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META-ANALYSIS

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Risk factors of the severity of COVID-19: A meta-analysis

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Abstract

Objective: We intend to identify some probable risk factors that are responsible for the severity of COVID-19 using a meta-analysis.

Methods: The literature exploration lasted up to 18 April 2020 and through PubMed, Google Scholar, EMBASE and Cochrane Library we have identified 10 pertinent publications. To paraphrase the outcomes of autonomous researches, we have performed a random-effect meta-analysis.

Results: A total of 2272 patients' information was extracted from the selected literature. We have found gender (male) (Risk ratio [RR] = 1.29, 95% Confidence Interval [CI] 1.07 to 1.54), hypertension (RR = 1.79, 95% CI 1.57 to 2.04), diabetes (RR = 1.57, 95% CI 1.25 to 1.98), fatigue or myalgia (RR = 1.17, 95% CI 1.02 to 1.35), and smoking history (RR = 1.71, 95% CI 1.25 to 2.35) are potential risk factors for the severity of COVID-19. We found fever (RR = 1.21, 95% CI 0.66 to 2.22), cough (1.13, 95% CI 0.98 to 1.30) and diarrhoea (RR = 1.14, 95% CI 0.93 to 1.40) as insignificant risk factors for COVID-19 severity.

Conclusions: The findings of this research may be beneficial to identify patients with higher risks to provide additional medical attention from the very beginning of the treatment.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) originated from Wuhan (Hubei state, China), carrying similar DNA structure to SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) has spread throughout the world creating massive panic to the human life.[1,2] The disease has the worst feature to transmit from person to person,[3] considering this feature and its lofty infection rate on January 30, 2020, the World Health Organization (WHO) declared COVID-19 as a global emergency.

To date, it has infected more than 13.9 million people and over 5 lakh have died. The outbreak has hit the USA, Brazil and India very badly. This three-country together holds over 6.7 million total identified cases and over 41% of the total death because of COVID-19.[4] As no proven treatment/medicine or vaccine is available to date[5] the harm of COVID-19 has already overtaken SARS and MARS.[6]

Although the infection rate is very high, all the patients getting infected by this disease don't always die. The global recovery rate is about 59.4% and the death rate is about 4.25% until July 17, 2020.[4] This information suggests that there may be some factors that influence the risk of death or critical medical states of the patients. That's why it is important to identify and estimate such risk factors to predict the severe complication of the patients for avoiding or to minimise the severity.[7]

Researchers are trying to identify risk factors that deteriorate the health state of the COVID-19 patients mostly by using meta-analysis and systematic review. Some earlier investigations reported that males are more likely to die or to go through the critical states of COVID-19.[8,9] There is an ongoing debate on whether smoking is a risk factor for COVID-19 severity. Although some regard it as a

risk factor,[9,10] others found no significant alliance between smoking and the severity of COVID-19.[8,11] Other clinical traits termed as risk factors in the publications are hypertension,[12,13] diabetes[13,14] and fever.[8]

In this study, we endeavour to identify some demographic and clinical characteristics which can be appraised as risk factors for the severity of COVID-19 by summarising findings of the published literature.

Review criteria

- Several articles searching tools, e.g., PubMed, Google Scholar, EMBASE, and Cochrane Library, were adopted to find pertinent literature to identify risk factors of COVID -19 severity.
- The searching was based on specific keywords and extended to April 18, 2020, from April 2, 2020.
- The methodology of reviewing is embodied in the materials and methods section.

Message for the clinic

- Male and patients with smoking history are at high risk of experiencing a severe medical condition by COVID-19.
- Besides, chronic diseases like diabetes, hypertension, and fatigue/myalgia can worsen the COVID-19 patient's status.
- So special medical attention is recommended for these susceptible groups from the beginning.

2 | MATERIALS AND METHODS

2.1 | Literature search

The literature search lasted from April 2, 2020 to April 18, 2020. Both of the authors searched through PubMed, Google Scholar, EMBASE and Cochrane Library using keywords: "COVID-19", "Novel Coronavirus", "COVID-19 characteristics", "COVID-19 patient" and "China coronavirus". We initially identified all the studies conformed to the keywords without any further investigations.

2.2 | Inclusion criteria

Based on the following criteria, we have included literature in the current study: (a) bivariate data available for the severity (death/ICU (Intensive Care Unit)/severe state/others) of COVID-19 patients, (b) multiple factors available for the severity of the disease, (c) full-text access to the article, (d) information presented in English language, (e) peer-reviewed accepted/published articles, and (f) literature published in and after December 2019 (after the first patient identified). We illustrate the systematic selection procedure of literature in Figure 1.

2.3 | Outcomes and covariates

The authors extracted the number of patients who have undergone the severity of COVID-19 and are stable/recovered under various factors like gender, smoking history, fatigue or myalgia, cough, fever, diarrhoea, hypertension and diabetes. The term severity in this study represents death/ICU/severe state or any other critical medical state. We also extracted the authors' names, publication year, study design, sample size, country and other related information from the finally selected studies.

2.4 | Statistical analysis

Considering the primary goal of the study we performed random effect meta-analysis where the effect sizes were computed from the raw information dragged from individual studies. We considered the effect size for the study to be a Risk Ratio [RR] and reported with a 95% confidence interval. I^2 statistic reported in the forest plot reflects relative between studies heterogeneity and P value (two tail with level 0.05) determines the significance of the heterogeneity test. Microsoft Excel 2013 was used to create metadata, get their univariate characteristics, and export to other software for further analysis. Random effect meta-analysis and relevant forest plots were generated using statistical software R version 3.5.1.

3 | RESULTS

We have extracted 2272 patients' information from 10 autonomous studies[15-24] and incorporated them into this research. The highest sample size for the isolated study was 1099, and 34 was the smallest sample size, other study characteristics are summarised in Table 1.

Table 2 demonstrates that the bulk of the COVID-19 patients included in the study through a methodical scheme are male (60%). The clinical characteristics of the patients comprise diabetes (11.2%), hypertension (21.3%), fever (90.2%), cough (65%), fatigue or myalgia (41.0%), and diarrhoea (9.2%). Only 11.3% of the patients smoke cigarettes (current or past smoker).

Forest plot in (Figure 2) illustrates that only six studies were entailed for the meta-analysis for characteristic smoking history where all ten studies availed information about the gender of the patients.

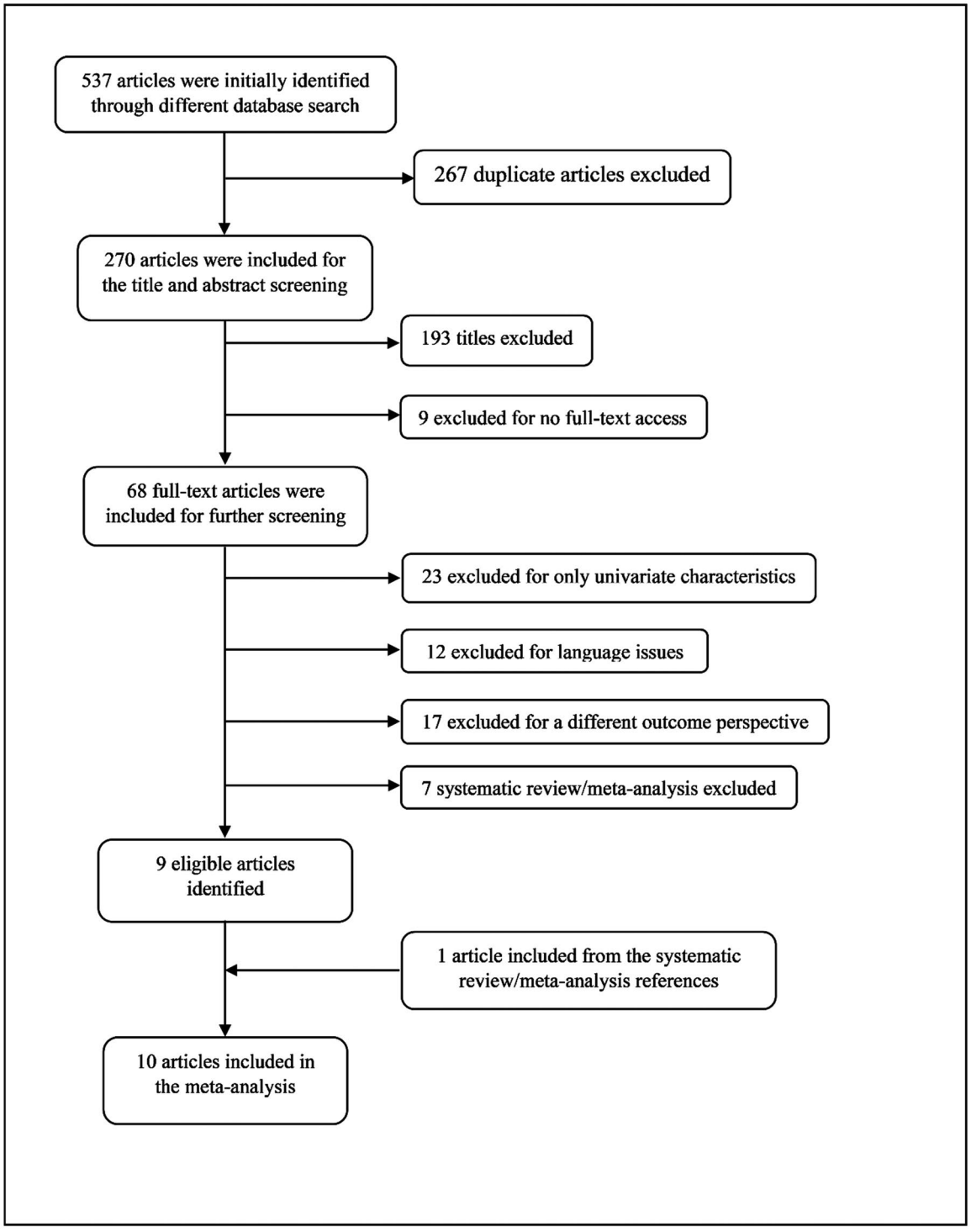

FIGURE 1 Flow chart showing the study selection procedure

From the random-effect meta-analysis, we see that patients with smoking history have a higher risk to experience a severe state of COVID-19 (RR = 1.71; 95% CI, 1.25 to 2.35) or 71% higher risk pertained to a non-smoker patient. The pooled risk ratio for the male suggests higher risk compared to female patients (RR = 1.29; 95% CI, 1.07 to 1.54). In both cases between-study heterogeneity is low and the test of heterogeneity is insignificant (I^2 = 38%, P = .15; and I^2 = 33%, P = .15, respectively).

Figure 3 displays individual and pooled risk ratios for patients with diabetes and hypertension. Although six isolated studies

TABLE 1 Characteristics of the selected literatures

Author	Population with placing	Size	Study design	Time period	Outcome	Factors included in the study
Chen et al[15]	Covid-19 positive patient from Tongji Hospital in Wuhan, China	274	Retrospective study	Jan 13, 2020 to Feb 12, 2020	Death	Gender, smoke, diabetes, hypertension, fever, cough, fatigue or myalgia and diarrhoea
Deng et al[16]	Patients from two tertiary hospitals in Wuhan, China	225	Retrospective study	Jan 1, 2020 to Feb 21, 2020	Death	Gender, diabetes, hypertension, fever, cough, fatigue and diarrhoea
Guan et al[17]	Confirmed patients from 552 hospitals in 30 provinces, China	1099	Retrospective study	Dec 11, 2019 to Jan 29, 2020	Severe	Gender, smoking history, diabetes, hypertension, fever, cough, fatigue or myalgia and diarrhoea
Huang et al[18]	All Covid-19 patients from a designed hospital in Wuhan, China	41	Retrospective study	Dec 16, 2019 to Jan 2, 2020	ICU	Gender, smoking history, diabetes, hypertension, fever, cough, fatigue or myalgia and diarrhoea
Lei et al[19]	Clinical data from Renmin, Zhongnan, Tongji and Central Hospital, China	34	Retrospective study	Jan 1, 2020 to Feb 5, 2020	ICU	Gender, diabetes, hypertension, fever, cough, fatigue or myalgia, and diarrhoea
Liu et al[20]	Patients from three tertiary hospitals in Wuhan, China	78	Retrospective study	Dec 30, 2019 to Jan 15, 2020	Progression	Gender, smoking history, hypertension, diabetes, and cough
Wang et al[21]	Consecutive hospitalised patient at Zhongnan Hospital in Wuhan, China	138	Retrospective study	Jan 1, 2020 to Jan 28, 2020	ICU	Gender, diabetes, hypertension, fever, cough, fatigue or myalgia and diarrhoea
Yang et al[22]	Adult patients in Wuhan Jin Yin-tan hospital, China	52	Retrospective study	Dec 2019 to Jan 26, 2020	Non-survivor	Gender, smoking history, diabetes, fatigue or myalgia, hypertension and cough
Zhang et al[23]	All hospitalised patients from Wuhan hospital, China	140	Retrospective study	Jan 5, 2020 to Jan 24, 2020	Severe	Gender, smoking history, diabetes, hypertension, fever, cough, fatigue or myalgia, and diarrhoea
Zhou et al[24]	Adult (>=18 years) patients from Jinyintan Hospital and Wuhan Pulmonary Hospital, China	191	Retrospective multi-centre cohort study	Dec 29, 2019 to Jan 31, 2020	Non-survivor	Gender, smoking history, diabetes, hypertension, fever, cough, fatigue or myalgia, and diarrhoea

TABLE 2 Baseline characteristics of COVID-19 patients for different studies

Characteristics	Chen et al[15]	Deng et al[16]	Guan et al[17]	Huang et al[18]	Lei et al[19]	Liu et al[20]	Wang et al[21]	Yang et al[22]	Zhang et al[23]	Zhou et al[24]	Overall
Male	171 (62.4)	124 (55.1)	637 (58.1)	30 (73.2)	14 (41.2)	39 (50.0)	75 (54.3)	35 (67.3)	71 (50.7)	119 (62.6)	1315 (60.0)
Smoking history	19 (6.9)	–	158 (14.6)	3 (7.3)	–	5 (6.4)	–	–	9 (6.4)	11 (5.8)	205 (11.3)
Diabetes	47 (17.2)	26 (11.6)	81 (7.4)	8 (19.5)	8 (23.5)	5 (6.4)	14 (10.1)	9 (17.3)	17 (12.1)	36 (22.6)	251 (11.2)
Hypertension	93 (33.9)	58 (25.8)	165 (15.0)	6 (14.6)	13 (38.2)	8 (10.3)	43 (31.2)	–	42 (30.0)	58 (30.4)	468 (21.3)
Fever	249 (90.9)	189 (84.0)	975 (88.7)	40 (97.6)	31 (91.2)	–	136 (98.6)	51 (98.1)	110 (91.7)	180 (94.2)	1961 (90.2)
Cough	185 (67.5)	85 (37.8)	745 (67.8)	31 (75.6)	18 (52.9)	34 (43.6)	82 (59.4)	40 (76.9)	90 (75.0)	151 (79.1)	1461 (65.0)
Fatigue or myalgia	137 (50.0)	57 (25.3)	419 (38.1)	18 (43.9)	25 (73.5)	–	96 (69.6)	6 (11.5)	90 (75.0)	44 (23.0)	892 (41.0)
Diarrhoea	77 (28.1)	33 (14.7)	42 (3.8)	1 (2.6)	2 (5.9)	–	14 (10.1)	–	18 (12.9)	9 (4.7)	196 (9.2)

Note: Data are presented as n, and (n/N *100%); where n is the number of patients with certain characteristics and N is the total number of available patients observed in the study under that certain characteristics.

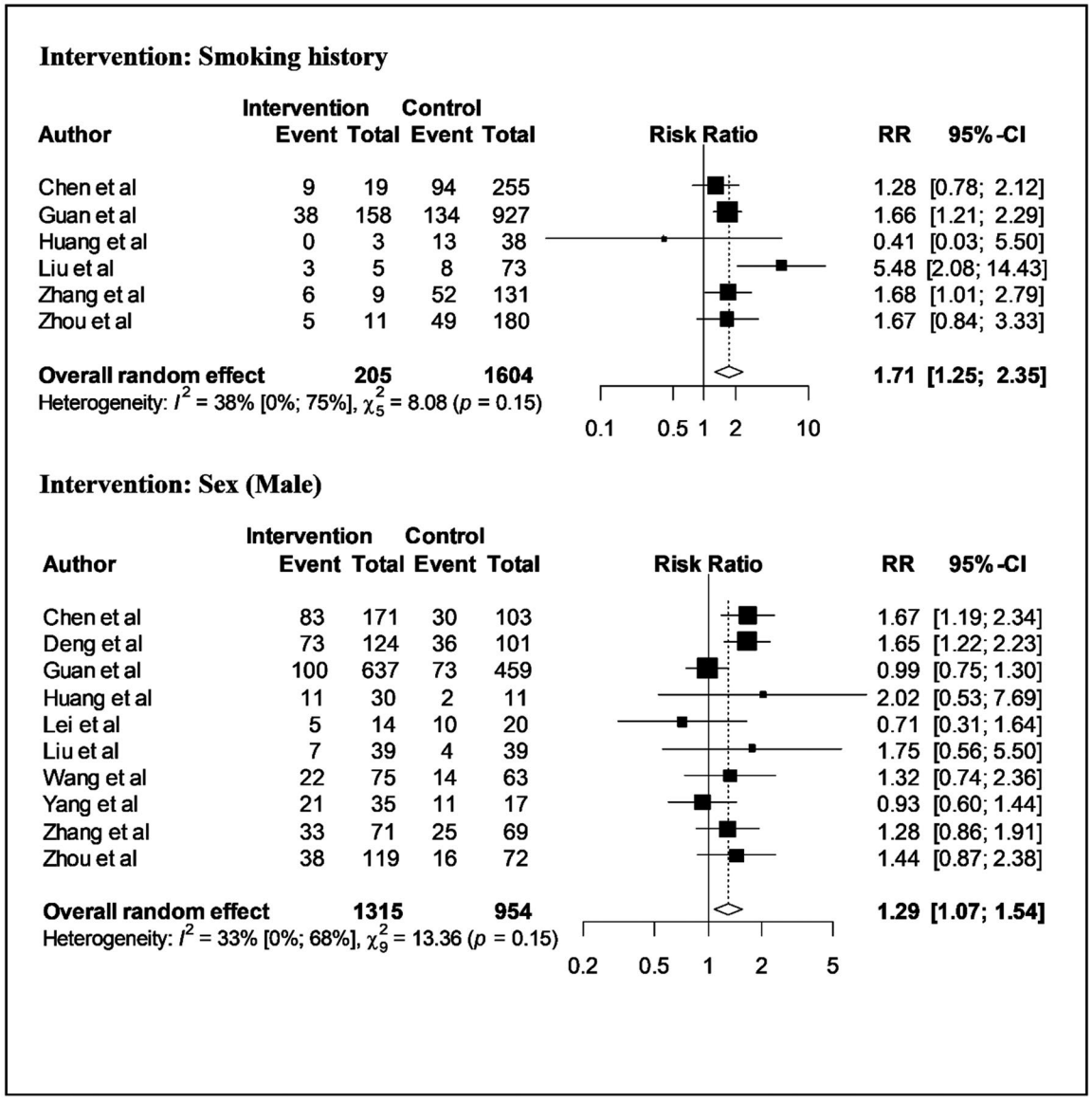

FIGURE 2 Forest plot for factors smoking history and gender (male) illustrating the distribution of the risk ratio of COVID-19 severity

data implies that diabetes is an insignificant risk factor but the overall effect is significant and indicates a higher risk to undergo brutal state for a patient with diabetes (RR = 1.57; 95% CI, 1.25 to 1.98). The heterogeneity is moderate (I^2 = 54%) and the test for heterogeneity is significant (χ^2 = 19.59, P = .02). Also, patients with hypertension have a higher risk (RR = 1.79; 95% CI, 1.57 to 2.04) compared to patient those who are not suffering from hypertension with insignificant heterogeneity, I^2 = 0% (P = .50).

Eight and nine studies were involved in the analysis for factors diarrhoea and fatigue or myalgia of patients, respectively (Figure 4). In both cases the heterogeneity is very low and is insignificant (I^2 = 8%, P = .37) and (I^2 = 0%, P = .86), respectively). The pooled random effect infers diarrhoea have an insignificant impact on the severity of COVID-19 (RR = 1.14; 95% CI, 0.93 to 1.40). But the overall RR = 1.17 (95% CI, 1.02 to 1.35) suggests that patients with fatigue or myalgia have a 17% higher risk to go through a severe state of COVID-19.

From Figure 5, we glimpse that cough and fever have no considerable relation with the severity of COVID-19. The pooled effect reflects patient with cough symptom has RR = 1.13 (95% CI, 0.98 to 1.30) and patient with fever has RR = 1.21 (95% CI, 0.66 to 2.22). Although for cough symptom the between-study heterogeneity is nil and insignificant (I^2 = 0%,

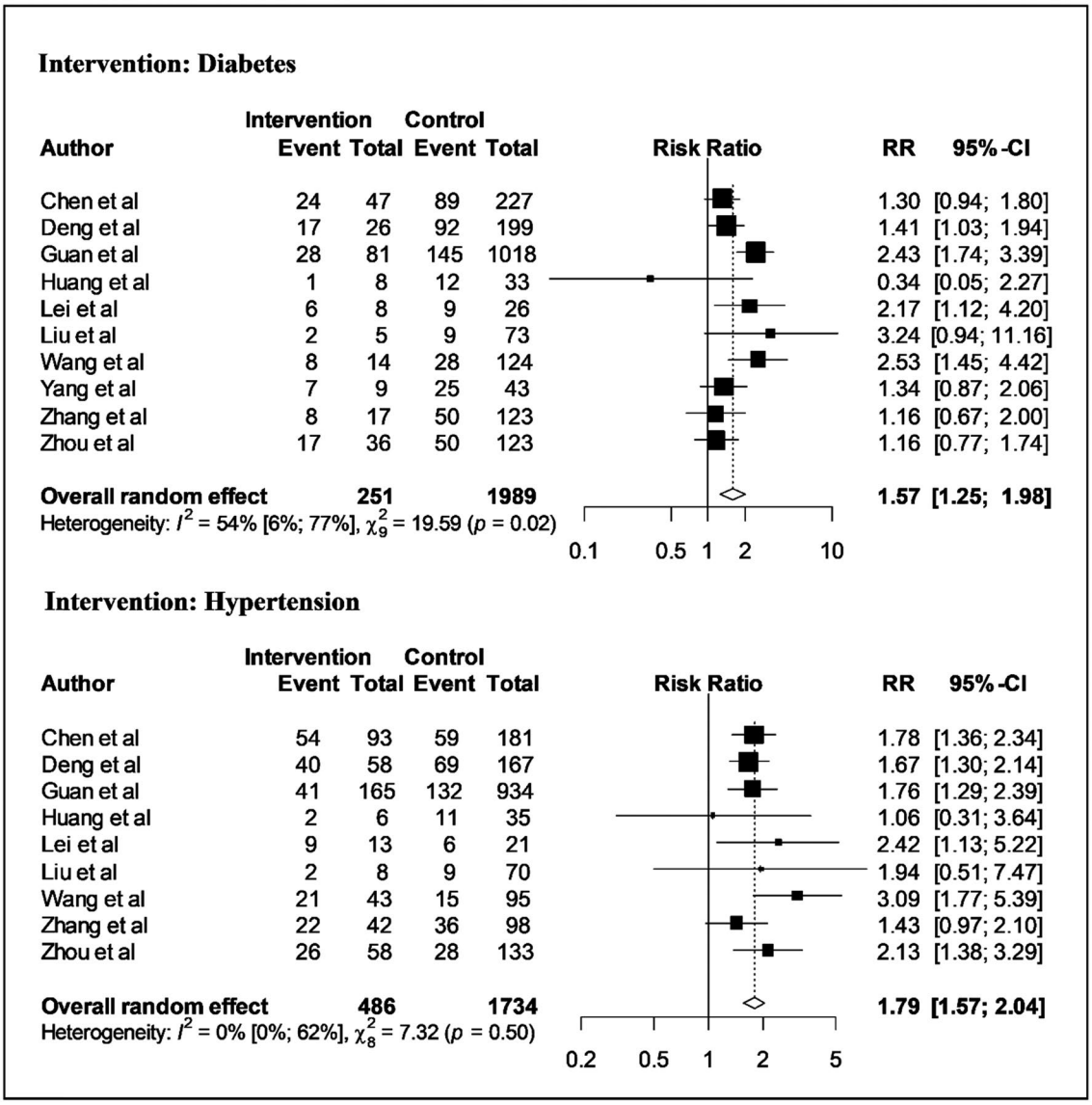

FIGURE 3 Forest plot for factors diabetes and hypertension illustrating the distribution of the risk ratio of COVID-19 severity

P = .48), it is very big and also significant for fever (I^2 = 85%, P < .01).

4 | DISCUSSION

This study through an organised way incorporated 10 publications and performed a random-effect meta-analysis to identify some risk factors that are probably accountable for the severity of COVID-19. Although none of the articles incorporated in the current research reports any effect size, we computed the effect size (risk ratio) from the published data. The pooled effect size with confidence interval deemed to avouch a factor as a significant risk factor.

We found that male patients have a reasonably higher risk to undergo the severity of COVID-19 compared to female patients echoing with some previous studies.[8,9] An explanation of this can be, the male has weaker immunity because of genetic and hormonal factors and has shown higher mortality in several infectious diseases.[25,26]

Although some aforementioned studies[8,11] found smoking as an insignificant factor to worsen the state of COVID-19 patients, we have found smoking as a significant factor. Smoking is associated with lower or impoverished immunity of smokers, which can explain why smokers might have elevated risks. Some previous studies[9,10]

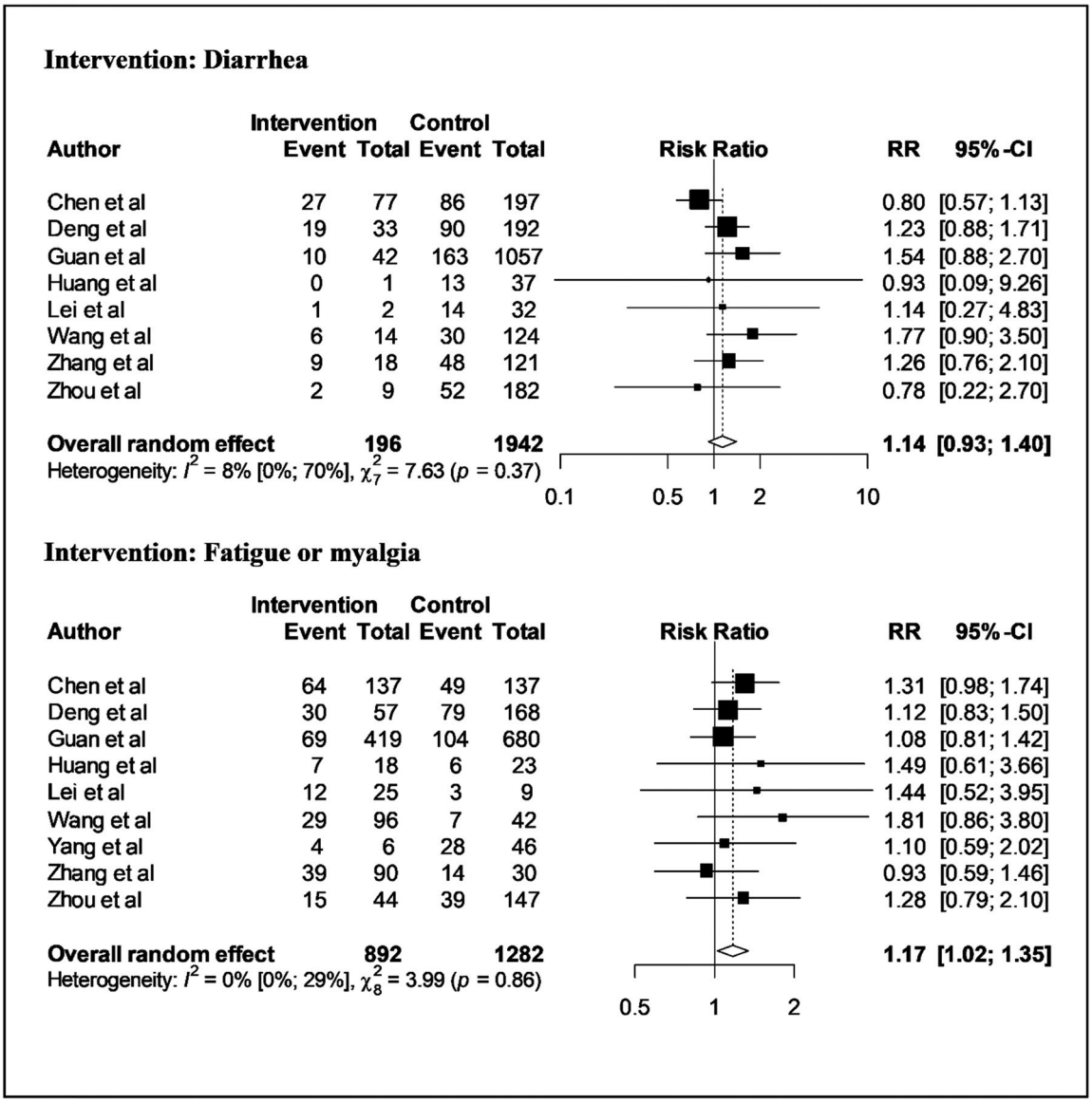

FIGURE 4 Forest plot for factors diarrhoea and fatigue or myalgia illustrating the distribution of the risk ratio of COVID-19 severity

supports our finding, they documented smoking as a significant risk factor, and smokers have a higher risk to undergo a severe state of COVID-19. In a previous study,[27] smoking was also reported as a risk factor for the critical illness of MERS (Middle East Respiratory Syndrome) too.

We incorporated some clinical traits of the patients like cough, fever, fatigue or myalgia, diarrhoea, diabetes and hypertension in this study. Among those, we have found that fatigue or myalgia, hypertension and diabetes are significant risk factors that might lead to a critical state of COVID-19 patients. Some previous studies[8,13,14] also reported both diabetes and hypertension are significant risk factors of COVID-19 progression. These two comorbidities negatively affected MERS-CoV patients' too.[28]

From the random-effect meta-analysis, we conclude that fever, cough and diarrhoea are insignificant risk factors for the severity of COVID-19. But a previous meta-analysis[8] published fever as a significant risk factor for the severity of COVID-19.

In conclusion, we consider gender (male), smoking history, diabetes, hypertension, and fatigue or myalgia as significant risk factors for the severity of COVID-19. It may require additional medical attention for patients with higher risk from the very beginning of the treatment. We also hope that the findings of this study may assist experts in vaccine development programs.

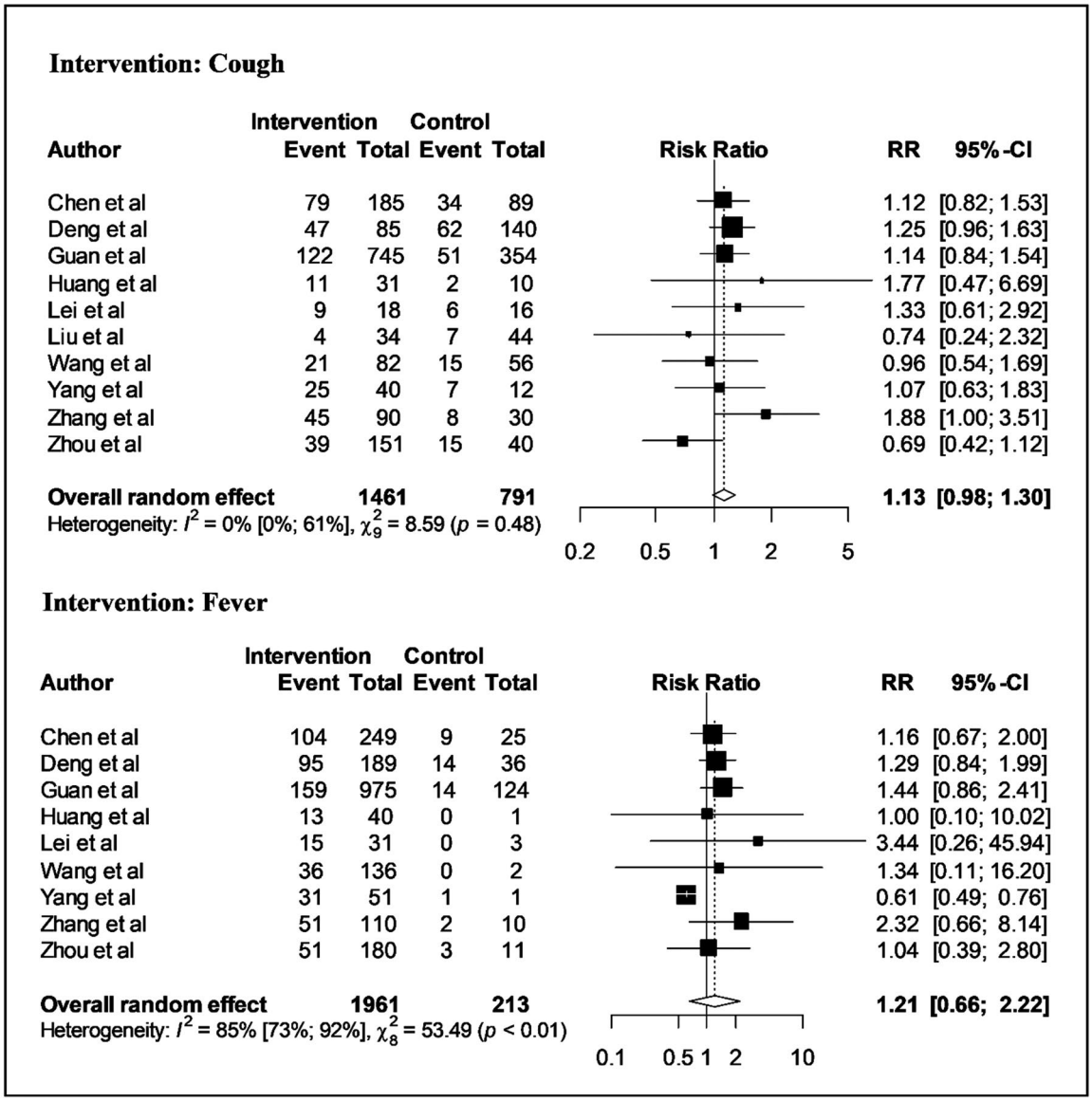

FIGURE 5 Forest plot for factors cough and fever illustrating the distribution of the risk ratio of COVID-19 severity

DISCLOSURES

None declared.

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This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

DATA AVAILABILITY STATEMENT

We extracted the data from different published studies, which can be accessed publicly. The publications are available from various authors.[15-24]

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