This meta-analysis was based on a total of 23007 patients from 43 studies. The pooled prevalence of diabetes in patients infected with COVID-19 was found to be 15% (95% CI: 12%–18%), $p = <0.0001$. Mortality risk was found to be significantly higher in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes with a pooled risk ratio of 1.61 (95% CI: 1.16–2.25%), $p = 0.005$. Likewise, risk of ICU admission rate was significantly higher in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes with a pooled risk ratio of 1.88 (1.20%–2.93%), $p = 0.006$.

Conclusion: This meta-analysis found a high prevalence of diabetes and higher mortality and ICU admission risk in COVID-19 patients with diabetes.

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1. Introduction

The recent outbreak of the novel coronavirus or COVID-19 was first reported in Wuhan, China on December 31, 2019 [1]. This disease outbreak, which was initially misinterpreted as pneumonia cases, was declared to be a public emergency of international concern by the World Health Organisation (WHO) on January 30, 2020. Within a few weeks, from an endemic it became a pandemic. Previous outbreaks from this family of viruses include the SARS-

CoV outbreak in 2002 and the MERS-CoV in 2012 [2]. According to a WHO Situation report published on July 6, 2020, COVID-19 has spread to more than 188 countries infecting over 11.3 million people globally with a mortality rate of 4.69% [3].

COVID-19 is mainly transmitted through respiratory droplets and close contact [4]. Patients mostly experience either mild symptoms—fever, fatigue, and dry cough, or maybe asymptomatic [4,5]. Patients also later develop anorexia, myalgia, dyspnea or in some cases severe pneumonia or acute respiratory distress syndrome [6–9]. Severe or critical illness has been reported in 20% of the patients in a study by Yao et al. post-hospital admission [10].

About 20–51% of patients hospitalized with COVID-19 are found to have at least one comorbid condition. Diabetes, hypertension,

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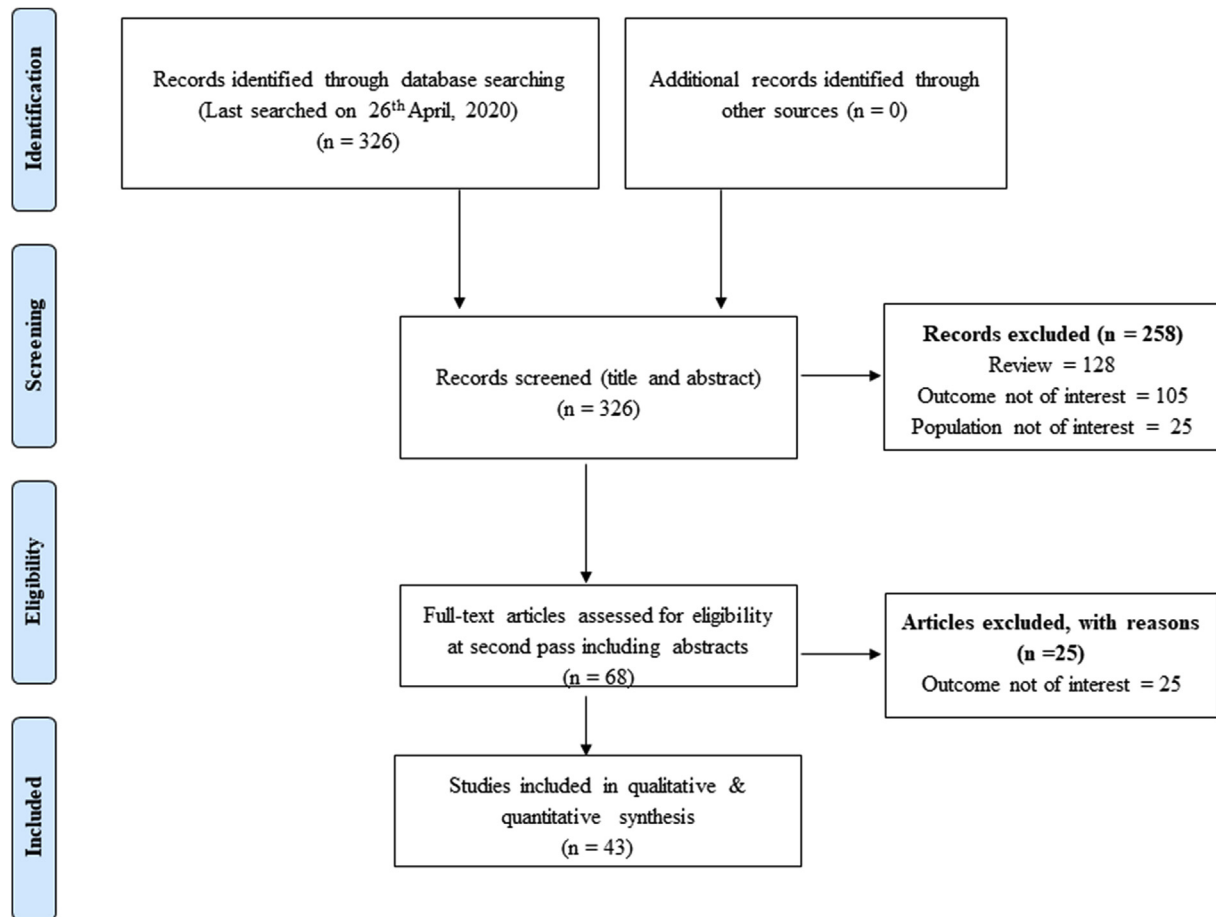


Fig. 1. PRISMA chart demonstrating study selection process.

and other cardiovascular diseases are found to be most prevalent among them [7,11,12]. Diabetes is considered a risk factor for a rapid progression and poor prognosis of COVID-19 [13]. Chinese centre for disease control and prevention reported a 6.3% prevalence of diabetes among patients infected with COVID-19. Diabetes prevalence was found to be 18.75% in COVID-19 patients in Spain [14]. In another study conducted by Huang et al., one-fifth of the patients had diabetes mellitus as comorbidity [11]. It is postulated that the angiotensin-converting enzyme 2 (ACE2) is responsible for this correlation [15].

Various studies have shown diabetes mellitus as one of the most common comorbidities in COVID-19 patients but its exact prevalence is still unclear [16–18]. Given the rapid spread of COVID-19 and diabetes is one of the most common diseases leading to multi-systemic complications, we performed a meta-analysis to determine the prevalence of diabetic mellitus in COVID-19 patients. We also computed mortality and ICU admissions risk in in COVID-19 patients with diabetes compared to COVID-19 patients without diabetes..

2. Material and methods

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Refer Supplementary file S1 for the PRISMA checklist.

2.1. Data sources and search strategy

All the studies assessing the prevalence and impact of diabetes in patients with COVID-19 were searched in PubMed via Medline using pre-defined search terms from inception till April 26, 2020. Search terms were framed through a combination of keywords related to “coronavirus 2019 OR novel coronavirus OR COVID-19” AND “diabetes OR type 2 diabetes mellitus OR T2DM or type-1 diabetes mellitus OR T1DM.” A detailed search string is available as a supplementary file S2. We included articles published in other languages only if the abstract was available in English and sufficient information was mentioned in the abstract. Bibliography of potentially relevant studies was also reviewed manually to identify any additional articles.

2.2. Study selection and exclusion criteria

Study selection was performed by two independent reviewers (Salman Hussain and Harveen Baxi). We selected all those studies that reported the prevalence of diabetes and associated outcomes (mortality, ICU admission) in confirmed COVID-19 patients. We included only published peer-reviewed studies that had presented their findings on at least ten confirmed COVID-19 patients. In the first screening, articles were screened based on the title and abstract. Then, a second screening was done on all the eligible studies from the first screening for a full-text review. When two studies were using the same database, then the study with more detailed and with larger study duration were included. All those studies

Table 1
Study design characteristics of included studies.

Study author & year	Study design	Country	Total no. of patients	Mean/ Median age (years)	Males (%)	Confirmation of COVID-19	Diabetes (N)	Study Quality
Arentz M et al., 2020[21]	Retrospective	USA	21	70 (43–92)	52%	RT-PCR	7	High
Barrasa H et al., 2020[14]	Prospective cohort	Vitoria, Spain	48	63.3 ± 12	56%	RT-PCR	9	High
Cao et al., 2020 [22]	Retrospective Cohort	Wuhan, China	102	54 (37–67)	52%	RT-PCR	11	High
Chen T et al., 2020 [23]	Single centered, Retrospective study	Wuhan, China	203	54 (41–68)	53.20%	CT, RT-PCR, Chinese National Health Committee version 3–6	16	High
Cheng Y et al., 2020 [24]	Prospective cohort	Wuhan, China	701	63 (50–71)	52.40%	CT; RT-PCR; fever or respiratory symptoms; leukopenia or lymphopenia	100	High
Chow N et al., 2020 [25]	Retrospective (MMWR report)	USA	7162	NR	NR	RT-PCR	784	High
Deng Y. et al., 2020 [26]	Retrospective study	Wuhan, China	225	54.5(47.5, 65.5)	55.11%	Diagnosis and treatment protocol of National Health Commission of the People's Republic of China.	26	High
Du R et al., 2020 (a) [16]	Prospective cohort	Wuhan, China	179	57.6 ± 13.7	54.20%	WHO interim guidance	33	High
Du R. et al. (b) [27]	Multi- Center Observational study	Wuhan, China	109	70.7 ± 10.9	67.90%	WHO interim guidance	34	High
Du Y. et al., 2020 [28]	Retrospective, observational study	Wuhan, China	85	65.8	72.90%	National Institute for Viral Disease Control and Prevention, China (5th edition), CT, RT-PCR	19	High
Feng Y. 2020 [29]	Multi- Center Retrospective cohort study	Wuhan, Shanghai, Anhui, China	476	53 (40–64)	56.90%	National Health Commission of China guidelines, CT, RT-PCR	49	High
Guo W et al., 2020 [13]	Retrospective	Wuhan, China	174	59 (49–67)	43.70%	RT-PCR	24	High
Gupta N et al., 2020 [30]	Retrospective observational case study	New Delhi, India	21	40.3 (16–73)	66.70%	Based on symptoms	3	Low
He X et al., 2020 ^a [31]	Retrospective study	Wuhan, China	54	68 (59.8, 74.3)	NR	Based on symptoms	13	Low
Huang C et al., 2020 [11]	Retrospective	Wuhan, China	41	49 (41–58)	73%	RT-PCR	8	Low
Jeong E et al., 2020 [18]	Cohort	Korea	66	77 (35–93)	56.10%	Korea centers for disease control and prevention	23	Medium
Lei S. et al., 2020 [32]	Multicenter Retrospective study	Wuhan, China	34	55 (43–63)	41.20%	RT-PCR	8	High
Li J et al., 2020 [33]	Retrospective cohort	Wuhan, China	658	57.5 (42–67)	45.10%	CT, Lab(viral nucleic acid test)	129	High
Li T et al., 2020 [34]	Cross sectional	Wuhan, China	182	68.5 ± 8.8	35%	RT-PCR, Next generation sequencing	51	High
Li X et al., 2020 [35]	Retrospective	Wuhan, China	25	71.88	40%	RT-PCR	10	Medium
Lian J. et al., 2020 [36]	Retrospective study	Zhejiang province, China	788	54.71 ± 9.34	51.64%	RT-PCR	57	High
Liang W et al. [37]	Retrospective Cohort Study	In and outside Hubei, China	1590	48.9 ± 16.3	57.30%	RT-PCR	130	High
Liu K et al., 2020 [12]	Retrospective	Hubei Province	137	55 ± 16	44.50%	RT-PCR	14	High
Liu R. et al., 2020 ^a [38]	Retrospective study	Jiangsu, China	33	50 ± 12	60.60%	CT	1	Done from abstract Low
Liu Y et al., 2020 [39]	Retrospective	Shenzhen, China	12	53.66	66.66%	RT-PCR	2	Low
Mo P et al., 2020 [40]	Retrospective	Wuhan, China	155	54 (42–66)	55.50%	RT-PCR	15	High
Qin C et al., 2020 [41]	Retrospective cohort	Wuhan, China	452	58 (47–67)	52%	RT-PCR	75	High
Richardson S et al., 2020 [42]	Retrospective cohort	New York, USA	5700	63 (52–75)	60.30%	RT-PCR	1808	High
Shao F et al., 2020 [43]	Retrospective observational study	Wuhan, China	136	69 (61–77)	66.20%	Interim guidelines WHO	27	Medium
Sun C. et al., 2020 [44]	Retrospective study	Henan Province, China	150	45 ± 16	44.66%	CT	9	Low
Wan S et al., 2020 [45]	Retrospective	Chongqing, China	135	47 (36–55)	53.30%	RT-PCR	12	High
Wang D et al., 2020 [6]	Retrospective	Wuhan, China	138	56 (42–68)	54.30%	WHO Interim Guidance	14	High
Wang L. et al., 2020 [68]	Retrospective	Wuhan, China	116	54 (38–69)	57.80%	RT-PCR	18	High
	Retrospective study	Wuhan, China	339	71 ± 8	48.96%	Chest X-ray, CT	54	High

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Table 1 (continued)

Study author & year	Study design	Country	Total no. of patients	Mean/Median age (years)	Males (%)	Confirmation of COVID-19	Diabetes (N)	Study Quality
Wang Lang et al., 2020 [46]								
Wang X et al., 2020 [47]	Retrospective	Wuhan, China	1012	50 (39–58)	51.80%	RT-PCR	27	High
Yan K et al., 2020 [48]	Retrospective study	San Diego, California, USA	128	48.25	47.65%	RT-PCR	14	High
Yao Q et al., 2020 [10]	Retrospective cohort study	Hubei, China	108	52(37–58)	39.80%	CT, RT-PCR	5	High
Yuan M et al., 2020 [49]	Retrospective	Hubei Province	27	60 (47–69)	45%	RT-PCR	6	High
Zhang G. et al., 2020 [50]	Single center, retrospective study	Wuhan, China	221	55.0 (39.0–66.5)	48.90%	WHO interim guidance	22	High
Zhang J et al., 2020 [51]	Retrospective	Wuhan, China	140	57	57%	CT, RT-PCR	17	High
Zheng K et al., 2020 [53]	Retrospective	Wenzhou, China	214	66	25.8%	RT-PCR	16	High
Zhang P et al., 2020 [52]	Multicenter retrospective cohort	Wuhan, China	522	64 (56–68)	55.30%	CT; RT-PCR	126	High
Zhou F et al., 2020 [54]	Retrospective cohort study	Wuhan, China	191	56 (46–67)	62%	RT-PCR	36	High

CT: computerized tomography; MMWR: Morbidity and Mortality Weekly Report; RT-PCR: Reverse Transcription-Polymerase Chain Reaction.

^a Represents abstract.

which included patients with suspected COVID-19 cases, case-study, review, commentary, and editorial were qualified for the exclusion. Studies with incomplete information were also excluded.

2.3. Primary outcomes

The primary outcome was to compute the pooled prevalence of diabetes among patients infected with COVID-19. The secondary outcomes were mortality risk and ICU admission risk in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes.

2.4. Data extraction and study quality

Data were extracted by two independent reviewers (Harveen Baxi and Md Sarfaraj Hussain) from each eligible study using a standardized data extraction template. Information like study author, study year, study design, study location, total confirmed COVID-19 patients, mean age, male population, ascertainment of COVID-19, and the number of diabetic patients was extracted from each qualified study.

Modified version of the Newcastle–Ottawa Scale was used to judge the study quality of the included cross-sectional studies [19]. As per this scale, a study can get a maximum of 5 points, where, studies achieving a score of ≥ 3 are qualified as low risk of bias and high risk of bias if the score attainment was < 3 [19]. For cohort studies, Newcastle–Ottawa Scale was used for the quality assessment [20]. According to this scale, a study was classified as high quality (≥ 8 points), medium quality (6–7), and low quality of the study (> 6 points).

2.5. Statistical analysis

Heterogeneity among studies was assessed using the Cochrane Q test or I^2 statistic. Cochrane Q ($p < 0.10$) or I^2 statistics ($> 50\%$) were considered as the presence of statistically significant heterogeneity. The pooled prevalence of diabetes among COVID-19 patients was computed using a random-effect model. The risk of

mortality and ICU admission in COVID-19 patients with diabetes compared to COVID-19 patients without diabetes was also computed using random-effect model. Sensitivity analysis was performed by omitting each study at a time to explore the effect of individual study on the pooled prevalence and mortality risk. Stata (version 12.0; Stata Corporation, College Station, Texas, USA) and Review Manager (RevMan) v5.3 (Review Manager, 2014) was used for the meta-analysis.

3. Results

Our search run yielded a total of 326 articles. A total of 68 articles qualified in the initial phase based on the title and abstract screening. Finally, 43 articles were found to be eligible for the meta-analysis in the final screening [6,10–14,16,18,21–54]. A detailed description of the study selection is shown in the PRISMA chart (Fig. 1). We found two studies using national health commission data from China [37,55], so, the study with larger study duration and detailed information were included in the meta-analysis [37]. Similarly, we found two morbidity and mortality weekly (MMWR) reports [25,56], and the report with detailed information was included [25].

Among the included studies, 39 studies were retrospective in nature, three were prospective, and one study was cross-sectional. The majority of the included studies were from Wuhan and other provinces of China, while, quite a few from the U.S., and single studies from Spain, Korea, and India. The sample size of the studies varied from 12 to 7162. Almost all the included studies used RT-PCR for the confirmed diagnosis of COVID-19 (Table 1). The majority of included studies were of high quality.

3.1. Primary outcomes

This meta-analysis was based on a total of 23007 patients from 43 studies. Primary studies included in this meta-analysis reported diabetes prevalence in COVID-19 patients within the range of 2.66% to 40% with a pooled prevalence of 15% (95% CI: 12% to 18%), $p < 0.0001$ (Fig. 2). Prevalence was computed using a random-effect

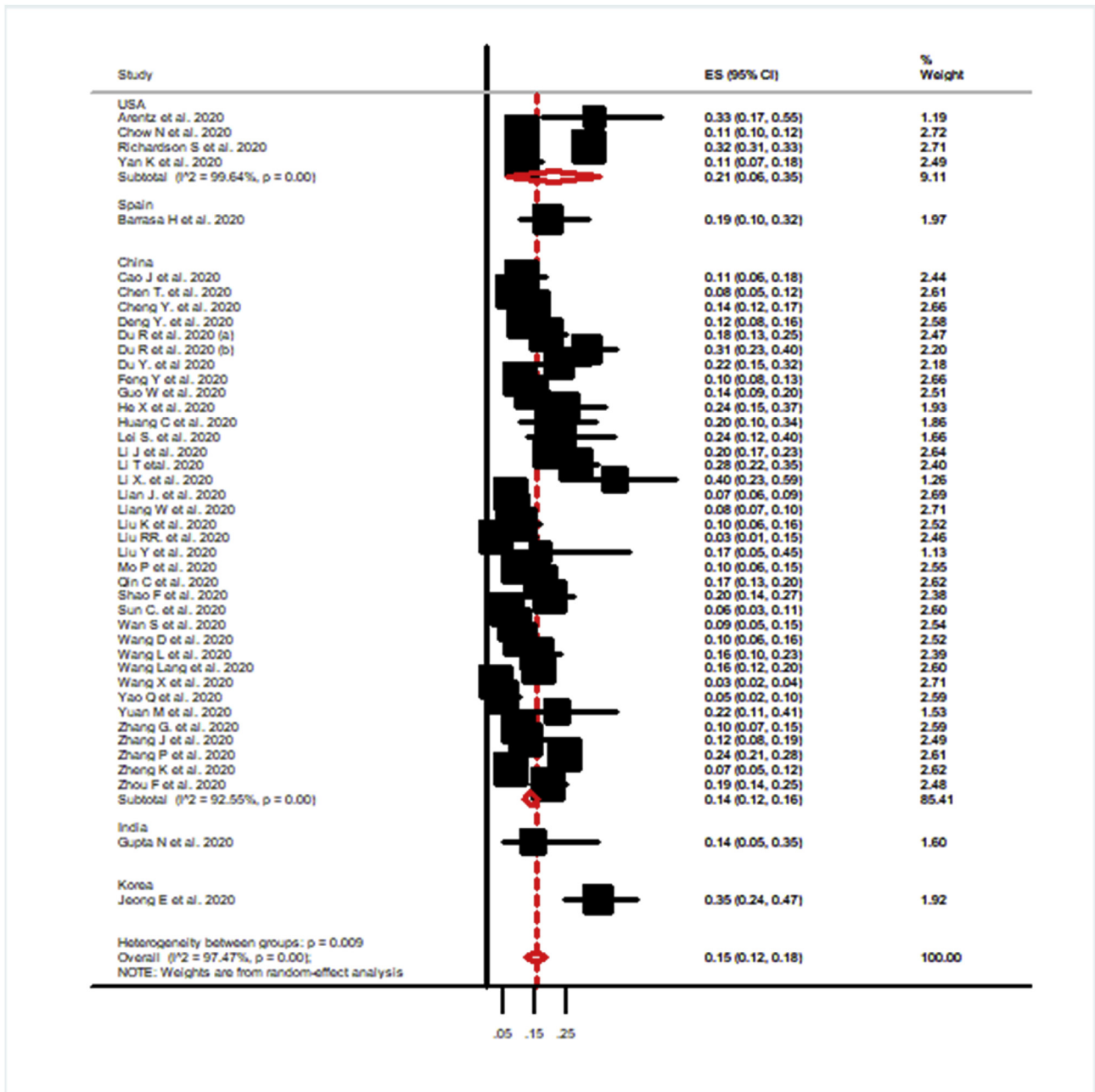


Fig. 2. Pooled prevalence of diabetes in COVID-19 patients.

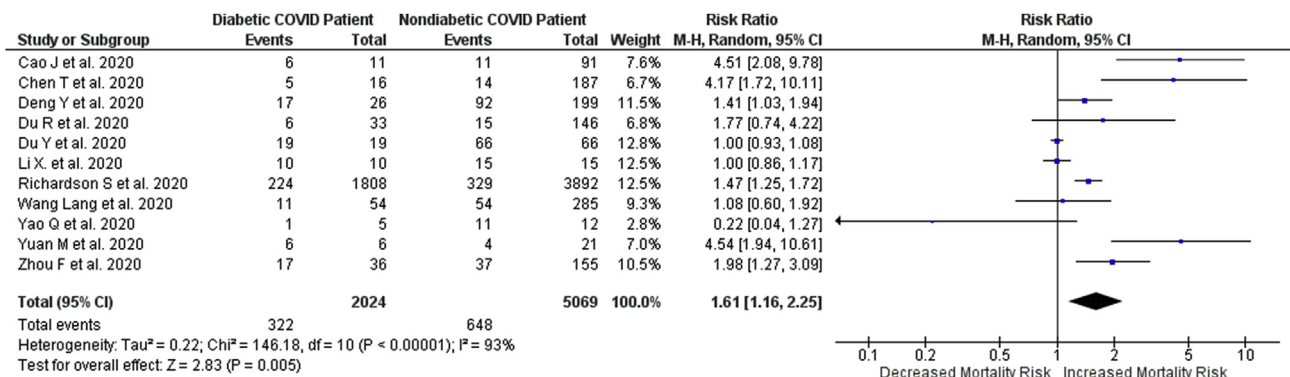


Fig. 3. Forest plot showing the pooled risk of mortality in COVID-19 patients with diabetes.

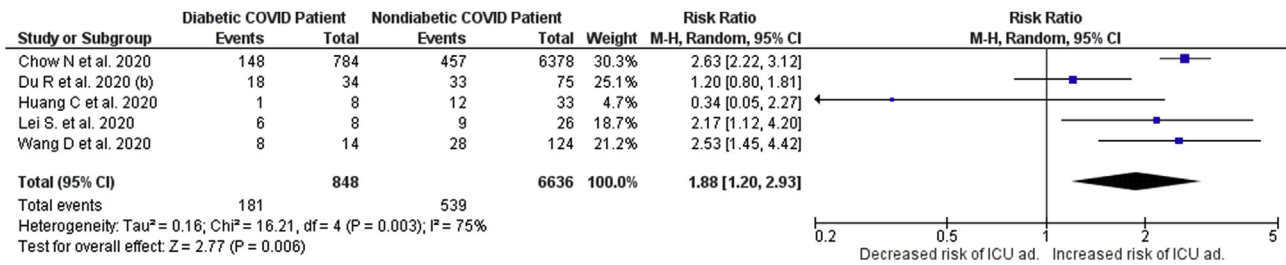


Fig. 4. Forest plot showing the pooled risk of ICU admission in COVID-19 patients with diabetes.

model because of the presence of significant heterogeneity ($I^2 = 97.47\%$). When the prevalence was stratified based on the country, we found a prevalence of 21% (95% CI: 6% to 35%) in the U.S. and 14% (95% CI: 12% to 16%) in China. The single studies from Korea, Spain, and India reported a prevalence of 35%, 19%, and 14% respectively.

3.2. Secondary outcomes

Mortality risk was found to be significantly higher in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes with a pooled risk ratio of 1.61 (95% CI: 1.16–2.25%), $p = 0.005$ (Fig. 3). Likewise, the risk of ICU admission rate was significantly higher in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes with a pooled risk ratio of 1.88 (1.20%–2.93%), $p = 0.006$ (Fig. 4).

3.3. Sensitivity analysis

Each study was omitted from the pooled analysis one by one and omission of any specific studies did not demonstrate any alteration in the pooled analysis.

4. Discussion

Diabetes is considered a global public health problem and is one of the leading causes of mortality and morbidity. Diabetes makes the patients more prone to develop infectious diseases due to the dysregulation of the immune system and is considered as a risk factor for the progression and poor prognosis of COVID-19 [13,57,58]. A plethora of evidence has linked diabetes with higher mortality risk during SARS and MERS-CoV epidemic [59,60]. So, the present study was planned to assess the prevalence and impact of diabetes in patients infected with COVID-19. The current study found a high prevalence of diabetes among people infected with COVID-19. Our findings were differing from the recent meta-analysis which reported a prevalence of only 9.7% [61]. The possible reason for the higher prevalence in the current study could be due to the inclusion of all evidence to date while the meta-analysis reporting low prevalence rate was based on the findings of seven studies only. It should be noted that the prevalence of diabetes in COVID-19 patients varies worldwide. Richardson et al. [6] conducted a study on 5700 COVID-19 patients and reported a diabetes prevalence of 33.8%. A Korean study using data from centers for disease control and prevention also reported a high prevalence (34.84%) of diabetes in patients infected with COVID-19 [18]. Findings from an Indian study reported a prevalence of only 14.28% [30].

The impact of COVID-19 on mortality and ICU admission rate was also estimated in patients with diabetes as compared to non-diabetes patients. We found that the risk of mortality was significantly higher in COVID-19 patients with diabetes. Our finding was

in alignment with the findings of other studies that suggested that diabetes patients with COVID-19 have a higher risk of developing medical complications including death [17,62,63]. The possible reason for higher mortality in patients with diabetes could be due to missed blood glucose monitoring, isolation from physicians, and inappropriate discontinuation of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) [64,65]. The novel coronavirus uses the same receptor, ACE II, as that for SARS-CoV [66]. So, the patients with diabetes who are receiving ARBs and ACEIs as a part of their diabetic treatment regimen may have higher expression of ACE II which novel coronavirus utilizes for the entry into the host and promotes disease to reach the fatal stage [67].

ICU admission risk was also significantly higher in diabetic patients infected with COVID-19. Our finding was in alignment with the findings of a nationwide study using national health commission data from China which found diabetes as an independent risk factor for the increased rate of ICU admission [55].

4.1. Strengths and limitations

Our study has several strengths. Firstly, this is the most updated and comprehensive meta-analysis with a focus on diabetes as a comorbidities in COVID-19 patients. Secondly, we have presented a separate result related to the mortality and ICU admission risk in COVID-19 with diabetes as compared to COVID-19 patients without diabetes. Thirdly, the majority of included studies in the meta-analysis had confirmed the diagnosis of COVID-19 using RT-PCR data. Lastly, we have included only peer-reviewed articles in the meta-analysis. Nevertheless, this study also has limitations. First, the variation in the sample size of the included studies. Second, the inclusion of observational study design studies and the aspect that only quite a few studies stratified the findings based on ICU and non-ICU COVID patients. Third, there will be a probability of overlapping samples as most of the studies were from China. Lastly, we were not able to stratify our findings based on the type of diabetes due to the unavailability of information.

We recommend future studies to investigate the mechanistic association of diabetes and COVID-19.

5. Conclusion

This meta-analysis found a high prevalence of diabetes in patients infected with COVID-19. Significantly higher mortality and ICU admission risk were observed in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes. Strong precautionary measures should be taken to prevent the spread of COVID-19 infection among patients with diabetes.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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