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SYSTEMATIC-REVIEW ARTICLE

Accumulating Impact of Smoking and Co-morbidities on Severity and Mortality of COVID-19 Infection: A Systematic Review and Meta-analysis

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Abstract: ***Background*:** High prevalence, severity, and formidable morbidity have marked the recent emergence of the novel coronavirus disease (COVID-19) pandemic. The significant association with the pre-existing co-morbid conditions has increased the disease burden of this global health emergency, pushing the patients, healthcare workers and facilities to the verge of complete disruption.

***Methods*:** Meta-analysis of pooled data was undertaken to assess the cumulative risk assessment of multiple co-morbid conditions associated with severe COVID-19. PubMed, Scopus, and Google Scholar were searched from January 1st to June 27th 2020 to generate a well-ordered, analytical, and critical review. The exercise began with keying in requisite keywords, followed by inclusion and exclusion criteria, data extraction, and quality evaluation. The final statistical meta-analysis of the risk factors of critical/severe and non-critical COVID-19 infection was carried out on Microsoft Excel (Ver. 2013), MedCalc (Ver.19.3), and RevMan software (Ver.5.3).

***Results*:** We investigated 19 eligible studies, comprising 12037 COVID-19 disease patients, representing the People's Republic of China (PRC), USA, and Europe. 18.2% (n = 2200) of total patients had critical/severe COVID-19 disease. The pooled analysis showed a significant association of COVID-19 disease severity risk with cardiovascular disease (RR: 3.11, $p < 0.001$), followed by diabetes (RR: 2.06, $p < 0.001$), hypertension (RR: 1.54, $p < 0.001$), and smoking (RR: 1.52, $p <$ 006).

***Conclusion*:** The review involved a sample size of 12037 COVID-19 patients across a wide geographical distribution. The reviewed reports have focussed on the association of individual risk assessment of co-morbid conditions with the heightened risk of COVID-19 disease. The present meta-analysis of cumulative risk assessment of co-morbidity from cardiovascular disease, diabetes, hypertension, and smoking signals a novel interpretation of inherent risk factors exacerbating COVID-19 disease severity. Consequently, there exists a definite window of opportunity for increasing survival of COVID-19 patients (with high risk and co-morbid conditions) by timely identification and implementation of appropriately suitable treatment modalities.

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1. INTRODUCTION

The emergence of novel coronavirus (nCoV), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and novel coronavirus associated diseases (COVID-19) has resulted in a global medical emergency, affecting the human population in 219 countries and territories [1, 2]. It has created an unprecedented health challenge for mankind in general and medical sciences in particular. Globally, as of 25th July 2021 (05:00 GMT), the total number of confirmed cases has crossed 194 million, with over 4.1 million deaths [3].

Co-morbidities, such as obesity, diabetes, cardiovascular disease, *etc*., have been recognised as life-threatening risk factors in various serious diseases, such as cancer and multi-organ failure; they are also considered as potent indicators of poor prognostic outcomes [4, 5]. Survival and severity of COVID-19 disease in patients with co-morbid conditions

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have been one of the most persistent challenges for healthcare professionals [6]. As of now, there is no universally defined standard treatment protocol available to cure COVID-19 and/or vaccine to reduce the spread of the infection. Timely identification and management of high-risk co-morbid condition patients and subsequent treatment intervention are mandatory to reduce fatality.

COVID-19 patients with co-morbid systemic diseases like diabetes, hypertension, cardiovascular conditions, chronic liver disease, and cancer have an incremental risk of serious clinical complications (acute respiratory distress syndrome (ARDS) & respiratory failure, sepsis, acute cardiac injury (ACI), heart failure, and acute kidney injury) [7, 8].

Cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (C OPD), hypertension, diabetes, age over 65 years, and smoking have been often described as independent risk factors for poor clinical outcomes in COVID-19 patients [9, 10]. Meta-analysis studies have shown that individual co-morbid risk factors (diabetes, IL-6 levels, pregnancy, arterial hypertension) are associated with severity and non-severity of COVID-19 disease [11-13], but their sample size and single-factor analysis may be a limitation for strong evidence.

Previous pooled meta-analysis studies have indicated male gender, diabetes, hypertension, cardiovascular disease, COPD, and malignancies as significant risk factors for severity and adverse clinical outcome of COVID-19 disease [5, 8, 11, 12, 14-16]. However, cumulative risk assessment of multiple co-morbid conditions with severity and mortality of COVID-19 disease has not been reported in previous meta-analysis studies. Smoking has been reported in multiple epidemiological studies as one of the most significant risk factors for diabetes, lung diseases, cardiovascular disease, cancer, *etc*. In addition, co-morbidities, such as diabetes, are reported to predispose individuals to enhanced risk of infections, cardiovascular diseases, *etc*.

Therefore, in our meta-analysis, we aimed to pool and analyse two or more co-morbid factors, such as smoking, diabetes, hypertension and cardiovascular disease. In addition, an appraisal of their cumulative risk associated with clinical outcomes in terms of severity, morbidity and mortality of hospitalized COVID-19 patients has been reviewed.

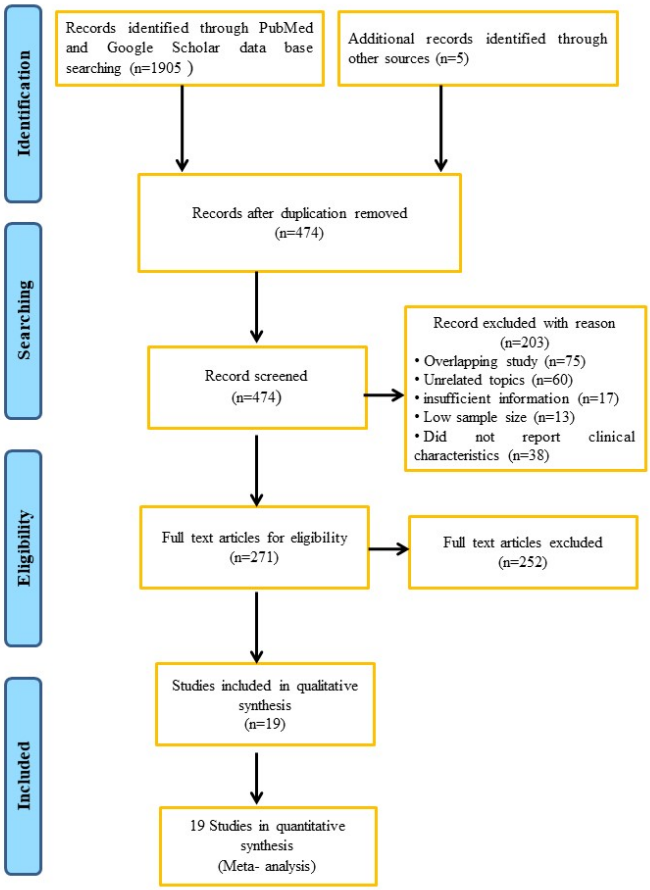


Fig. (1). Flow chart of the study selection. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. METHODS

2.1. Search Approach and Literature Selection Criteria

Relevant *e*-literatures were retrieved from the PubMed, Scopus, and Google Scholar search engines published during 1st January to 27th June 2020 using the keywords coronavirus or COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 or SARS-CoV-2 or SARS2, recovered or death mortality, or smoking effect and Acute Respiratory Distress Syndrome (ARDS) or ICU. No language limitations were made compulsory on the search. The systematic review and meta-analysis in this work was carried out in accordance with PRISMA and MOOSE guidelines, and the supplementary checklist has been furnished [16, 17].

2.2. Inclusion and Exclusion Criteria

The titles and abstracts of potentially significant studies retrieved by the electronic search were critically reviewed. Subsequently, full-text articles were accessed for comprehensive assessment, and the relevant studies generated were included in the systematic review and meta-analysis. The enclosure criteria were as following: all case studies of COVID-19, all confirmed positive cases with laboratory-identified SARS-CoV-2 infection by real-time reverse-transcriptase polymerase chain reaction (RT-PCR), demographic data (sex, age, smoking habit, study period, location, deaths, and recovery of patients), clinical symptoms (fever, cough, shortness of breath, muscle ache, confusion, headache sore throat, rhinorrhea, chest pain, diarrhoea, nausea, vomiting, hypertension, diabetes, cardiovascular disease, chronic liver disease and cancer) and treatments (antibiotics, antiviral treatment, corticosteroids, intravenous immunoglobin, high-flow nasal cannula, oxygen therapy, non-invasive mechanical ventilation, invasive mechanical ventilation, ECMO and adrenal replacement therapy). All the data thus engendered were segregated as severe and non-severe cases. The exclusion categories were the absence of laboratory and radiological characteristics, treatment results, medical relevance, and case reviews.

2.3. Data Extraction and Quality Evaluation

Three authors independently screened and evaluated all the retrieved data, including their titles and abstracts. All relevant information on baseline details, such as clinical manifestations, risk factors, and co-morbid conditions, were maintained using Microsoft Office Excel (Ver. 2013) tool. Data presented in this study was considered as basic data on gender, age, diagnosis, and treatment strategies. Data extraction and quality evaluation of the presence of diabetes, hypertension, cardiovascular diseases, liver disease, cancer, and smoking habit in tandem with COVID-19 disease severity, complications, and mortality, were in line with the objectives of the review.

2.4. Statistical Analysis

All meta-analysis was performed using Microsoft Excel (Ver. 2013), MedCalc (Ver.19.3), and RevMan software (Ver.5.3). For dichotomized data, risk ratio (RR) and 95% confidence interval (CI) were applied, while heterogeneity and the random-effect model were used for analysing continuous data and considerable heterogeneity, respectively [14]. The degree of disease severity was categorized as low (25%), moderate (50%), and high (75%) by using Chi-square and I^2 tests [11]. In addition, funnel plots were applied to check the probable bias in published data [18].

3. RESULTS

3.1. Characteristics and Quality Parameters of Searched Literature

A preliminary search for relevant *e*-literature in various databases resulted in 1910 articles involving a study on SARS-Cov-2 disease. A total of 474 duplicate articles were removed by carefully checking the titles and abstracts and using the quotation director's ability to create partitions by recognizing duplications. For individual citations of the same paper, the citations were screened and de-copied. Post appraisal of same creator, title, distribution date, volume, issue, and test measure, the citations were recorded on a Microsoft Excel spreadsheet. Another 203 articles were excluded for overlapping study (n=75), unrelated topics (n=60), insufficient information (n=17), low sample size (n=13) and lack of clinical characteristics (n=38). In addition, the lack of information on co-morbid systemic disease leads to the exclusion of another 271 articles. Thus, in the qualitative and quantitative synthesis of the current COVID-19 meta-analysis reports, only nineteen (19) retrospective studies fitted the inclusion criteria (Fig. **1**). These retrospective studies involved a sample size of 12037 COVID-19 patients drawn from a wide range of geographical locations.

3.2. Demographic Characteristics

The demographic characteristics of the COVID-19 patients (n=12037) included in the current study are presented in Table **1**. Meta-analysis of gender information, based on 17 retrospective literatures, shows 55.68% male (n=2581) and 42.76% females (n=1982) in COVID-19 patients. The sex ratio (male to female) in severe (2.66) and non-severe (1.21) COVID-19 patient groups had no statistical significance. The prevalence significance exhibited for males [Prevalence (%): 56.71, 95% (CI): (53.20-60.19), $p<0.0001$, I^2: 80.54%] was higher as compared to females (Supplementary Fig. **2**). The majority of the COVID-19 patients were from China, followed by the USA and France. The median age ranged from 23 to 91 years, and the mean age was ~60 years.

3.3. Clinical Characteristics of COVID-19 Disease

The clinicopathological characteristics of COVID-19 patients are tabulated in Supplementary Table **1**. The most reported symptoms among COVID-19 patients were fever (47.57%), cough (44.67%), shortness of breath (6.51%), headache (5.60%), diarrhoea (5.89%), nausea and vomiting (4.80%). We categorized COVID-19 cases into two sub-

Table 1. Main Characteristics of the included patients in meta-analysis.

Authors	Period of Recruitment	Country	Number of Cases	Deaths (%)	Recovered (%)	Male/Female (%)	Age (Year) P-Value	Mean (Year) (Median)
Guan W J. *et al.,* 2020 [1]	11-12-2019 to 29-12-2019	China	1099	15 (1.4)	9 (0.8)	640/459 (58.2/41.7)	<65/≥65 0.9	47.0 (35.0-58.0)
Tao Guo*et al.,* 2020 [19]	23-01-2020 to 23-02-2020	China	187	43 (23.0)	144 (77.0)	91/96 (48.7/51.3)	<.001	58.5 (14.7)
Zhang X *et al.,* 2020 [20]	17-01-2020 to 8-02-2020	China	645	NA	NA	295/278 (51.5/48.5)	<0.001	46.7
Zhang JJ *et al.,* 2020 [21]	16-01-2020 - 03-02-2020	China	140	NA	NA	71/69 (50.7/49.3)	<50/≥5 <0.01	57.0 (25.0-87.0)
Chen T *et al.,* 2020 [22]	13-01-2020 to 12-02-2020	China	274	113 (41.2)	161 (58.8)	171/103 (62.4/37.6)	<60/≥60 <0.001	62.0 (44.0-70.0)
Simonnet A *et al.,* 2020 [23]	27-02-2020 to 05-04-2020	France	124	NA	NA	90/34 (72.6/27.4)	0.87	60.0 (51-70)
Goyal P *et al.,* 2020 [24]	03-03-2020 to 27-03-2020	USA	393	40 (10.2)	260 (66.2)	238/155 (60.6/39.4)	<60/≥60 <.001	62.2 (48.6-73.7)
Mo P *et al.,* 2020 [25]	01-01-2020 to 05-02-2020	China	155	22 (14.2)	NA	86/69 (55.5/44.5)	<0.001	54.0 (42.0-66.0)
Hu L *et al.,* 2020 [26]	08-01-2020 to 20-02-2020	China	323	NA	NA	166/157 (51.4/48.6)	<65/≥65 <0.0001	61.0 (23.0-91.0)
Wan S *et al.,* 2020 [27]	23-01-2020 to 08-02-2020	China	135	1 (0.7)	15 (11.1)	72/63 (53.3/46.7)	<65/≥65 <.0001	47.0 (36.0-55.0)
Liu W*et al.,* 2020 [28]	30-12-2019 to 15-01-2020	China	78	2 (2.6)	67 (77.0)	39/39 (50.0/50.0)	<60/≥60 0.001	38.0 (33.0-57.0)
Dreher M *et al.,* 2020 [29]	February to March 2020	China	50	7 (14.0)	35 (70.0)	33/17 (66.0/34.0)	NA	65.0 (58.0-76.0)
Huang C *et al.,* 2020 [30]	31-12-2019 to 01-01-2020	China	41	6 (14.6)	28 (68.3)	30/11 (73.0/27.0)	0·60	49.0 (41.0-58.0)
Peng YD *et al.,* 2020 [31]	20 -01-2020 to15-02-2020	China	112	17 (15.2)	95 (84.8)	53/59 (47.3/52.7)	0.61	57.5 (54.0- 63.0)
Zhou F *et al.,* 2020 [32]	29-12-2019 to 31-01-2020	China	191	54 (28.3)	137 (71.7)	119/72 (62.0/38.0)	<0·0001	56.0 (46.0-67.0)
Fleming K *et al.,* 2020 [33]	12-02-2020 to 28-03-2020	USA	7,162	184 (2.6)	NA	NA	NA	NA
O'Reilly GM *et al.,* 2020 [34]	1-14 April 2020	Australia	240	NA	NA	NA	NA	60.0 (21.0)
Shi Y *et al.,* 2020 [35]	Until 17 Feb, 2020	China	487	NA	NA	259/228 (53.2/46.8)	<0.001	NA
Wu C *et al.,* 2020 [36]	25-12-2019 to 26-01 2020	China	201	44 (21.9)	40 (19.9)	128/73 (63.7/36.3)	<.001	51.0 (43.0-60.0)

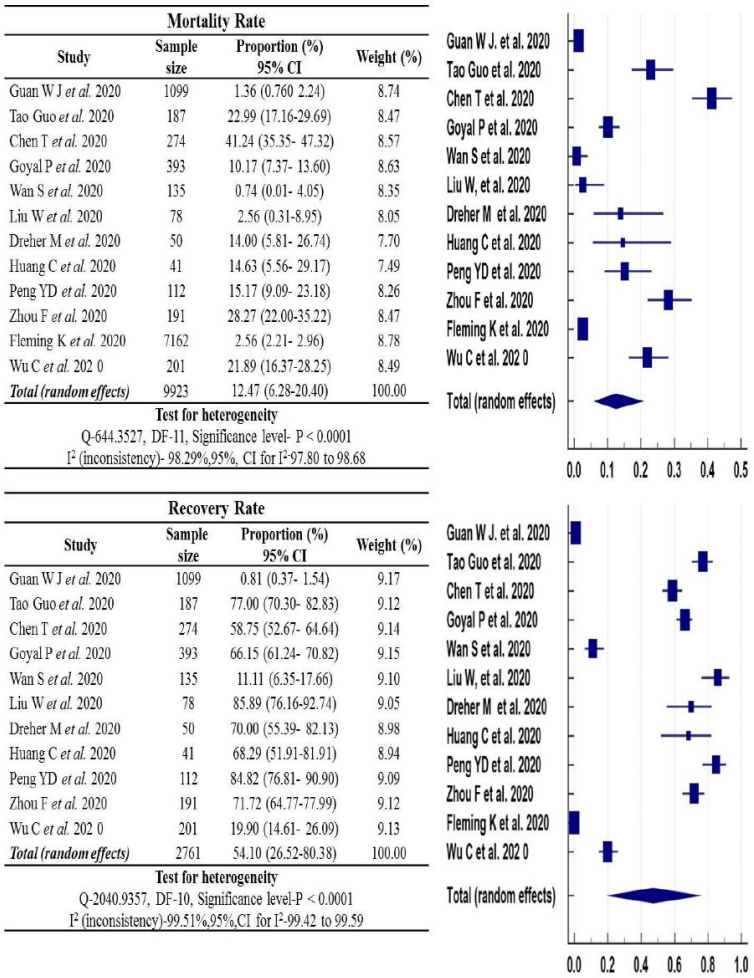
groups *viz.* critical/severe (18.27%, n=2200) and non-critical/non-severe (81.73%, n=9837) groups. Our pooled analysis showed that patients with critical/severe condition had lower prevalence rate compared to non-critical/severe patients [Prevalence (%): 32.96%, 95% (CI): 19.90-47.52] (Supplementary Fig. **1**). The random effect model showed significant heterogeneity for critical/severe condition COVID-19 patients [I^2: 99.46%, p<0.001] (Supplementary Fig. **1**). In the studies selected, most of the COVID-19 disease patients, particularly in the critical/severe category, were clinically managed with antibiotics (30.65%), antiviral (41.34%), corticosteroids (22.86%), intravenous immunoglobin (4.46%), oxygen (30.41%) and non-invasive mechanical ventilation (16.15%) treatment. The modalities are summarized in Supplementary Table **1**.

3.4. Recovery and Mortality Rate of COVID-19 Disease

Among COVID-19 patients under critical/severe category, the recovery and mortality rate showed statistically significant association. Random-effects meta-analysis of selected studies, among critical/severe category COVID-19 patients, has shown higher recovery rate [Prevalence (%): 54.10, 95% (CI): (26.52-80.38), p<0.0001, I^2: 99.51%, n=2761] compared to the mortality rate [Prevalence (%):12.47, 95% (CI): (6.28-20.40), p<0.0001, I^2:98.29%, n=9923] (Fig. **2**).

3.5. Association of Smoking with the Severity of COVID-19 Disease

The exposure to smoking (including current and ex-smokers) among severe and non-severe COVID-19 category of patients was 10.24% (204/1991) and 5.71% (546/9559),



Mortality Rate

Study	Sample size	Proportion (%) 95% CI	Weight (%)
Guan W J *et al.* 2020	1099	1.36 (0.760 2.24)	8.74
Tao Guo *et al.* 2020	187	22.99 (17.16-29.69)	8.47
Chen T *et al.* 2020	274	41.24 (35.35- 47.32)	8.57
Goyal P *et al.* 2020	393	10.17 (7.37- 13.60)	8.63
Wan S *et al.* 2020	135	0.74 (0.01- 4.05)	8.35
Liu W *et al.* 2020	78	2.56 (0.31-8.95)	8.05
Dreher M *et al.* 2020	50	14.00 (5.81- 26.74)	7.70
Huang C *et al.* 2020	41	14.63 (5.56- 29.17)	7.49
Peng YD *et al.* 2020	112	15.17 (9.09- 23.18)	8.26
Zhou F *et al.* 2020	191	28.27 (22.00-35.22)	8.47
Fleming K *et al.* 2020	7162	2.56 (2.21- 2.96)	8.78
Wu C *et al.* 202 0	201	21.89 (16.37-28.25)	8.49
Total (random effects)	9923	12.47 (6.28-20.40)	100.00

Test for heterogeneity

Q-644.3527, DF-11, Significance level- P < 0.0001

I^2 (inconsistency)- 98.29%,95%, CI for I^2-97.80 to 98.68

Recovery Rate

Study	Sample size	Proportion (%) 95% CI	Weight (%)
Guan W J *et al.* 2020	1099	0.81 (0.37- 1.54)	9.17
Tao Guo *et al.* 2020	187	77.00 (70.30- 82.83)	9.12
Chen T *et al.* 2020	274	58.75 (52.67- 64.64)	9.14
Goyal P *et al.* 2020	393	66.15 (61.24- 70.82)	9.15
Wan S *et al.* 2020	135	11.11 (6.35-17.66)	9.10
Liu W *et al.* 2020	78	85.89 (76.16-92.74)	9.05
Dreher M *et al.* 2020	50	70.00 (55.39- 82.13)	8.98
Huang C *et al.* 2020	41	68.29 (51.91-81.91)	8.94
Peng YD *et al.* 2020	112	84.82 (76.81- 90.90)	9.09
Zhou F *et al.* 2020	191	71.72 (64.77-77.99)	9.12
Wu C *et al.* 202 0	201	19.90 (14.61- 26.09)	9.13
Total (random effects)	2761	54.10 (26.52-80.38)	100.00

Test for heterogeneity

Q-2040.9357, DF-10, Significance level-P < 0.0001

I^2 (inconsistency)-99.51%,95%,CI for I^2-99.42 to 99.59

Fig. (2). Pooled prevalence of mortality and recovery rate in critical/severe patients. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

respectively. The relative risk (RR) estimation of COVID-19 disease among patients with smoking history exhibited a statistically significant association with severity of COVID-19 disease [RR: 1.52, 95% (CI): (1.12-2.06), p<0.006]. Funnel plot evaluation of publication bias among the pooled and selected studies indicated significant heterogeneity [I^2: 59.89%, p<0.001] (Fig. **3**).

3.6. COVID-19 Disease Risk Association with Cancer Co-morbidities

A total of 19 retrospective studies were considered, based on relative risk induced by co-morbidities (n=2200) in severe COVID-19 disease cases [1, 19-36]. The resultant associations of co-morbidities and COVID-19 severity are presented in Figs. (**3**-**5**). Cancer increased the relative risk of COVID-19, which was 1.9-fold higher for the critical patient group [95% (CI): 0.92-3.71, p=0.07] and the heterogenicity between the critical and non-critical group was I^2: 0.00%, p=0.74. However, no significance was observed in the case of cancer alone (Fig. **3**).

3.7. Prevalence of Hypertension

The pooled analysis of the prevalence of hypertension among critical (32.3%) and non-critical (22.9%) COVID-19 patients displayed a significant increase in the risk of severity of COVID-19 disease in the critical group [RR: 1.59, 95% (CI): 1.26-1.99, p<0.0001]. Cochran Q statistics showed significantly higher heterogeneity (75.67%) among studies [I^2: 75.54%, p<0.0001], as shown in Fig. (**4**).

3.8. Prevalence of Diabetes Mellitus

Diabetes was almost two times higher (20.1%; 444/2200) in critical COVID-19 patients as compared to non-critical COVID-19 patients (9.1%; 896/9837). The relative risk of COVID-19 disease severity was found to be statistically significant for the critical group *versus* the non-critical group [RR: 2.06, 95% (CI):1.52-2.79, p<0.001]. The heterogenicity observed among the COVID-19 patients with diabetes patients was significantly high [I^2: 76.99%, p<0.0001] (Fig. **4**).

Smoking habit

Study	Critical/ Severe	Non-Critical/ Severe	RR [95% CI]	Weight (%)
Guan WJ *et al.* 2020	38/173	120/926		
Tao Guo *et al.* 2020	7/52	11/135	1.65 [0.67-4.03]	6.78
Zhang X *et al.* 2020	37/573	4/72	1.162 [0.42-3.16]	5.94
Zhang JJ *et al.* 2020	6/58	3/82	2.82 [0.73-10.84]	4.03
Chen T *et al.* 2020	9/113	10/161	1.28 [0.53-3.05	6.98
Goyal P *et al.* 2020	6/130	14/263	0.86[0.34- 2.20]	6.45
Mo P *et al.* 2020	4/85	2/70	1.64 [0.31-8.72	2.90
Hu L *et al.* 2020	26/172	12/151	1.90 [0.99- 3.63]	9.06
Wan S *et al.* 2020	1/40	8/95	0.29 [0.03-2.29]	2.07
Liu W *et al.* 2020	3/11	2/67	9.13 [1.71- 48.61]	2.89
Huang C *et al.* 2020	0/13	3/28	0.29 [0.01-5.34]	1.11
Zhou F *et al.* 2020	19/54	65/137	0.74 [0.49-1.10]	11.79
Fleming K *et al.* 2020	38/457	208/6705	2.68 [1.92-3.73]	12.55
O'Reilly GM *et al.* 2020	4/11	50/229	1.66 [0.73-3.77]	7.39
Shi Y *et al.* 2020	6/49	34/438	1.57 [0.69-3.56]	7.42
Total (random effects) P=0.006	204/1991	546/9559	1.52 [1.12-2.06]	100.00

Test for heterogeneity
Q-32.1628, DF-14, Significance level-P = 0.0015
I^2 (inconsistency)-59.89%%, 95% CI for I^2-29.40 to 77.27

Cancer

Study	Critical/ Severe	Non-Critical/ Severe	RR [95% CI]	Weight (%)
Guan W J *et al.* 2020	3/173	7/926	2.29 [0.59- 8.78]	26.80
Zhang X *et al.* 2020	6/573	0/72	1.65 [0.09- 29.04]	5.88
Zhang JJ *et al.* 2020	3/58	3/82	1.41 [0.29- 6.75	20.40
Liu W *et al.* 2020	2/11	2/67	6.09 [0.76- 21.60]	14.53
Dreher M *et al.* 2020	4/24	3/26	1.44[0.36- 5.80]	25.83
Zhou F *et al.* 2020	0/54	2/137	0.50 [0.02- 10.28]	5.47
Total (random effects) P=0.07	18/893	17/1310	1.91 [0.92- 3.71]	100.00

Test for heterogeneity
Q-2.9587, DF-5, Significance level-P = 0.7448
I^2 (inconsistency)-0.00%-95% CI for I^2-0.00 to 37.09

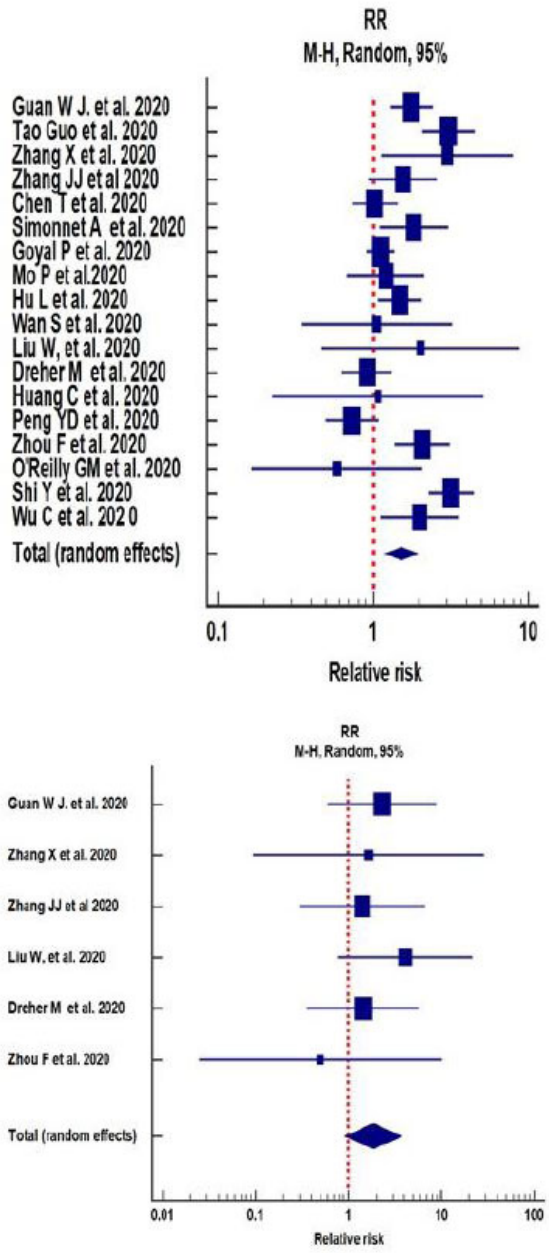


Fig. (3). Forest plot of the relative risk in smoking habits and cancer associated with COVID-19 infected cases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.9. Prevalence of Cardiovascular Diseases

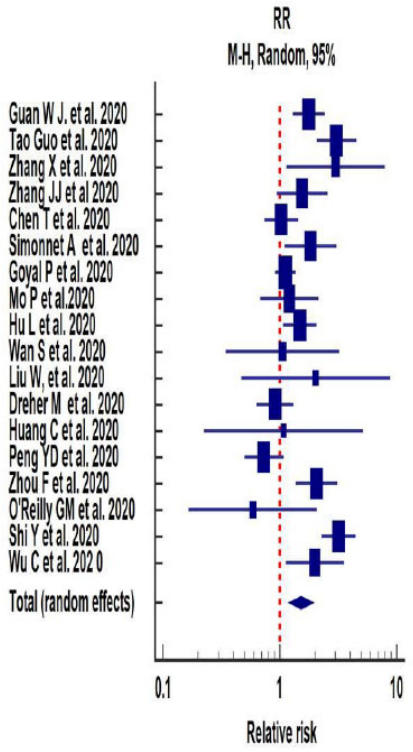
Cardiovascular diseases were higher (14.3%; 299/2080) in the critical COVID-19 patient's group compared to the non-critical patients (7.0%; 684/9705) group. The random-effect model was employed on 16 a pooled analysis of cardiovascular diseases in COVID-19 patients. The cardiovascular diseases increased the relative risk of severity of COVID-19 disease between critical and non-critical COVID-19 patients by 3.11-fold [95% (CI): 2.07-4.67, p<0.001]. The heterogenicity between the critical and non-critical group of COVID-19 patients was also found to be statistically significant [I^2: 74.26%, p<0.0001] (Fig. **5**).

3.10. Prevalence of Chronic Liver Disease

According to our statistical analysis, the incidence rate of chronic liver disease in hospitalized COVID-19 patients was 1.12-fold higher for the critical patient group [95% (CI): 0.68-1.84, p=0.64] and the heterogenicity was I^2: 26.27%, p=0.193. To estimate the pooled prevalence, a fixed model was used, and the results are shown in Fig. (**5**).

Hypertension				
Study	**Critical/ Severe**	**Non-Critical/ Severe**	**Relative risk [95% C]**	**Weight (%)**
Guan W J *et al.* 2020	41/173	124/926	1.77 [1.29- 2.42]	7.36
Tao Guo *et al.* 2020	33/52	28/135	3.06 [2.07- 4.51]	6.86
Zhang X *et al.* 2020	96/573	4/72	3.01 [1.14- 7.95]	3.40
Zhang JJ *et al.* 2020	22/58	20/82	1.55 [0.94- 2.57]	6.06
Chen T *et al.* 2020	54/113	39/161	1.97 [1.41- 2.75]	8.49
Simonnet A *et al.* 2020	48/85	12/39	1.83[1.10- 3.04]	6.04
Goyal P *et al.* 2020	70/130	127/263	1.11[0.91-1.36]	8.00
Mo P *et al* .2020	22/85	15/70	1.20 [0.68 2.14]	5.57
Hu L *et al.* 2020	66/172	39/151	1.48 [1.06- 2.06]	7.26
Wan S *et al.* 2020	4/40	9/95	1.05 [0.34- 3.23]	2.83
Liu W *et al.* 2020	2/11	6/67	2.03 [0.46- 8.81]	1.91
Dreher M *et al.* 2020	16/24	19/26	0.91 [0.63- 1.31]	7.01
Huang C *et al.* 2020	2/13	4/28	1.07 [0.22- 5.14]	1.73
Peng YD *et al.* 2020	10/16	82/96	0.73[0.49- 1.07]	6.86
Zhou F *et al.* 2020	26/54	32/137	2.06 [1.36- 3.10]	6.71
O'Reilly GM *et al.* 2020	2/11	71/229	0.58 [0.16- 2.08	2.38
Shi Y *et al.* 2020	26/49	73/438	3.18 [2.27- 4.45]	7.21
Wu C *et al.* 202 0	23/84	16/117	2.00 [1.12- 3.55]	5.58
Total (random effects) P<0.001	563/1743	720/3132	1.59 [1.26- 1.99]	100.00
Test for heterogeneity				
Q- 75.6798, DF- 17, Significance level-P < 0.0001				
I^2 (inconsistency), 77.54%, 95% CI for I^2, 64.90 to 85.62				

Diabetes				
Study	**Critical/Severe**	**Non-Critical/Severe**	**Relative risk [95% CI]**	**Weight (%)**
Guan W J *et al.* 2020	28/173	53/926	2.82 [1.84- 4.33]	7.44
Tao Guo *et al.* 2020	16/52	12/135	3.46 [1.76- 6.81	6.07
Zhang X *et al.* 2020	44/573	4/72	1.38 [0.51- 3.73	4.48
Zhang JJ *et al.* 2020	8/58	9/82	1.25 [0.51- 3.06]	4.96
Chen T *et al.* 2020	24/113	23/161	1.48 [0.88- 2.49	6.95
Simonnet A *et al.* 2020	23/85	5/39	2.11 [0.86- 5.13]	4.97
Goyal P *et al.* 2020	36/130	63/263	1.15 [0.81- 1.64]	7.82
Mo P *et al.*2020	12/85	3/70	3.29 [0.96-11.21	3.58
Hu L *et al.* 2020	33/172	14/151	2.06 [1.15- 3.71]	6.58
Wan S *et al.* 2020	9/40	3/95	7.12 [2.03-24.95]	3.48
Liu W *et al.* 2020	2/11	3/67	4.06 [0.76- 21.60]	2.37
Dreher M *et al.* 2020	15/24	14/26	1.16 [0.72- 1.86]	7.21
Huang C *et al.* 2020	1/13	7/28	0.30 [0.04- 2.25]	1.82
Peng YD *et al.* 2020	4/16	19/96	1.26 [0.49- 3.23]	4.73
Zhou F *et al.* 2020	17/54	19/137	2.27 [1.27- 4.02]	6.65
Fleming K *et al.* 2020	148/457	582/6705	3.73 [3.20- 4.35	8.56
O'Reilly GM *et al.* 2020	1/11	35/229	0.59 [0.08-3.95]	1.96
Shi Y *et al.* 2020	7/49	22/438	2.84 [1.28- 6.31]	5.43
Wu C *et al.* 202 0	16/84	6/117	3.71 [1.51- 9.09]	4.83
Total (random effects) P=<0.001	444/2200	896/9837	2.06 [1.52- 2.79]	100.00
Test for heterogeneity				
Q-73.6808, DF-17, Significance level- P < 0.0001				
I^2 (inconsistency)- 76.99%, 95% CI for I^2-64.84 to 85.13				



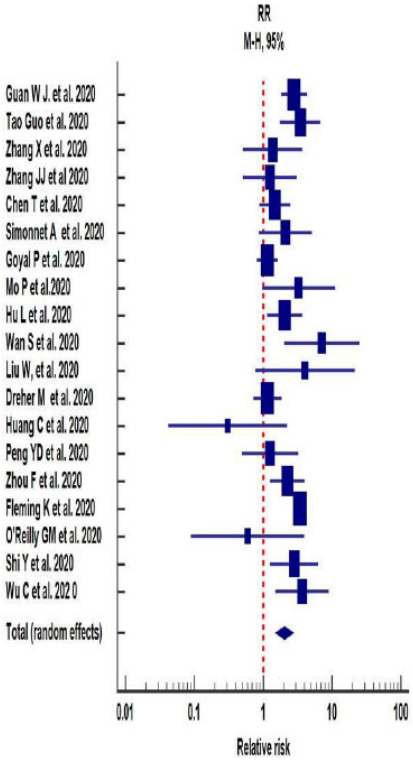


Fig. (4). Forest plot of the relative risk in hypertension and diabetes associated with COVID-19 infected cases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

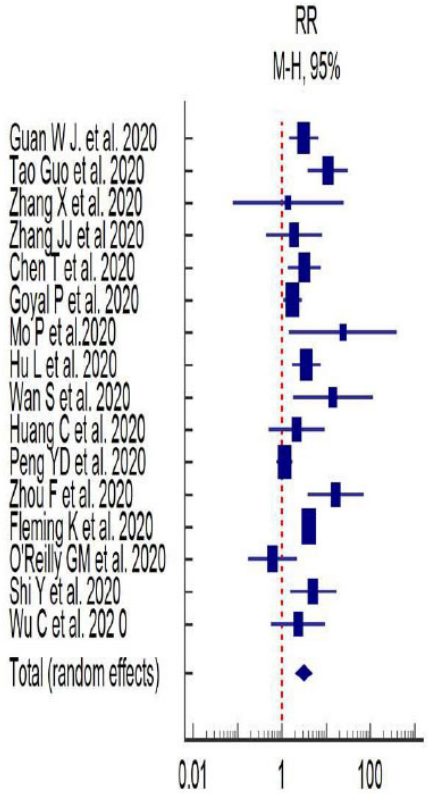
Cardiovascular disease

Study	Critical/ Severe	Non-Critical/ Severe	Relative risk [95% CI]	Weight (%)
Guan W J *et al.* 2020	10/173	17/926	3.14 [1.46- 6.76]	8.22
Tao Guo *et al.* 2020	17/52	4/135	11.03 [3.89-31.25]	6.66
Zhang X *et al.* 2020	5/573	0/72	1.39 [0.07- 25.04	1.70
Zhang JJ *et al.* 2020	4/58	3/82	1.885 [0.43- 8.10]	4.69
Chen T *et al.* 2020	16/113	7/161	3.25 [1.35-7.65]	7.75
Goyal P *et al.* 2020	25/130	29/263	1.74 [1.06-2.85]	10.05
Mo P *et al.* 2020	14/85	0/70	-	1.96
Hu L *et al.* 2020	33/172	8/151	3.62 [1.72- 7.51]	8.35
Wan S *et al.* 2020	6/40	1/95	14.25 [1.77- 11.58	3.10
Huang C *et al.* 2020	3/13	3/28	2.15 [0.50-9.26	4.90
Peng YD *et al.* 2020	10/16	52/96	1.15 [0.75- 1.75]	10.00
Zhou F *et al.* 2020	13/54	2/137	16.49 [3.84- 70.65]	4.91
Fleming K *et al.* 2020	132/457	481/6180	3.71[3.13- 4.38]	10.88
O'Reilly GM *et al.* 2020	2/11	67/229	0.62 [0.17- 2.21]	5.66
Shi Y *et al.* 2020	4/49	7/438	5.10 [1.55- 16.83]	6.01
Wu C *et al.* 202 0	5/84	3/117	2.32 [0.57- 9.44]	5.11
Total (random effects) P<0.001	299/2080	684/9705	3.11 [2.07-4.67]	100.00

Test for heterogeneity

Q-67.0298, DF-15, Significance level- P < 0.0001

I^2 (inconsistency)- 74.26%, 95% CI for I^2-57.92 to 84.27



Liver diseases

Study	Critical/ Severe	Non-Critical/ Severe	Relative risk [95% CI]	Weight (%)
Guan W J *et al.* 2020	1/173	22/926	0.24 [0.03- 1.79]	5.35
Tao Guo *et al.* 2020	5/52	14/135	0.92[0.35-2.44]	16.43
Zhang X *et al.* 2020	23/573	2/72	1.44 [0.34- 6.00	9.45
Zhang JJ *et al.* 2020	4/58	4/82	1.41 [0.36- 5.42]	10.34
Mo P *et al.*2020	5/85	2/70	2.05 [0.41- 10.29]	7.75
Hu L *et al.* 2020	2/172	3/151	0.58 [0.09- 3.45]	6.56
Wan S *et al.* 2020	1/40	1/95	2.37 [0.15- 37.04]	3.19
Dreher M *et al.* 2020	2/24	7/26	0.310 [0.07- 1.34]	9.15
Huang C *et al.* 2020	0/13	1/28	0.69 [0.03- 15.89]	2.50
Fleming K *et al.* 2020	7/457	33/6705	3.11 [1.38- 6.99	19.18
Shi Y *et al.* 2020	2/49	20/438	0.89 [0.21- 3.71]	9.46
Total (random effects) P=0.64	52/1696	109/8728	1.12 [0.68- 1.84]	100.00

Test for heterogeneity

Q-12.6297, DF-10, Significance level-P = 0.1939

I^2 (inconsistency)-26.27% 95% CI for I^2-0.00 to 60.13

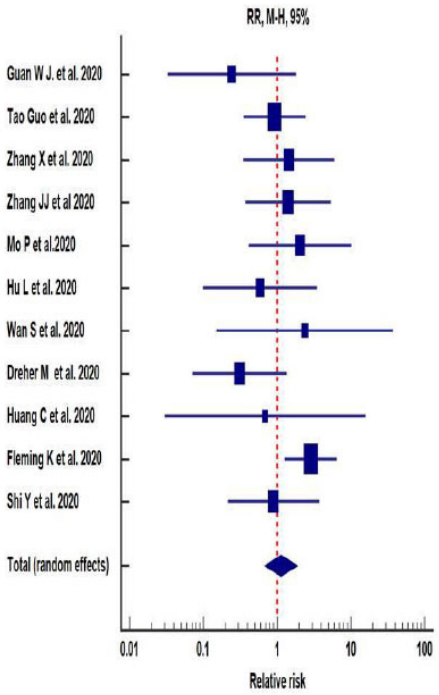
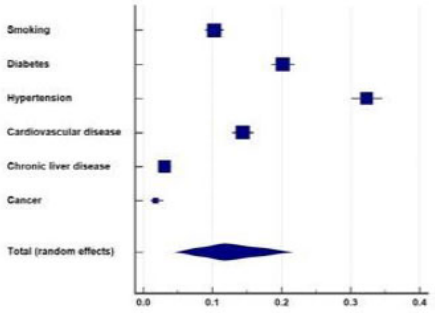


Fig. (5). Forest plot of the relative risk in cardiovascular and liver diseases associated with COVID-19 infected cases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Study	Sample size	Proportion % (95% CI)	Weight (%)
Smoking	1991	10.24 (8.94-11.66)	16.68
Diabetes	2200	20.18 (18.52- 21.92)	16.69
Hypertension	1743	32.30 (30.10- 34.55	16.67
Cardiovascular disease	2080	14.37 (12.89- 15.95)	16.69
Chronic liver disease	1696	3.06 (2.298-4.00)	16.67
Cancer	893	1.79 (1.027 to 2.89)	16.59
Total (fixed effects)	10603	13.30 (12.66-13.96)	100.00
Total (random effects)	10603	11.76 (4.735- 21.38)	100.00

Test for heterogeneity
Q-931.7774, DF-5, Significance level, P < 0.0001,
I2 (inconsistency)-99.46%, 95% CI for I2, 99.31 to 99.58



Study	Critical/ Severe	Non-Critical/ Severe	Relative risk (95% CI)	Weight (%)
Smoking	204/1991	546/9559	1.79 (1.53-2.09)	19.93
Diabetes	444/2200	896/9837	2.21 (1.99-2.45)	20.25
Hypertension	563/1743	720/3132	1.40 (1.28- 1.54)	20.46
Cardiovascular disease	290/2080	684/9705	3.11 (2.07-4.67)	19.75
Chronic liver disease	52/1696	109/8728	2.45 (1.77-3.40)	13.96
Cancer	16/893	17/926	0.97 (0.49-1.79)	6.50
Total (random effects) P<0.001	1578/10603	2972/41887	1.83 (1.49-2.25)	100.00

Test for heterogeneity
Q-70.636,DF-5, Significance level-P < 0.0001
I^2 (inconsistency)-92.92%-95% CI for I^2-87.31 to 96.05

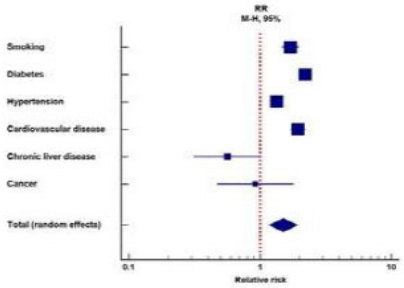


Fig. (6). Forest plot of the relative risk in *comorbidities* associated with COVID-19 infected cases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

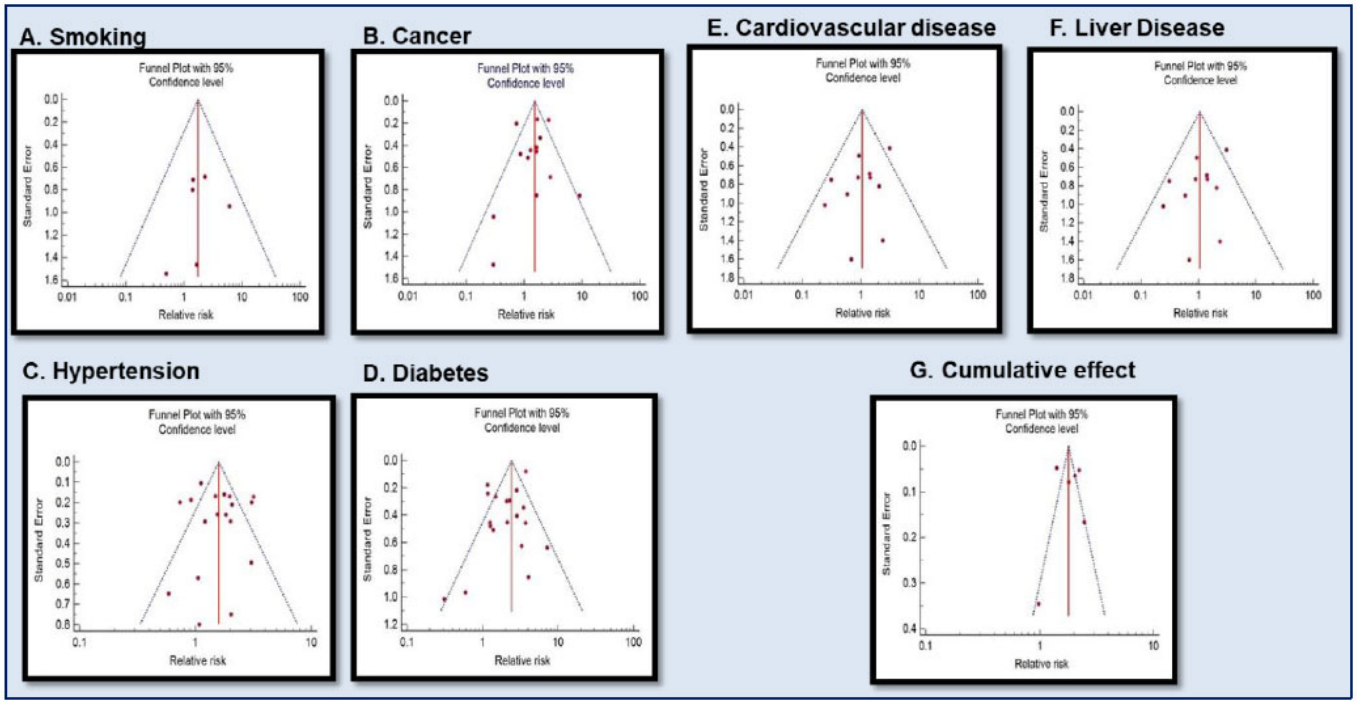


Fig. (7). Funnel plot for Meta-analysis of the relative risk of underlying disease in COVID-19 infected cases, [**A**] Smoking, [**B**] Cancer, [**C**] Hypertension, [**D**] Diabetes, [**E**] Cardiovascular disease, [**F**] Liver disease [**G**] Cumulative effect. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Statistical significance was not observed for chronic liver disease in COVID-19 patients in the critical group when compared to the non-critical group.

3.11. Relationship of the Smoking Habit, Diabetes, Hypertension, Cardiovascular Disease, Chronic Liver Disease and Cancer with COVID-19 Disease Severity

The complex association of smoking habits and co-morbidities (diabetes, hypertension, cardiovascular disease, chronic liver disease, and cancer) with the severity of COVID-19 disease among critical and non-critical COVID-19 patients group cases are presented in Fig. (**6**). It is evident that diabetes significantly increased the relative risk of COVID-19 disease severity by 2.06-fold, followed by cardiovascular disease (3.11-fold) and smoking habit (1.52-fold). Smoking habit and other co-morbidities in combination significantly increased the relative risk of COVID-19 disease severity by 1.83-fold [95% (CI): 1.49-2.25, $p<0.001$]. The heterogenicity between the critical and non-critical group of COVID-19 patients was also found to be statistically significant [I^2: 99.92%, $p<0.0001$] (Fig. **6**). Significant heterogeneity was also observed among all analysed co-morbidities except for cancer and chronic liver disease. The relative risk of smoking and other co-morbidities in COVID-19 disease severity was expressed in the form of a funnel plot (Fig. **7**).

4. DISCUSSION

In this systematic review and meta-analysis, a total of 19 clinical retrospective studies represented the data culled from 12037 COVID-19 patients. There exists a definite window of opportunity for enhanced COVID-19 patients' survival, in spite of high risk and co-morbid conditions, by timely identification and implementation of appropriately suitable treatment modalities.

Although COVID-19 patients mostly belonged to the 45-60-year age group [13, 15, 18] in a few studies, our meta-analysis indicated that a majority of severe COVID-19 patients were from the higher age bracket of 50-60 years. The distinct age-related variation (older adults *versus* younger children) in the severity of COVID-19 symptoms has recently been attributed to a potential mechanistic pathway [37]. Novel Coronavirus, the causative agent of COVID-19, interacts with angiotensin-converting enzyme 2 (ACE2), a cellular binding site expressed in the heart, kidney, and pulmonary alveolar type II cells [38]. ACE2 is a possible facilitator for SARS-CoV2 spike protein binding on lung cell surface receptors [39]. The expression of TMPRSS2, another cellular protein in the lung tissue, was assessed using mouse models. Very low levels were seen in younger mouse, against the significantly higher levels in the older mouse. The expression of TMPRSS2 was also reported to be significantly higher in the lung tissues of older COVID-19 patients [37]. Therefore, it has been hypothesized that higher TMPRSS2 expression in older individuals may be associated with severity and COVID-19 symptoms and suggests potential therapeutic application in devising a new treatment strategy for COVID-19 [37].

Both male and female sexes have different energy consumption and energy requirement, which depends upon the interaction between sex hormones and environmental factors [40]. Females have a better capacity of producing antibodies that provide effective resistance to COVID-19 infection; consequently, females may be at a lower risk of COVID-19 infection [40]. According to another theory, women may be less vulnerable to viral infection than men, possibly because of the protection of X chromosome and sex hormones, which play a cardinal role in innate and adaptive immunity [41]. Whereas in men, increased risk of COVID-19 infection may also be associated with poor lifestyle habits, such as smoking and underlying diseases [42]. In our meta-analysis and other COVID-19 studies, it was found that the majority of critical or fatal COVID-19 patients were male [23, 30]. The results of our demographic study showed a higher prevalence of COVID-19 disease in the male *versus* the female population, which is consistent with analytical results from earlier meta-analysis reports and related research [14, 23, 30, 36]. Our meta-analysis shows a significantly higher prevalence rate (54%) of pooled severity compared to pooled mortality (12.44%) in COVID-19 patients (Fig. **2**). Similar observations were also reported in a previous meta-analysis study [15]. Early detection of severe and critical COVID-19 symptoms in diseased cases may hold better promise and significance in improving the therapeutic intervention efficacy and subsequent reduction in mortality [43, 44]. However, our prognosis of pooled analysis between critical/severe COVID-19 patients and non-critical/ severe patients indicated a significantly higher mortality risk prevalence (32%) for critical/severe COVID-19 patients (Supplementary Fig. **1**). However, previous studies observed no statistical significance among the severe condition of COVID-19 patients with the prognostic outcome [8]. Application of a more comprehensive evaluation of larger COVID-19 patient samples in conjunction with accurate and suitable statistical methodologies may lead to a better understanding of COVID-19 prognosis influencing factors.

The antagonistic effect of smoking on pulmonary immune function advanced the progression of severe COVID-19 disease [45]. Smoking is thus a significant risk factor for the emergence of acute respiratory distress syndrome (ARDS) and the associated economic burden of patient care in severe cases of COVID-19 in a dose-dependent manner [46]. Hypothetically, smoking might impact the consequences of COVID-19 patients directly by inducing inflammation and damaging endothelial function in the cardiopulmonary systems [46, 47]. The fact that smoking increases the expression of ACE2 in the secretory cells of the respiratory tract corroborated the enhanced access into respiratory epithelial cells by SARS-CoV-2 interaction with ACE2 (angiotensin-converting enzyme 2) receptors [48, 49]. Consequently, the high expression of ACE2 in smokers might play an important role in inducing direct damage to the epithelial cell or through downstream inflammatory cascade events [46]. Our previous report substantiates the cumulative risk of COVID-19 disease severity due to smoking, hypertension, and cardiovascular diseases [13]. In our pre-

sent investigations, smokers had a 1.51-fold greater risk of COVID-19 disease compared to non-smokers. Our current findings are not only consistent with previous meta-analysis findings [50] but suggest that current and previous smoking habits may have an association with COVID-19 disease severity risk prevalence. Smoking has been correlated with adverse COVID-19 disease progression; this is due to the deleterious impact of tobacco use on lung health and its underlying association with a plethora of respiratory ailments [51].

It has been hypothesized, but not verified that the pre-existing use of type 1 receptor blockers (ARBs) for angiotensin II will upregulate membrane-bound ACE2, thus raising human susceptibility to virus entry [52]. It is likewise conceivable that people with pre-existing chronic conditions, such as high blood pressure and coronary heart disease (receiving ARBs) may be more susceptible to SARS-CoV-2 severity, including mortality [38].

ACE2 has a diversity of physiological roles that revolve around its trivalent function [39]. *ACE2* is extensively expressed in the kidneys, cardiovascular system, lungs, gut, central nervous system, and adipose tissue. ACE2 may be a critical link between immunity, inflammation, cardiovascular disease [53].

The diabetic individual has a higher risk of respiratory infections due to a compromised immune system, especially innate immunity [54]. Besides, diabetes is characterized by exaggerated proinflammatory cytokine response, particularly interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α in the absence of appropriate immune stimulation. This may be further complicated in response to a cytokine stimulus observed in patients with COVID-19 disease due to acute respiratory distress syndrome (ARDS) [55]. A thorough review of the recent meta-analysis showed that diabetes plays a significant role in the severity of COVID-19 disease and associated mortality [7, 14]. Our meta-analysis has emphatically shown the associated risk posed by diabetes for mortality and severity of COVID-19 disease [56].

Our meta-analysis findings are consistent with the previously published study, that hypertension posed a higher risk for COVID-19 disease severity, particularly among critical cases. According to another pooled meta-analysis study, hypertension is associated with a 2.54-fold increased risk for critical/severe COVID-19 disease, particularly among older age groups [57]. Acute cardiac injury is frequently reported in patients with COVID-19 [58]. COVID-19 may perhaps attack cardiomyocytes through different pathways [59]. Higher-level expression of ACE2 directly in the myocardium may lead to the release of cytokine and chemokine signals in COVID-19, which invariably resulted in myocardial inflammation in severe cases [59]. Our meta-analysis showed a 3.11-fold higher risk of severity of COVID-19 in patients with cardiovascular disease.

Liver disease of advanced stage and post-liver transplantation patients are more susceptible to COVID-19 infection [60]. However, in the present meta-analysis, no significant association between chronic liver disease and mortality in severe COVID-19 disease was evident. Our analysis has also not found a significant association between the severity of COVID-19 disease and cancer. However, cancer patients have a higher risk of COVID-19 disease severity compared to those without cancer (39% *vs.* 8%; hazard ratio (39% *vs.* 8%, HR: 5.34; 95% (CI): 1.80-16.18, $p<0.0026$) [61]. It is hypothesized that cancer-induced inflammation and cytokine-associated lung injury may have a role in COVID-19 disease, but it may not be a universal mechanism in all types of cancer patients. The individualistic variation in the genotype of inflammation and cytokine-associated genes may also have a role in cancer-induced lung injury and subsequent COVID-19 disease severity [61].

Our pooled meta-analysis data underscores the significant association of extant co-morbidity (predominantly smoking, diabetes, hypertension, and cardiovascular disease) with severity and rapid deterioration of COVID-19 disease-related symptoms. Though many reports cite the co-morbidity arising out of individual systemic diseases [7, 8, 13], there is a definite paucity on the combined presence of multiple co-morbid conditions with severity and mortality of COVID-19 disease. Diabetes mellitus in the presence of hypertension in males is known to synergistically amplify the severity of coronary artery disease (CAD) [62]. To the best of our knowledge, our pooled meta-analysis is the first report showing the synergistic association of the smoking habit, diabetes, hypertension, and cardiovascular diseases as significant co-morbidity factors for COVID-19 disease severity.

CONCLUSION

We conclude that the cumulative action of multiple co-morbidities involving smoking, diabetes, hypertension, and cardiovascular diseases may reinforce COVID-19 disease severity and mortality. The findings of our meta-analysis provide unambiguous insight into cumulative co-morbid risk factors and their intense adverse impact on COVID-19 disease. We would also like to stress the need to develop personalized, effective therapeutic regimens for better management of disease severity and treatment outcome in individuals with co-morbid health risks.

AUTHORS' CONTRIBUTIONS

RK conceived and designed the manuscript; RK, MMP, AH, and PC contributed to materials/analysis,; RK, AH, MMP, DB, BG, AKR and AKB wrote the paper,; all authors reviewed and approved the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

The systematic review and meta-analysis in this work was carried out in accordance with PRISMA and MOOSE guidelines.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Table **S1**. Descriptive clinical symptoms and treatments of patients.

Fig. (**S1**). The pooled prevalence of critical/severe patients in COVID-19.

Fig. (**S2**). Pooled prevalence of gender in COVID-19.

Fig. (**S3**). Checklist: PRISMA 2009 checklist

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