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Coronavirus disease (COVID-19): A systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events

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ABSTRACT

Background and aims: Currently there is limited knowledge on medical comorbidities and COVID-19; we conducted a systematic review and meta-analysis to evaluate the impact of various morbidities on serious events in COVID 19.

Methods: PubMed, Cochrane Central Register of Clinical Trials were searched on April 28, 2020, to extract published articles that reported the outcomes of COVID-19 patients. The search terms were “coronavirus” and “clinical characteristics”. ICU admission, mechanical ventilation, ARDS, Pneumonia, death was considered serious events. The comorbidities assessed in the study were Hypertension (HTN), Diabetes mellitus (DM), Cardiovascular diseases (CVD), Chronic obstructive pulmonary disease (COPD) and Chronic Kidney disease (CKD). Subsequently, comparisons between comorbidity patient group and the non-comorbidity patient groups, in terms of serious events were made using the pooled estimates of odd's ratio (OR)

Results: We identified 688 published results and 16 studies with 3994 patients were included in the systematic review. Serious events were seen in 526(13.16%) patients. Presence of hypertension with OR 2.95, diabetes mellitus with OR 3.07, Cardio vascular disease with OR 4.58, COPD with OR 6.66 and Chronic kidney disease with OR 5.32 had significant association in patients with COVID 19 on having serious events. Presence of diabetes mellitus (OR 2.78) had a significant impact on death in COVID 19 patients with a p-value 0.004.

Conclusions: Presence of medical comorbidities in COVID-19 leads to higher risk of developing serious events i.e. ICU admission, mechanical intubation and mortality. The presence of Diabetes mellitus has a significant impact on mortality rate in COVID-19 patients.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic which started in China in late 2019 and has now spread across the globe in 2020 [1–4]. Clinicians are fighting against this new disease and are focusing on various factors that may lead to better survival outcomes. The common symptoms of COVID -19 infection are fever,

cough, myalgia and fatigue [5–8]. In a study by Guan et al. [5] there was analysis of patients with COVID-19 in China and had described various clinical characteristics and their association with the severity of disease. Previous coexisting illness was seen in severe disease group in 39% patients as compared to 21% patients in non severe disease group [5]. The treatment of corona virus infection with underlying comorbidity could increase severity of disease and may be associated with high risk of ventilator support and ICU care [5–22]. Emami et al. [23] had performed a metaanalysis and described the prevalence of various comorbidity associated with hospitalized COVID-19 patients. The limitation of the study by

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Table 1
Sample size of selected studies and their characteristics.

	Country of Origin	Study type	Year of publication	Journal	Total no. of Patients
Guan Wei-Jie [5]	China	Retrospective cohort	December-19	NEJM	1099
Nanshan Chen [6]	China	Retrospective cohort	January-20	Lancet	99
Chaolin Huang [7]	China	Retrospective cohort	January-20	Lancet	41
Kui Liu [8]	China	Retrospective cohort	January-20	Chinese Medical journal	137
Heshui Shi [9]	China	Retrospective cohort	February-20	Lancet	81
Xiaobo Yang [10]	China	Retrospective cohort	February-20	Lancet	52
Dawei Wang [11]	China	Retrospective cohort	February-20	JAMA	138
Chaomim Wu [12]	China	Retrospective cohort	March-20	JAMA	201
Fei Zhou [13]	China	Retrospective cohort	March-20	Lancet	191
Wanbo Zu [14]	China	Retrospective cohort	March-20	Journal of Medical Virology	32
Jian Wu [15]	China	Retrospective cohort	March-20	Clinical Infectious disease	80
Wenhua Liang [16]	China	Retrospective cohort	April-20	Lancet	1590
Shaoqing Lei [17]	China	Retrospective cohort	Apr-20	E Clinical Medicine	34
Jie Li [18]	China	Retrospective cohort	Feb 2020	Pre-print version (MedRxiv)	17
Xiao [19]	China	Retrospective cohort	Feb 2020	BMJ	62
Zhang [20]	China	Retrospective cohort	Feb 2020	Allergy	140

Table 2
Summary of demographics data.

	Total no. of Patients	Male (%)	Female (%)	Median age of all patients (Years)	Severe Events	Definition of serious events
Guan Wei-Jie et al. [5]	1099	58.1	41.9	47	67	ICU admission/mechanical ventilation/death
Nanshan Chen et al. [6]	99	67.66	32.3	55.5 (Mean)	11	death
Chaolin Huang et al. [7]	41	73	27	49 (Mean)	13	ICU admission
Kui Liu et al. [8]	137	44	55.5	57	16	death
Heshui Shi et al. [9]	81	52	48	49.5		
Xiaobo Yang et al. [10]	52	67	33	59.7 (Mean) SD13.3	32	death
Dawei Wang et al. [11]	138	54.3	45.7	56	36	ICU admission
Chaomim Wu et al. [12]	201	67.3	36.3	51	84	ARDS
Fei Zhou et al. [13]	191	62	38	56	54	death
Wanbo Zu et al. [14]	32	47	53	46		
Jian Wu et al. [15]	80	48.75	51.25	46.1+-15.4 (Mean)		
Wenhua Liang et al. [16]	1590	–	–	48.7 years: Total patients 63.1 years: Cancer patients	127	
Shaoqing Lei te al [17]	34	41.2	58.8	55 (43–63)	15	ICU admission
Jei Li [18]	17	52.9	47	45 (22–65)	12	Prolonged hospitalization Pneumonia
Xiao [19]	62	58	42	41 (32–52)	1	ICU admission
Zhang [20]	140	50	50	57	58	ICU admission

Emami et al. [23] was that this study had only description on prevalence of associated comorbidity in corona infection and lacked results on effect of comorbidities on severity of disease and treatment outcomes [23].

The medical facilities in all countries including developed and developing nations are highly strained and exhausted in the care of COVID-19. In published literature on COVID-19 there are limited guidelines on management of associated medical comorbidities [24,25]. So there is a need to formulate a treatment strategy for various major medical comorbidities. This may be helpful for clinicians to identify high risk patients during admission process at COVID centre. Currently the number of patients in this pandemic on rise and a better understanding of high risk comorbidities may be helpful the physicians. The patients with comorbidities can be given safety guidelines to avoid visiting infected zones and contact with possible infected person.

Since several newer studies on corona infection have recently become available we aimed to study the effect of medical comorbidities on COVID-19 on important objectives. The important objectives include a. Serious events includes: ICU admission, Novel coronavirus pneumonia(NCP), mechanical ventilation, ARDS, and death, mortality rate. In addition, we have also analyzed the prevalence of medical comorbidities in COVID-19. We have conducted a systematic review and metaanalysis to analyze the impact of various comorbidities in COVID-19.

2. Methods

2.1. Search strategy and selection criteria

For this systematic review and meta-analysis, we searched the literature on April 28, 2020, to identify published articles that reported the outcomes of COVID-19 patients. We did a systematic literature search on PubMed, Cochrane Central Register of Clinical Trials on published articles that reported the outcomes of COVID-19 patients under the PRISMA 2009 checklist criteria. The following search terms were used: “coronavirus” AND “clinical characteristics” AND “comorbidities”. The search terms were kept broad to encompass all possibilities for applicable studies. Some records were also retrieved via cross-references from published papers. There were no restrictions on the date of publication and the language of articles published. After eliminating duplicates, two investigators (AAS and KN) independently reviewed all abstracts: the full texts of articles regarded as potentially eligible for consideration were extracted for further analysis. We searched the reference lists of relevant articles by hand to identify further articles for analysis. Thereafter, eligible articles were selected for final analysis according to predefined inclusion and exclusion criteria. Disagreements between the authors were resolved by consensus. We included only human studies and articles with clearly defined clinical outcome measures. The exclusion criteria included animal studies; absence of a comparison group; absence or

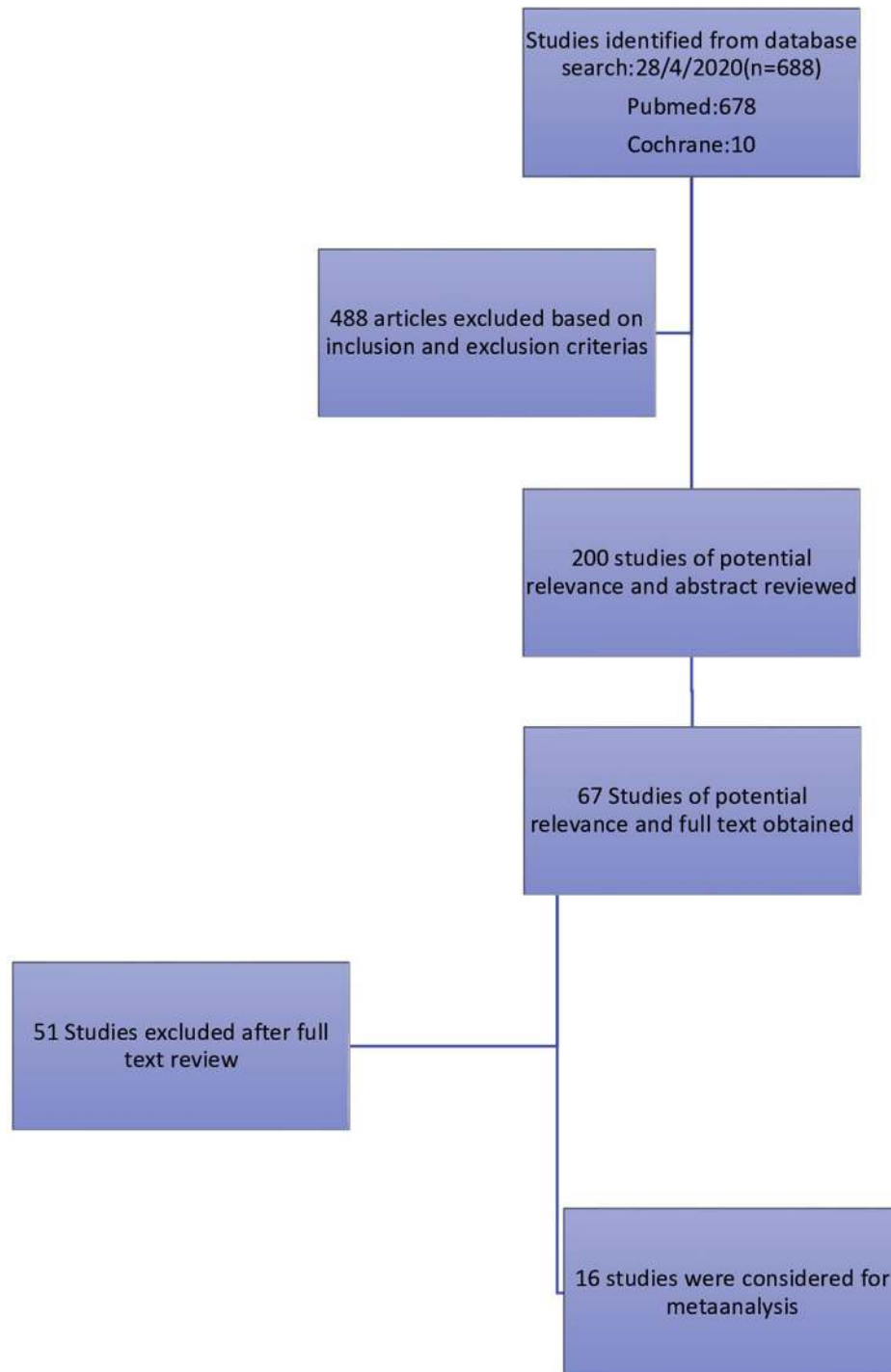


Fig. 1. Algorithm for database search and article selection.

unclear reporting of clinical outcome measures; isolated case reports or case series with sample size <5. Articles selected for the final analysis were independently graded using the Newcastle–Ottawa Scale for the Assessment of the Quality of Nonrandomized Studies in Meta-analyses (Table 1) [5–20].

2.2. Data analysis

We reviewed the final articles to extract the following information from each: first author; year of publication; study design;

study population characteristics for the COVID-19 patients with their various comorbidities. The specific outcome measures that were recorded for the meta-analysis were serious events that included ICU admission, Acute respiratory distress syndrome (ARDS), mechanical ventilation, Pneumonia, and death (Table 2).

When $p < 0.05$ or $I^2 > 50\%$, the assumption of homogeneity was rejected and a random-effects model was adopted. Subsequently, comparisons between various individual comorbid patients and the non-comorbid patient groups, in terms of serious events were made using the pooled estimates of odd's ratio (OR) (percentage and 95%

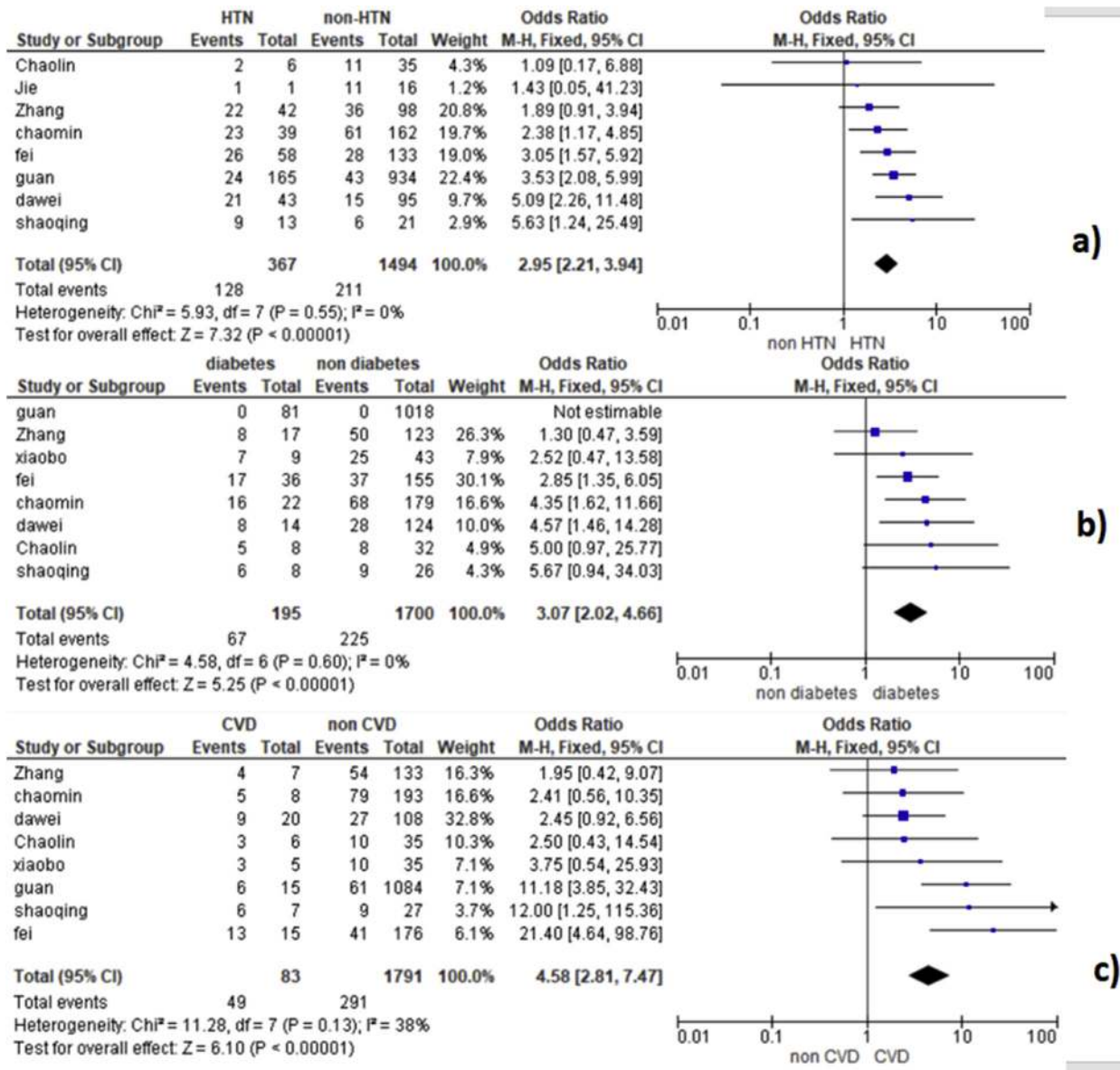


Fig. 2. Odds ratio(OR) for patients with a) Hypertension (HTN), b) Diabetes Mellitus and c) Cardiovascular diseases (CVD) for their impact on serious events in COVID-19.

CI). The level of significance was set at $p < 0.05$. All statistical analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

We identified 688 published papers and 16 studies were included in the analysis. These articles included a total of 3994 COVID-19 patients. From the initial search, a total of 678 articles were identified from PubMed, 10 from the Cochrane database. 488 articles were excluded based on the inclusion and exclusion

criteria. 200 abstracts were reviewed for potential relevance and 67 full texts were reviewed of which 51 articles were excluded.

We finally selected 16 articles for the meta-analysis (Fig. 1). The median age and male: female distribution of various studies have been elaborated in Table 2.

In this analysis, ICU admission, Novel coronavirus pneumonia (NCP), mechanical ventilation, ARDS, and death in various studies are considered as serious events. Serious events were seen in 526(13.16%) patients. Major comorbidities assessed in our study for their impact on serious events were Hypertension(HTN), Diabetes mellitus(DM), Cardiovascular diseases (CVD), Chronic obstructive pulmonary disease (COPD) and Chronic Kidney disease(CKD).

Comparison of patients with hypertension versus non-hypertension for their impact on serious events in COVID-19 patients.

The odds ratio of serious events between patients with hypertension and non-hypertensive patients was 2.95 with a 95% CI ranging from 2.21 to 3.94. The results indicate a significant effect of

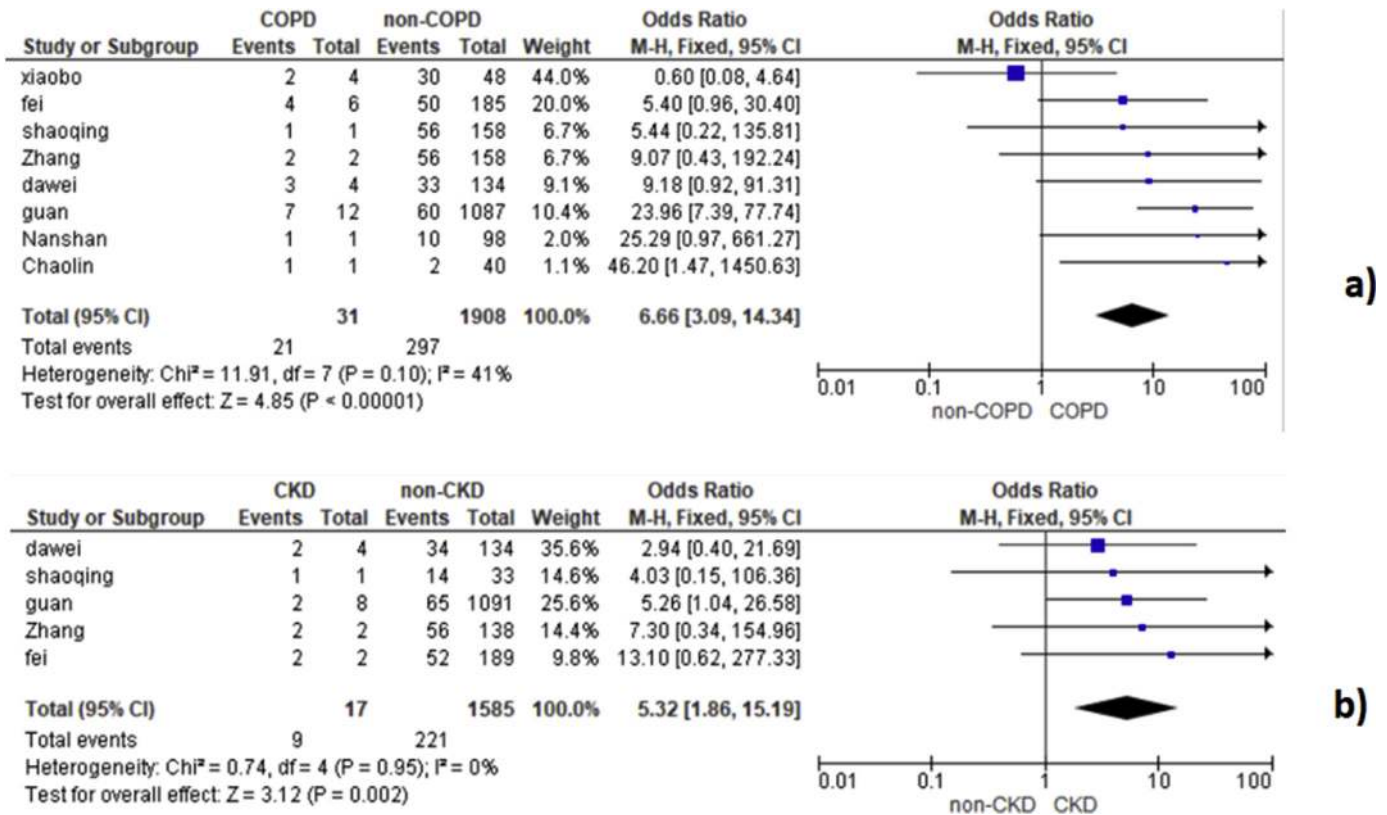


Fig. 3. Odds ratio(OR) for patients with a) Chronic obstructive pulmonary disease(COPD), b) Chronic kidney disease (CKD) on their impact on serious events in COVID-19.

hypertension as comorbidity on serious events in any form in COVID-19 patients (p < 0.001). We did a heterogeneity test with results of I² = 0%, p = 0.55 (Fig. 2a).

Comparison of patients with Diabetes mellitus versus non-diabetic patients for their impact on serious events in COVID-19 patients.

The odds ratio of serious events between patients with diabetes mellitus and non-diabetic patients was 3.07 with a 95% CI ranging from 2.02 to 4.66. The results indicate a significant effect of diabetes mellitus as comorbidity on serious events in any form in COVID-19 patients (p < 0.001). We did a heterogeneity test with results of I² = 0%, p = 0.60 (Fig. 2b).

Comparison of patients with cardiovascular diseases (CVD) versus non-CVD for their impact on serious events in COVID-19 patients.

The odds ratio of serious events between patients with cardiovascular diseases (CVD) and non-CVD patients was 4.58 with a 95% CI ranging from 2.81 to 7.47. The results indicate a significant effect of cardiovascular comorbidity on serious events in any form in COVID-19 patients (p < 0.001). We did a heterogeneity test with results of I² = 38%, p = 0.13 (Fig. 2c).

Comparison of patients with COPD versus non-COPD for their impact on serious events in COVID-19 patients.

The odds ratio of serious events between patients with COPD and non-COPD patients was 6.66 with a 95% CI ranging from 3.09 to 14.34 with p-value of less than 0.001. The results indicate a significant effect of COPD as comorbidity on serious events in any form in COVID-19 patients. We did a heterogeneity test with results of I² = 41%, p = 0.10 (Fig. 3a).

Comparison of patients with CKD versus non-CKD for their impact on serious events in COVID-19 patients.

The odds ratio of serious events between patients with CKD and non-CKD patients was 5.32 with a 95% CI ranging from 1.86 to 15.19

with a p-value of 0.002. The results indicate a significant effect of chronic kidney disease as comorbidity on serious events in any form in COVID-19 patients. We did a heterogeneity test with results of I² = 0%, p = 0.95 (Fig. 3b).

Impact of COPD, Diabetes mellitus, and CVD on mortality rate in COVID-19 patients.

Patients with COPD (OR 3.43, 95CI 0.49 to 23.94) (p = 0.21) and CVD (OR 4.69, 95CI 0.22 to 101.51) (p = 0.32) have a higher risk of death in COVID patients but this didn't reach statistical significance. In both cases, I² > 50%, so a fixed effect was changed to random effect. Patients with diabetes mellitus had a higher risk of mortality than non-diabetic patients (OR 2.28 95 CI 1.40 to 5.55) (p = 0.004). (Fig. 4).

3.1. The prevalence of various comorbidities in COVID-19 patients

The pooled prevalence of Cardiovascular disease (CVD) in COVID-19 infection from 8 studies with 1886 patients was 7%(95% CI, 4%–13%) We did a heterogeneity test between 13 studies with a result of I² = 78%, p < 0.01(Fig. 5a).

The pooled prevalence of Diabetes mellitus (DM) in COVID-19 infection from 8 studies with 1895 patients was 13%(95%CI, 10%–17%) We did a heterogeneity test between 13 studies with a result of I² = 81%, p < 0.01(Fig. 5b).

The pooled prevalence of Hypertension (HTN) in COVID-19 infection from 8 studies with 1861 patients was 24%(95%CI, 18%–30%) We did a heterogeneity test between 13 studies with a result of I² = 88%, p < 0.01(Fig. 5c).

The pooled prevalence of Chronic kidney disease (CKD) in COVID-19 infection from 5 studies with 1602 patients was 1%(95% CI, 1%–2%) We did a heterogeneity test between 13 studies with a result of I² = 34%, p < 0.19(Fig. 6a).

The pooled prevalence of Chronic obstructive pulmonary disease (COPD) in COVID-19 infection from 8 studies with 1794

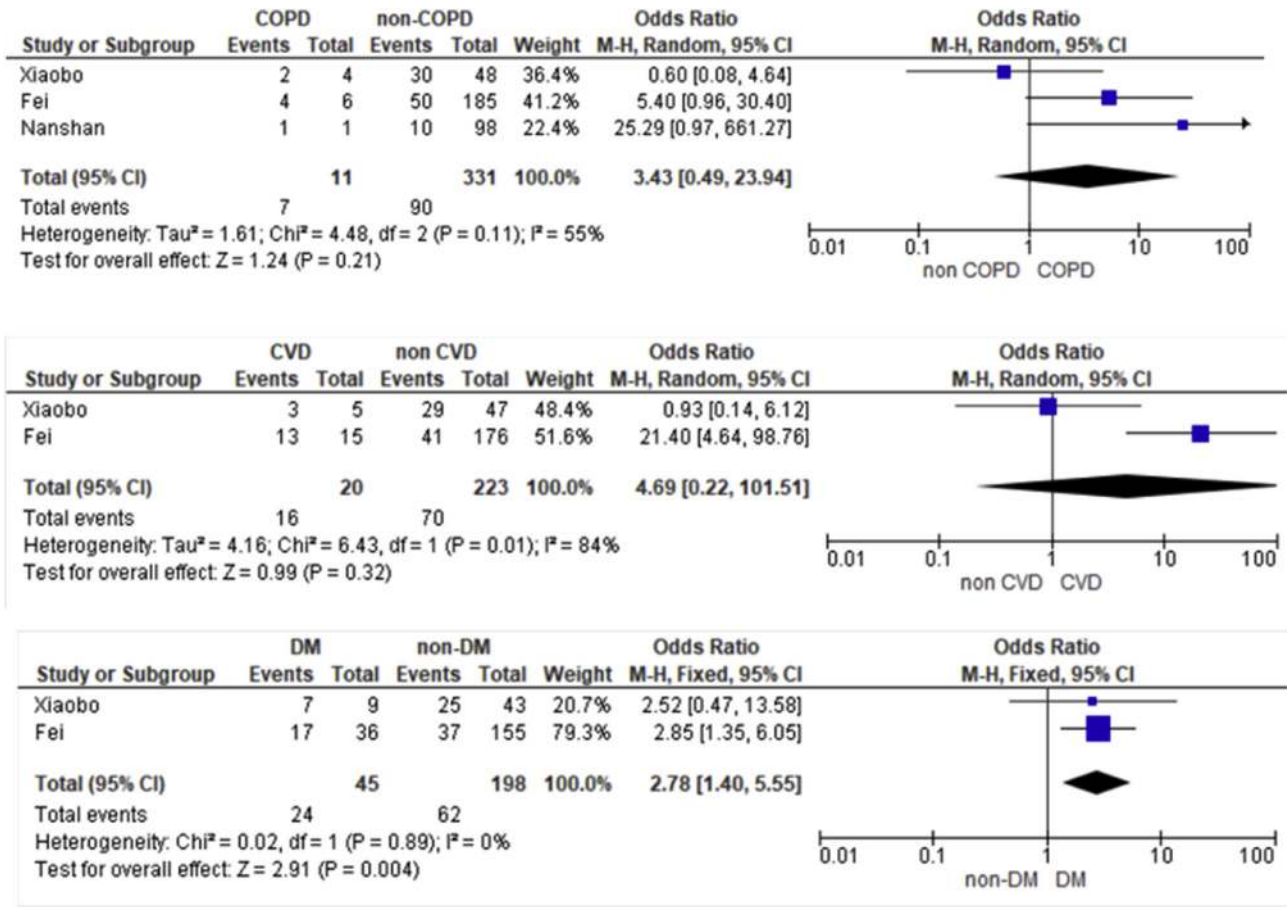


Fig. 4. Odds ratio(OR) for patients with a) Chronic obstructive pulmonary disease (COPD), b)Diabetes mellitus, and c) Cardiovascular disease (CVD) on mortality rate in COVID-19.

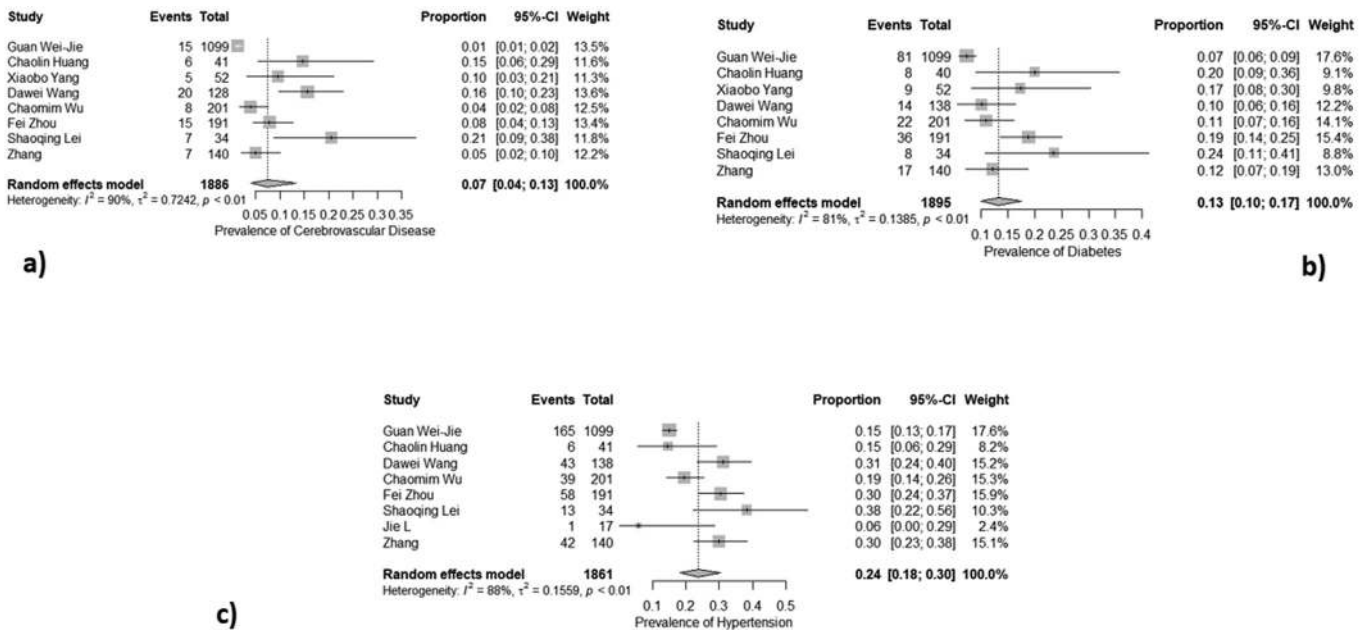


Fig. 5. The prevalence of comorbidity in COVID-19 patients: a) Cardiovascular disease (CVD) b) DM (Diabetes mellitus) c)Hypertension (HTN).

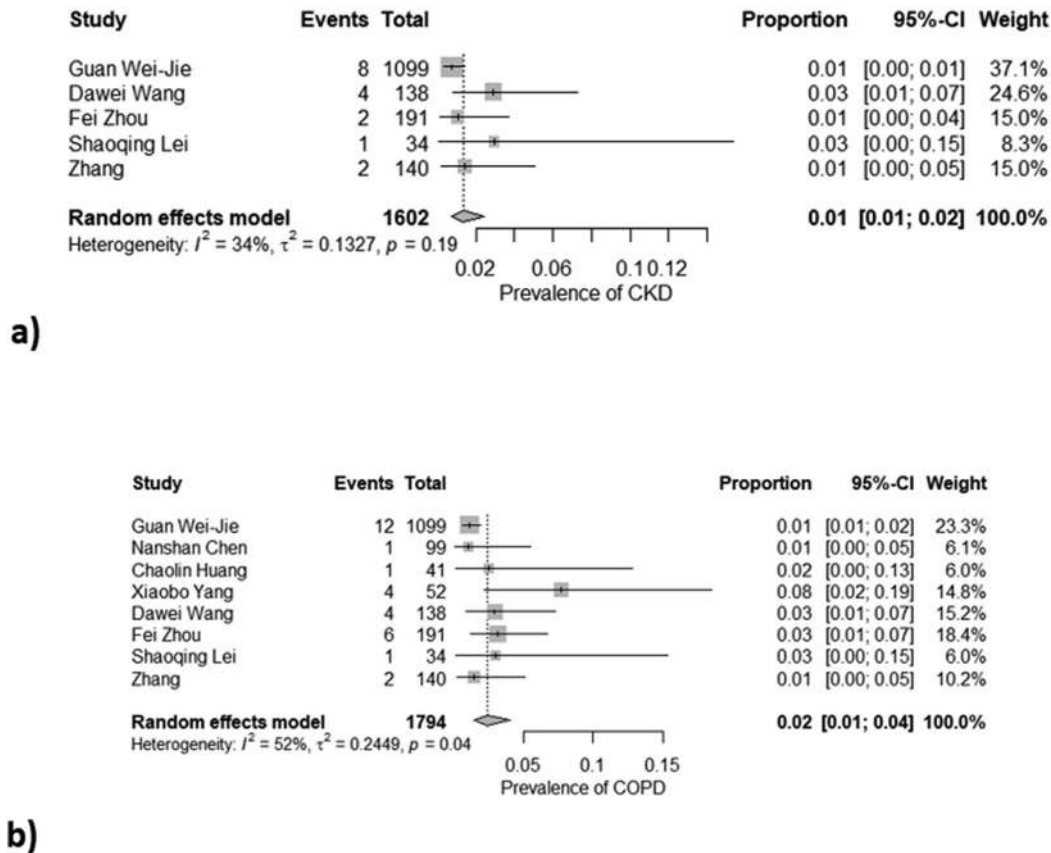


Fig. 6. The prevalence of comorbidities in COVID-19 patients. a) Chronic kidney disease (CKD) b) Chronic obstructive pulmonary disease (COPD).

patients was 2% (95%CI, 1%–4%) We did a heterogeneity test between 13 studies with a result of $I^2 = 52\%$, $p < 0.04$ (Fig. 6b).

4. Discussion

To best of our knowledge, this would be the most updated meta-analysis to report the prevalence and impact of medical comorbidities on serious events and mortality rate in COVID-19. In the current meta-analysis of 16 published studies with 3994 patients, we found out that comorbidities had a major effect on patients with COVID 19 and leads to higher chances of serious events. Presence of COPD had a 6.6 times higher risk of developing serious events in COVID 19 patients. Presence of chronic kidney diseases had a 5.3 fold increased risk having serious events. Also presence of cardiovascular diseases had 4.5 times greater chances of progressing to severe events. In present meta-analysis diabetic patients had 3.07 fold higher chances of severe events which were statistically significant (p value < 0.001). The presence of Diabetes mellitus statistically significant impact on death in COVID 19 patients.

A recent meta-analysis by Wang et al. [26] had analyzed the whether comorbidity increase risk of patient with COVID-19. They had concluded that Hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease were major risk factors for patients with COVID-19 [26]. However, the metaanalysis by Wang et al. [26] seems to have overlooked the published data on COVID-19. They had included on 6 published studies in their systematic review and meta analysis. The limited number of studies leads to lesser number of enrolled patients and leading to smaller sample size for analysis. We believe that these differences could have changed the outcomes.

Another meta-analysis by Bo li et al. [27] on the impact of cardiovascular diseases on COVID 19 disease They had found that hypertension and cardio-cerebrovascular diseases had a statistically significant impact on ICU admission, whereas diabetes mellitus had more ICU admission but that didn't reach statistical significance [27]. They also had included only 6 published studies in their systematic review and meta analysis [27]. The limited number of studies leads to lesser number of enrolled patients and leading to smaller sample size for analysis [27]. We believe that these differences could have changed the outcomes. Bo li et al. [27] had only analyzed the impact of cardiovascular disease and had not included analysis of other associated comorbidities in their study.

We do acknowledge a number of limitations in our systematic review and metaanalysis that included 16 studies and around 4000 patients. In present meta-analysis diabetic patients had 3.07 fold higher chances of severe events which were statistically significant (p value < 0.001). The prevalence of hypertension and diabetes in people infected with the virus is about the same as in the general population, even slightly lower. However, comparing the general population, the incidence of cerebrovascular disease in patients with COVID-19 was much higher. Due to the small sample size relation between cardiovascular comorbidities and death could not be determined [27].

The massive disease outbreak of COVID-19 has placed a significant burden on the health care system because of limited resources including personal protection equipment, medications, and ventilators [1,22,25]. Coronavirus is a newly identified pathogen with no pre-existing immunity to it and also there is no cure for it as of now. Various medical comorbidities in patient with corona infection may have impact on morbidity and mortality. The absence of immunity and lack of definitive medicines leads to a higher risk of disease

spread amongst the elderly population, immunocompromised patients, and patients with various preexisting diseases [3,5–9,21].

The pathogenesis of COVID 19 infections remains unclear and there is no specific targeted treatment protocol developed yet and the management currently of supportive care. Coronavirus has been postulated to cause direct injury to cardiomyocyte and the injury is higher in ICU patients about 13 times more than non-ICU patients. Huang et al. [7] found a higher concentration of inflammatory mediators in COVID patients which leads to T cellular response activation. Nashan et al. [6] suggested prompt administration of antibiotics to prevent infection and strengthening of immune support treatment might reduce complications and mortality in populations with a low immune function such as older people, diabetics, HIV infection, and patients on long term immunosuppressive agents.

Most of COVID infections in various retrospective studies were mild but 5–10% of cases had severe symptoms that progress rapidly and respiratory failure can occur within a short interval eventually leading to death. These serious events are seen mainly in patients with comorbidities. The analysis of association of comorbidities with severe events in COVID-19 can help policy makers and physicians focus more on these high risk patients. A high vigilance and proactive management in patients with medial comorbidity may help to reduce morbidity and mortality in corona infection. A universal protocol and guidelines can be created for patients with associated comorbidities.

4.1. Limitations of this study

The limitations of current were that an inherent bias could exist, particularly in terms of patient selection, heterogeneous medical treatment regimens. The results need to be concluded with caution since judgment criteria between severe and non-severe patients were not uniform. All patients with ICU admission, Pneumonia, mechanical ventilation, ARDS, and death were broadly considered as serious events. Another fact that some patients can have multiple comorbidities that can produce their added effect on serious events.

5. Conclusion

Patients with medical comorbidities are having high risk of developing serious events i.e. ICU admission, mechanical intubation and death. Diabetes mellitus is a comorbidity which is having a significant impact on death in COVID 19 patients. The knowledge of these comorbidities can help us better stratify COVID 19 patients at higher risk allowing a more targeted and specific approach in preventing fatal events.

Author contribution

Literature search, reading and data collection:KN,AS,SP. Responsible for data analysis and interpretation:AP,CD,KP. Part of manuscript preparation process:MS,AJ,VW. Involved in manuscript editing and proofreading:KN,AS,VW. Played their role in table preparation and image editing:SP,CD,MS. Part of final editing and finalising the manuscript:AJ,AS, KN.

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Ethical permission

Not required as this analysis do not involve patients directly.

Declaration of competing interest

Nothing to declare.

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