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Research Article

Effects of Cancer, Coronary Artery Disease and other Comorbidities on COVID-19 Related Mortality: A Meta-analysis and Meta-regression

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Abstract

Objective: To investigate Coronavirus Disease 2019 (COVID-19) associated mortality, the prevalence of different symptoms, and the prevalence and association between comorbidities and their effects on outcomes.

Methods: We performed a systematic literature search and meta-analysis on studies that assess COVID-19 patients' symptoms, comorbidities, and outcomes using pooled event rate (PER) and pooled event means (PEM). The primary outcome was the pooled all- cause short-term mortality. The secondary outcomes were length of hospital stay and symptom presentation. Meta-regression and leave-one-out analysis were conducted for mortality.

Results: 56 articles met our inclusion criteria with a total of 9074 patients. The PEM for age was 49.6 years. The PER for female gender was 46.79%. The PER for smoking, hypertension, cardiac comorbidities, diabetes was 10.96%, 24.47%, 20.30%; 12.34% respectively. The PER for CAD, COPD, history of cancer and chronic liver disease was 5.44%, 3.96%, 3.75% and 3.08%. The PER for fever, cough, sore throat and headache was 79.29%, 56.48%, 11.10%, 8.16%, respectively. The PER for diarrhea, chest pain, fatigue and vomiting was 11.32%, 13.43%, 27.72% and 11.98%, respectively. PEM for hospital stay was 10.9 days (95% CI 7.3- 16.1 days). The PER for hospital mortality was 11.17% (95% CI, 6.67% - 17.89%). Hospital mortality was significantly and positively associated with cardiac comorbidity and COPD. Age and cancer were not associated with higher hospital mortality.

Conclusion: Fever and cough are the most common presenting symptoms with estimated PER of 79.29% and 56.48% respectively. Hospital mortality is significantly and positively associated with cardiac comorbidities, CAD, and COPD, while not being significantly associated with patient age or cancer.

Keywords: COVID-19; Comorbidities; Meta-Analysis; Symptoms; Coronavirus; Mortality

1. Introduction

Beginning in December 2019, pneumonia cases with unknown origin began to arise in Wuhan, Hubei, China. High-throughput sequencing from lower respiratory tract samples has revealed a novel coronavirus that was named 2019 novel coronavirus (2019-nCoV) and also named SARS Coronavirus-2 [1]. The 2019 coronavirus (COVID-19) pandemic has infected more than ten million people and caused more than five hundred thousand deaths (by the end of June 2020) [2]. 2019-nCoV targets the respiratory tract and

shares many similar clinical symptoms with SARSCoV and Middle East respiratory syndrome Coronavirus (MERS) [1]. Common symptoms include fever, fatigue, and dry cough [3-7]. Previous studies have shown a relationship between cardiovascular metabolic diseases, SARS, and MERS [2, 8]. One study provided that 637 MERS-CoV cases showed diabetes and hypertension as prevalent in 50% of patients and cardiac diseases as 30% of cases [2].

Even though our understanding of Covid-19 transmission is consistently growing, it is widely believed that SARS-CoV-2 is transmitted via droplets and close contacts with people carrying the virus [2].

Additionally, it is also reported that the virus transmits

through various surfaces, gastrointestinal transmission [9], and airborne exposures [2, 10]. Although our knowledge of transmission and at-risk populations has significantly increased, our understanding of effective therapeutic interventions has been limited. There are several published studies that describe the epidemiological and clinical characteristics of recovered and mortality cases affected by COVID-19. In this report, we will comprehensively evaluate patient demographics, comorbidities, symptoms, mortality, and length of hospital stay.

2. Methods

2.1 Study design and sample selection

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11] and the PRISMA flow diagram is presented in Supplementary figure 1. A systematic review was performed to identify studies reporting on patients affected with COVID-19. Pubmed, Ovid's version of MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE January 2020 to Present), Ovid EMBASE (January 2020 to present), and The Cochrane Library (Wiley) were searched. Literature search was terminated on April 1st, 2020. The inclusion criteria were adult patients > 18 years, English-language and full-length articles about early outcomes of patients with COVID-19. In addition, references of recent meta-analyses and reviews on this topic were searched for potential additional studies (i.e. backward snowballing). In case of studies from the same or overlapping cohorts reporting different outcomes, the largest series was included for each outcome. Studies with patients <18 years and editorial or reviews were excluded.

2.2 Data Extraction

Studies were independently screened by 2 investigators (S.S. and M.B.). In case of any discrepancy, a consensus was reached with the aid of a third author (M.R.). Microsoft Office 365 Excel software (Microsoft, Redmond, Washington) was used for data extraction. The following variables were included: study demographics as sample size, number of centers, name of center, publication year, and country. Patient demographics and comorbidities variables on age, sex, smoking, diabetes mellitus, hypertension, chronic liver disease, cancer history, coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) and cardiac comorbidity were abstracted. Symptoms presentation variables such as fever, cough, sore throat, headache, diarrhea, chest pain fatigue and vomiting were retrieved (Supplementary Table 1). Continuous variables were reported as mean and standard deviation, while categorical variables were reported as counts and percentages. The quality of the included observational studies was assessed using the Newcastle- Ottawa Quality Assessment Scale (NOS) for cohort studies[12]. The comparison evaluation points were excluded, as the studies were analyzed as single arm. Thus, 6 stars was the highest possible score out of the 9 (Supplementary Table 2).

2.3 Outcomes

The primary outcome was the pooled all-cause short-term mortality. The secondary outcomes were the length of hospital stay and symptom presentation.

2.4 Data synthesis and statistical analysis

This is a single arm meta-analysis. The binary outcomes and continuous outcomes were reported as pooled event rate (PER) and pooled event means (PEM) with 95% confidence interval (CI) respectively were calculated using the generic inverse variance

method with logit transformation and log transformed mean, respectively. The DerSimonian-Laird method was used as between-study estimator [13]. Statistical significance will be set at P <0.05. Heterogeneity will be reported as low (I^2 = 0%-25%), moderate (I^2 = 26%-50%), high (I^2 > 50%), consistent with guidelines [14]. Individual study inference analysis was performed through a "leave-one-out" sensitivity analysis. Publication bias was analyzed by funnel plot visual assessment and Egger regression test. All statistical analyses were performed using "meta" and "metaphor" packages in R (version 3.6.2 R Project for Statistical Computing) within RStudio.

2.5 Meta-regression

Univariable meta-regression was performed to investigate the effect of different collected variables on the primary outcome including age, gender, hypertension, diabetes, COPD, smoking, chronic liver disease, cancer history, coronary artery disease, cardiac comorbidities. Studies were weighted by the inverse of the variance of the estimate for that study, and between-study variance was estimated with DerSimonian-Laird estimator. The results were reported as regression coefficient (i.e., beta).

3. Results

The literature search identified 2735 studies. No additional articles were identified through backward snowballing. 2598 studies were excluded due to title and abstract screening. 137 studies received full text screening. Fifty-six articles met our inclusion criteria with a total of 9074 patients, Supplementary Figure 1. 48 studies were from China, 3 from Korea, 2 from France, 1 from each of USA, Europe and Italy. Female percent range for included studies was 26.8% to 66.6%. The mean age ranged from 29.2 to 77 in included studies.

3.1 Meta-analysis

The PER for hospital mortality was 11.17% (95% CI, 6.67% - 17.89%), Figure 1. Among the analyzed studies, high heterogeneity (I^2 = 94%) was detected. Visual inspection of the funnel plot and Egger test did not reveal significant asymmetry for hospital mortality (Egger test p-value = 0.1308). The leave-one-out analysis is depicted in Supplementary Figure 2. Patients characteristics were as follows: the PEM for age was 49.6 years (95% CI 46.8-52.6); the PER for female gender was 46.79% (95% CI 44.48% - 49.11%); the PER for smoking was 10.96% (95% CI 7.35% - 16.02%); the PER for hypertension was 24.47% (95% CI 19.85% - 29.77%); the PER cardiac comorbidities was 20.30% (95% CI 9.43% - 38.40%); the PER for diabetes was 12.34% (95% CI 9.96% - 15.20%); the PER for CADwas 5.44% (95% CI 3.50% - 8.38%); the PER for COPD was 3.96% (95% CI 2.09% - 6.42%); the PER for history of cancer was 3.75% (95% CI 2.17% - 6.41%) and the PER for chronic liver disease was 3.08% (95% CI was 2.12% - 4.47%).

Patients characteristics are summarized in Supplementary Table 3 (forest plots can be seen in the Appendix Supplementary figures 3-6). As far as presenting symptoms concern, the PER for fever 79.29% (95% CI 73.56 – 84.04%); the PER for cough was 56.48% (95% CI 50.63% – 62.15%); the PER for sore throat was 11.10% (95% CI 6.94% - 17-28%); the PER for headache was 8.16% (95% CI 6.60% – 10.05%); the PER for diarrhea was 11.32% (95% CI 5.37% - 22.34%); the PER for chest pain was 13.43% (95% CI 7.58% - 22.70%); the PER for fatigue was 27.72% (95% CI 21.97% - 34.32%); the PER for vomiting was 11.98% (95% CI 2.87% - 38.54%) and the PEM for LOS was 10.9 days (95% CI 7.3 – 16.1 days). Symptom presentations are

summarized in Table 1, Figure 1 and Supplementary Figures 7-10.

3.2 Meta-regression

Hospital mortality was significantly and positively associated with cardiac comorbidity (Beta=0.0981, p=0.0009), coronary artery disease (Beta =0.0806, p=0.0270) and COPD (Beta =0.4581, p=0.0218). Age and cancer history were not associated with higher hospital mortality. See Figure 2 for bubble-plots and Table 2 for details.

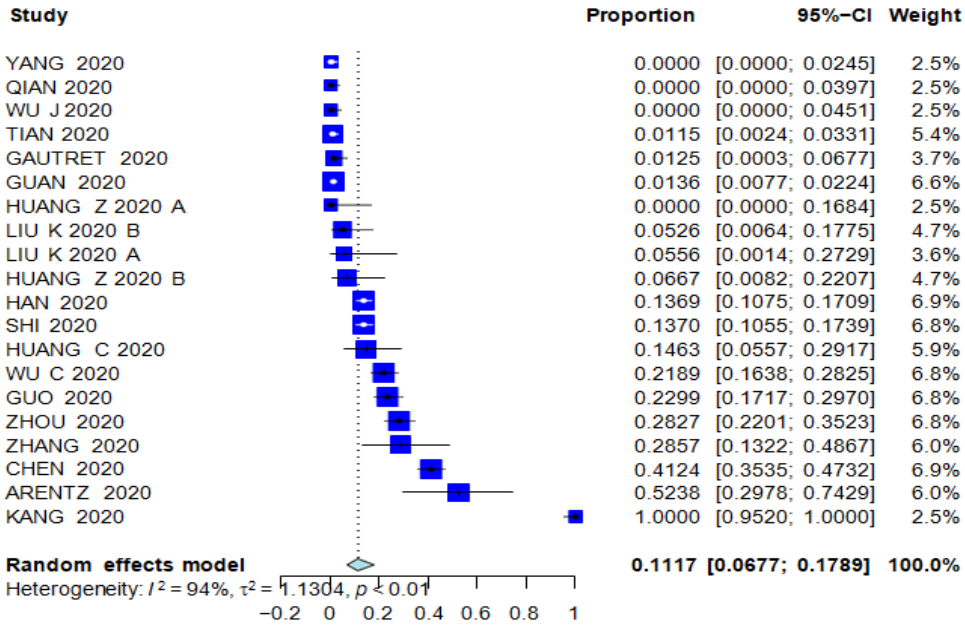

Figure 1: Forest Plot of hospital mortality.

Outcome	N. of Studies	Effect	95% CI	Heterogeneity (I^2, p-value)
Fever	41	79.29%	73.56% - 84.04%	94.1%, p<0.0001
Cough	43	56.48%	50.63% - 62.15%	93.5%, p<0.0001
Sore Throat	18	11.10%	6.94% - 17.28%	96.0%, p<0.0001
Headache	20	8.16%	6.60% - 10.05%	71.2%, p<0.0001
Diarrhea	28	11.32%	5.37% - 22.34%	97.3%, p<0.0001
Chest pain	7	13.43%	7.58% - 22.70%	78.8%, p<0.0001
Fatigue	25	27.72%	21.97% - 34.32%	92.2%, p<0.0001
Vomiting	13	11.98%	2.87% - 38.54%	98.2%, p<0.0001
Hospital mortality	20	11.17%	6.77% - 17.89%	94.3%, p<0.0001
Length of hospital stay	3	10.9 days	7.36 – 16.19 days	99.1%, p<0.0001

Table 1: Meta-analysis outcomes summary.

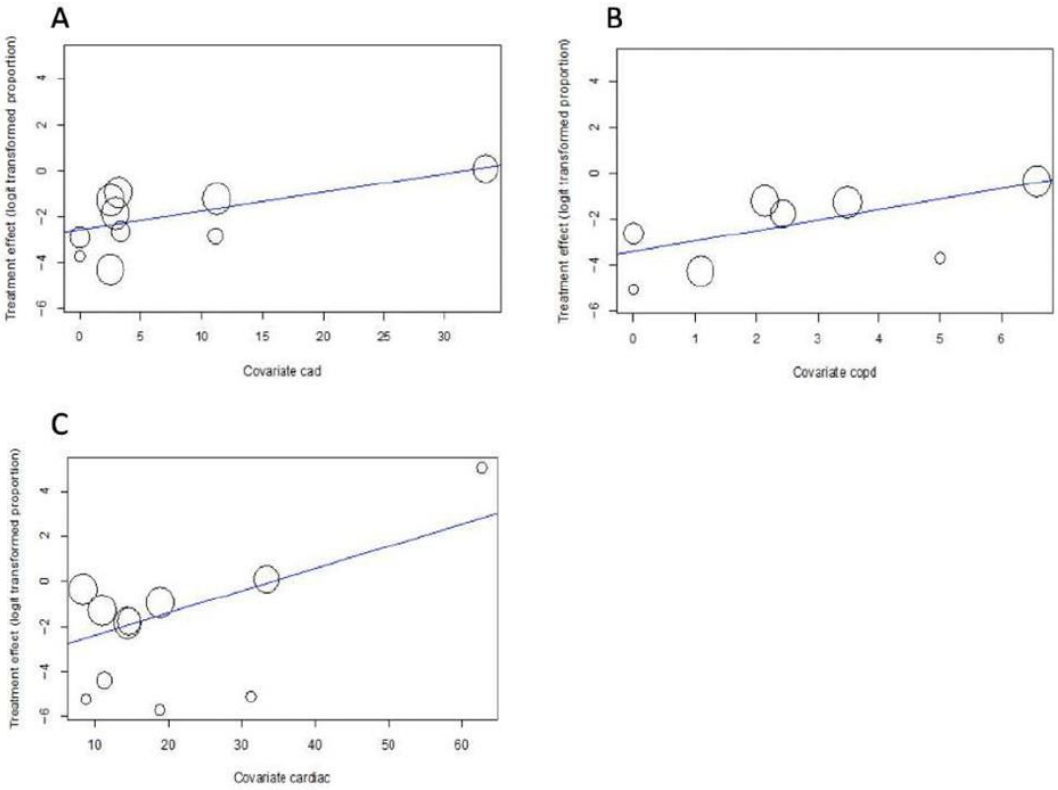

Figure 2: Meta-regression of cardiac comorbidity, CAD and COPD for hospital mortality bubble plot Figure A) Coronary Artery Disease (CAD), B) Chronic Obstructive Pulmonary Disease (COPD), C) Cardiac comorbidities on hospital mortality. Hospital mortality is significantly and positively associated with CAD (Beta=0.0806, p=0.0270), COPD (Beta =0.4581, p=0.0218) and cardiac comorbidity (Beta =0.0981, p=0.0009).

Outcome	No. of Studies	Hospital mortality (β ± SE, p-value)
Age	18	0.0038 ± 0.0136, 0.2770
Female gender	14	-0.0538 ± 0.0299, 0.0716
Smoking	11	-0.0164 ± 0.0331, 0.6207
Diabetes	12	-0.0064 ± 0.0148, 0.6638
Hypertension	10	-0.0017 ± 0.0160, 0.9136
Cardiac comorbidity	11	0.0981 ± 0.0294, 0.0009
CAD	10	0.0806 ± 0.0364, 0.0270
COPD	8	0.4581 ± 0.1997, 0.0218
Chronic liver disease	7	-0.0551 ± 0.1204, 0.6475
History of cancer	6	0.0170 ± 0.0236, 0.4715

CAD = Coronary Artery Disease; COPD = Chronic Obstructive Pulmonary Disease

Table 2: Meta-regression of different variables on hospital mortality.

4. Discussion

In this meta-analysis, we examined 56 studies with a total of 9,074 patients. This comprehensive analysis focused on numerous morbidities such as hypertension, cardiac comorbidities, COPD, coronary artery disease, diabetes, cancer, and chronic liver disease. The symptoms that were analyzed include fever, cough, sore throat, headache, diarrhea, chest pain, fatigue, and vomiting. Hospital mortality and length of stay were also analyzed. This meta-analysis indicated that the PER for hospital mortality was 11.17% (95% CI, 6.67% - 17.89%) which lies in the previously reported range of mortality rate, which is roughly 2.12%-18.9% [15-18]. Our analysis identified the most significant comorbidities being hypertension with PER of 24.47% (95% CI 19.85% - 29.77%), cardiac comorbidities which had a PER of 20.30% (95% CI 9.43% - 38.40%), and diabetes which had a PER of 12.34% (95% CI 9.96% - 15.20%). These results run parallel to previously conducted meta-analyses, which reported hypertension prevalence of about 20% and diabetes of about 10% [19]. A higher mortality rate of 11.17% can be attributed to a higher prevalence of significant comorbidities in our included studies. The most statistically significant presenting symptoms include fever and cough. Fever had a PER of 79.29% (95% CI 73.56 – 84.04%); while cough had a PER of 56.48% (95% CI 50.63% – 62.15%). Our results confirm that symptoms of fever and persistent cough are the most prevalent symptoms of COVID-19 worldwide [20].

Interestingly, the conducted meta-regression indicates that hospital mortality is significantly and positively associated with cardiac comorbidity (b=0.0981, p=0.0009), CAD (b=0.0806, p=0.0270), and COPD (b=0.4581, p=0.0218), but not with age. Based on this meta-regression, age is not significantly associated with hospital mortality, which opposes the current belief that is propagated in the medical community and media outlets. Recent studies portray that patients who are elderly carry a more significant risk factor for COVID-19 related mortality [18]. Against what we initially thought, in this meta-analysis, cancer did not affect overall mortality estimate. Immunocompromised patients tend to not respond normally to an infection due to an impaired or weakened immune system[21]. The inability to combat infection is attributed to numerous conditions including underlying disease (malignancy, organ or stem cell transplantation, systemic vasculitis, connective tissues diseases, etc.), associated conditions (diabetes, malnutrition, etc.) or drug-related immune suppression [21].

Up to our knowledge and compared to other meta-analysis conducted, this is the first meta-analysis to involve a meta-regression of numerous comorbidities effect on hospital mortality. Our results run in parallel with prior meta-analyses conducted, which link poor Covid-19 outcome with specific comorbidities. Our study is unique in that through a meta-regression we are able to add another dimension to statistical Covid-19 analysis, which depicted that hospital mortality was significantly and positively associated with cardiac comorbidity, CAD and COPD, while not being associated with patient age or cancer history. Other studies show that hypertension has a composite of poor outcome, comprising of mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care and disease progression [22]. Also, diabetes had a composite poor outcome, including mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care unit (ICU) care, and disease progression [23]. Yet, our study did not attribute higher incidence of mortality to these comorbidities. Another meta-regression showed that cardiovascular disease was

associated with increased composite poor outcome, which our analysis agrees with [24].

This meta-analysis should aid policymakers by providing insight that age might not be the most significant factor in COVID-19 mortality. It is important to educate the public, which mostly believes that age is the sole factor driving Covid-19 deaths. With a potential second wave on the rise in the United States, many citizens are beginning to exercise less caution in social distancing protocols. We believe this is dangerous because many of those people may have significant comorbidities that could place them in a zone of tremendous risk - without being aware of it. Based on the evidence, it is important that policymakers provide strict guidance to the groups that are at increased risk for severe COVID-19 [19]. As previous meta-analyses have concluded, results from published work should aid in group selection for ongoing clinical trials, and inform policymakers as to which groups should be prioritized if a vaccination becomes available [19]. The increased mortality of COVID-19 in hypertension, cardiac comorbidities, and diabetes patient groups should direct future preventative therapies and vaccination programs for these particular groups while maintaining mitigating prevention strategies [19].

5. Conclusion

Fever and cough are the most common presenting symptoms with estimated PER of 79.29% and 56.48% respectively. Hospital mortality is significantly and positively associated with cardiac comorbidities, CAD, and COPD, while not being significantly associated with patient age or cancer.

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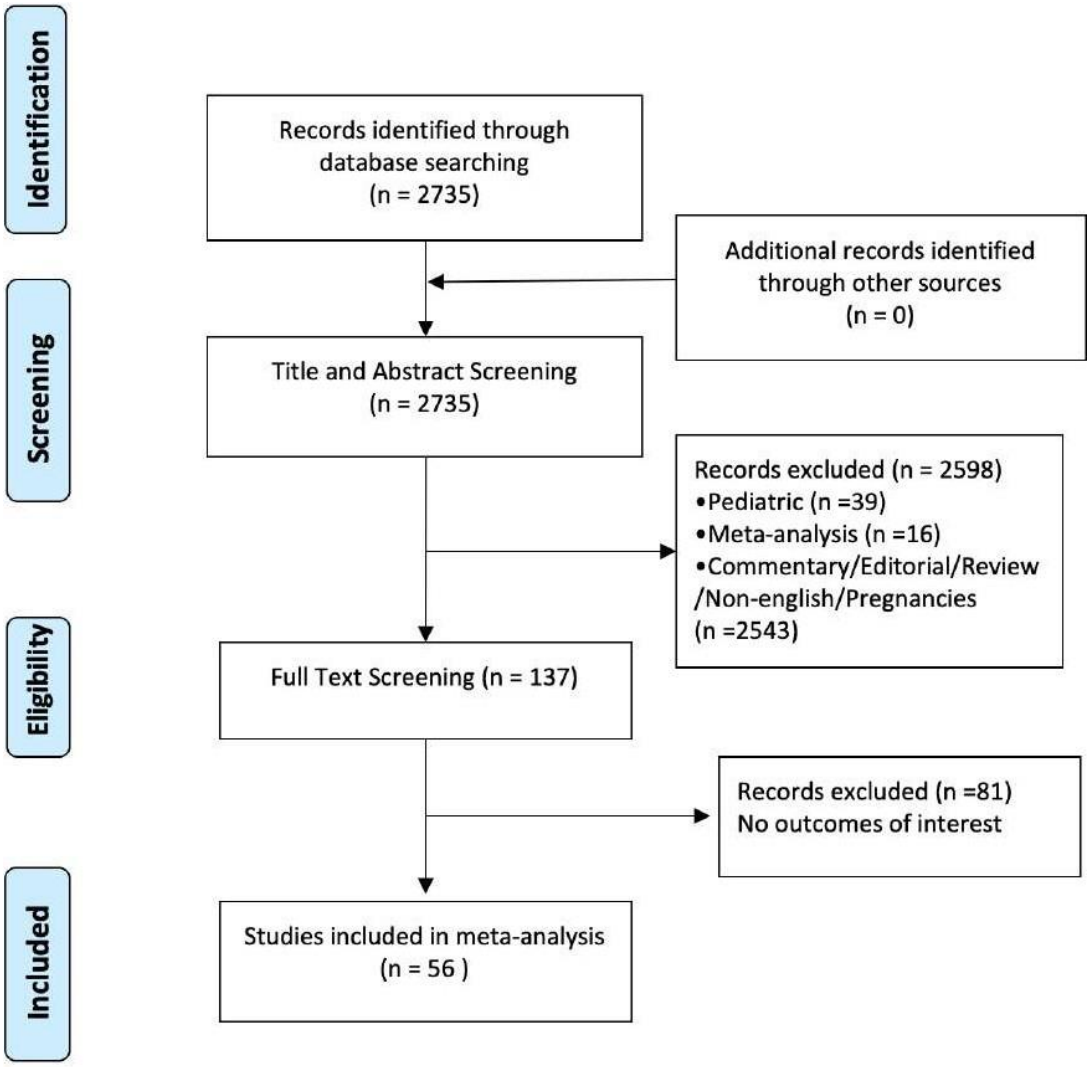


Supplementary Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Author	Nation	Institution	Patients	Age	Female	Smoking	Hypertension	Cardiac	Diabetes	CAD	COPD	Chronic liver disease
JIANG 2020 [25]	China	Taizhou Hospital of Zhejiang Province	60	41	25	7	5	NR	1	NR	1	2
HUANG Z 2020 [26]	China	Zhongshan Hospital, Shanghai	20 Group A	52.65+-13.12	10	NR	20	NR	0	0	1	NR
HUANG Z 2020 [26]	China	Zhongshan Hospital, Shanghai	30 Group B	67.7+-12.84	13	NR	30	NR	4	1	0	NR
LIU K 2020 [27]	China	Hainan General Hospital	36 Group A	69.4 +-8	12	NR	10	NR	NR	NR	NR	NR
LIU K 2020 [27]	China	Hainan General Hospital	36 Group B	68.9+-7.6	11	NR	8	NR	NR	NR	NR	NR
COLANERI 2020 [28]	Italy	IRCCS San Matteo, Pavia	44	NR	16	NR	15	NR	7	11	lung disease 2	NR
YAN 2020 [29]	China	Tongji Hospital	193	64 (49 to 73)	79	NR	73	NR	48	NR	14	1
HAN 2020 [30]	China	Sir Run Run Shaw Hospital	482	48 (37-56)	228	NR	NR	NR	NR	NR	NR	NR
JEONG 2020 [31]	Korea	National report death	66	77 (35-93)	29	NR	30	NR	23	NR	11 pulmonary	NR
WANG L 2020 [32]	China	The First Affiliated Hospital of Zhengzhou University	18	39 (29-55)	8	NR	5	NR	3	NR	NR	NR
WANG R 2020 [33]	China	Zhongnan Hospital	5	57.6 (+-7.42)	2	NR	NR	NR	1	NR	NR	NR
KANG 2020 [34]	Korea	National report death	75	NR	NR	NR	NR	47	35 endocrine	NR	18 respiratory	NR
KSID 2020 [35]	Korea	National report death	54	75.5 (66-80, 35-93)	21	NR	NR	32	16	NR	NR	NR
CHU 2020 [36]	China	Tongji Hospital	54	39 (26-73)	18	NR	NR	NR	NR	NR	NR	NR
LESCURE 2020 [37]	France	Bichat-Claude Bernard University Hospital and Pellegrin University Hospital	5	46	2	NR	1	NR	NR	NR	NR	NR
GUO 2020 [38]	China	Seventh Hospital of Wuhan City	187	58.5+-14.66	96	18	61	NR	28	21	4	NR
LIU K 2020 [39]	China	Hainan Provincial People's Hospital	18 Group A	68 (66.25-69.75)	6	8	5	NR	3	2	NR	NR
LIU K 2020 [39]	China	Hainan Provincial People's Hospital	38 Group B	47 (35.75-51.25)	19	14	5	NR	1	0	NR	NR

ZHANG 2020 [40]	China	Tongji Sino-French New To-wn Hospital, Union Red Cross Hospital, Union West Hospital	28	65 (56.0-70.0)	11	NR	NR	NR	4	NR	NR	2
CHEN 2020 [41]	China	Tongji Hospital	274	62.0 (44-70)	103	19	93	23	47	NR	18	NR
LIAN 2020 [42]	China	Zhejiang Province Hospitals	Group A 652	41.15+-11.38	303	46	73	NR	33	NR	0	25
LIAN 2020 [42]	China	Zhejiang Province Hospitals	Group B 136	68.28+-7.31	78	8	53	NR	24	NR	3	6
SHI 2020 [43]	China	Renmin Hospital of Wuhan University	416	64 (21-95)	211	NR	127	NR	60	44	12	NR
SUN 2020 [44]	China	National Centre for Infectious Diseases, Singapore	788	34 median	407	NR	NR	NR	54	NR	10	3
JIN 2020 [45]	China	Zhejiang Province Hospitals	GROUP A 74	46.14+-14.19	37	3	12	NR	7	1	0	8
JIN 2020 [45]	China	Zhejiang Province Hospitals	GROUP B 577	45.09+-14.45	283	38	88	NR	41	4	1	17
DENG 2020 [46]	China	Tongji Hospital and Central Hospital of Wuhan	GROUP A 109	69 (62,74)	36	NR	40	NR	NR	13	NR	NR
DENG 2020 [46]	China	Tongji Hospital and Central Hospital of Wuhan	GROUP B 116	40 (33,57)	65	NR	18	NR	NR	4	NR	NR
DING 2020 [47]	China	Tongji Hospital	5	50.2 +_8.80	3	NR	2	1	0	NR	NR	NR
YE 2020 [48]	China	Zhongnan Hospital	5	32.4+-5.08	3	NR	NR	NR	NR	NR	NR	NR
ARENTZ 2020 [49]	USA	Evergreen Hospital, Washington	21	NR	NR	NR	NR	NR	7	NR	7	NR
CHEN 2020 [50]	China	Shanghai Public Health Clinical Center	249	51 (36-64)	123	NR	NR	55	25	NR	NR	NR
GAO 2020 [51]	China	Fuyang Second People's Hospital	GROUP A 15	45.2+-7.68	6	NR	13	3	7	NR	8	NR
GAO 2020 [51]	China	Fuyang Second People's Hospital	GROUP B 28	42.96+-14	11	NR	6	1	6	NR	3	NR
QIAN 2020 [52]	China	Zhejiang Province Hospitals	91	50 (36.6-57)	54	NR	15	3	8	NR	NR	NR
HAN 2020 [53]	China	Wuhan No. 1 Hospital	108	45 (21-90)	70	NR	NR	NR	NR	NR	NR	NR
WANG Z 2020 [54]	China	Union Hospital	69	42 (35.0-62.0)	37	NR	9	8	7	NR	4	NR

XU 2020 [55]	China	Third Hospital of Changzhou	Group A 15	35 (29.0-51.0)	5	NR	NR	0	0	NR	NR	0
XU 2020 [55]	China	Third Hospital of Changzhou	Group B 17	37 (24.0-47.5)	10	NR	NR	2	1	NR	NR	0
XU 2020 [55]	China	Third Hospital of Changzhou	Group C 19	53.0 (35.0-65.0)	11	NR	NR	3	3	NR	NR	1
CHENG Z 2020 [56]	China	Ruijin Hospital, Shanghai	11	50.36+-15.50	3	NR	NR	NR	NR	NR	NR	NR
WU C 2020 [57]	China	Wuhan Jinyintan Hospital	201	51 (43-60)	73	NR	39	8	22	NR	5	7
ZHU 2020 [58]	China	First Affiliated Hospital of USTC, Hubei	32	46 (35-52)	17	6	7	NR	4	2	6	2
LIU KC 2020 [59]	China	6 hospitals in Anhui province	Group A 6	29.2+-10.9	3	NR	NR	NR	NR	NR	NR	NR
LIU KC 2020 [59]	China	6 hospitals in Anhui province	Group B 43	33.4+-12.2	15	NR	NR	NR	NR	NR	NR	NR
LIU KC 2020 [59]	China	6 hospitals in Anhui province	Group C 21	44.2+-12.0	11	NR	NR	NR	NR	NR	NR	NR
LIU KC 2020 [59]	China	6 hospitals in Anhui province	Group D 3	63+-21.2	3	NR	NR	NR	NR	NR	NR	NR
CHEN Q 2020 [60]	China	The First Affiliated Hospital of Wanan Medical College	9	42.11+-14.43	4	NR	NR	NR	NR	NR	NR	NR
ZHOU 2020 [61]	China	Jinyintan Hospital and Wuh-an Pulmonary Hospital	191	56.0 (46.0-67.0)	72	11	58	NR	36	15	6	NR
HU 2020 [62]	China	the Second Hospital of Nanjing	24	32.5 (19.0-57.0)	16	2	2	NR	2	1	NR	NR
RUAN 2020 [63]	China	Jin Yin-tan Hospital and Tongji Hospital	Group A 68	67	19	NR	29	13	12	NR	2	NR
RUAN 2020 [63]	China	Jin Yin-tan Hospital and Tongji Hospital	Group B 82	50 (44-81)	29	NR	23	0	13	NR	1	NR
GAUTRET 2020 [64]	France	University Hospital Institute Méditerranée Infection	80	52.5 (42-62)	37	NR	13	NR	9	6	NR	NR
ZHENG 2020 [65]	China	The First Hospital of Changsha	161	45 (33.5,57)	81	NR	22	NR	7	4	6	4
SPITERI 2020 [66]	Europe	Multicenter	38	NR	13	NR	NR	NR	NR	NR	NR	NR
WU J 2020 [67]	China	First People's Hospital of Yancheng City, the Second People's Hospital of Yancheng City, and the Fifth People's Hospital of Wuxi	80	46.1+-15.42	41	NR	NR	NR	NR	NR	0	1
GUAN	China	National report	1099	47 (35.0-	459	158	165	NR	81	27	12	NR

2020 [68]				58.0)								
XU X 2020 [69]	China	Guangzhou Eighth People's Hospital	90	50 (18-86)	51	NR	17	3	5	NR	1	NR
HUANG Y 2020 [70]	China	Zhongnan Hospital of Wuhan University	34	56.24+-17.14	20	NR	8	6	4	NR	1	1
TIAN 2020 [71]	China	hospitals of Beijing	262	47.5	135	NR	NR	NR	NR	NR	NR	NR
YANG 2020 [72]	China	Wenzhou central hospital, Ruian people's hospital and Yueqing people's hospital	149	45.11+-13.35	68	NR	NR	28	9 endocrine	NR	NR	NR
XU YH 2020 [73]	China	The Fifth Medical Center of Chinese PLA General Hospital, Affiliated Hospital of Hebei University	59	NR	21	NR	NR	NR	NR	NR	NR	NR
SHI 2020 [74]	China	Wuhan Jinyintan hospital or Union Hospital of Tongji Medical College	81	49.5+-11	39	NR	12	8	10	NR	NR	NR
YANG 2020 [75]	China	Wuhan Jin Yin-tan hospital	52	59.7+-13.3	17	0	NR	7	9	5	4	NR
QIN 2020 [76]	China	Union Hospital, Tongji Medical College	4	55.5+-4.72	2	NR	NR	NR	NR	NR	NR	NR
ZHANG J 2020 [77]	China	No. 7 Hospital of Wuhan	140	57 (25-87)	69	9	42	NR	17	7	2	8
CHEN 2020 [5]	China	Jinyintan Hospital in Wuhan	99	55.5+-13.1	32	NR	NR	40	NR	NR	NR	NR
HUANG C 2020 [3]	China	Multicenter	41	49(41.0-58.0)	11	3	6	6	8	NR	1	1
ZHANG [78] 2020	China	Zhejiang Province Hospitals	Group A 72	34.9	39	68	68	72	68	NR	72	70
ZHANG [78] 2020	China	Zhejiang Province Hospitals	Group B 573	46.65	278	536	477	477	529	NR	572	550

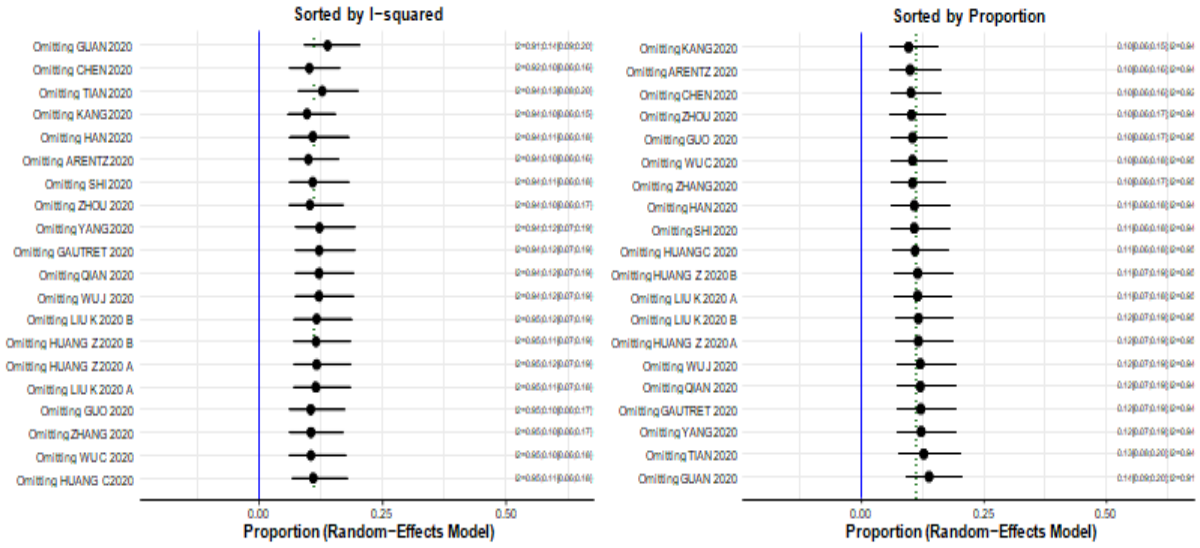
CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, NR: Not Reported

Supplementary Table 1: Patient demographic data.

Study	Selection	Outcome	Total
JIANG 2020 [25]	***	***	******
HUANG Z 2020 [26]	***	***	******
LIU K 2020 [27]	***	***	******
COLANERI 2020 [28]	***	***	******
YAN 2020 [29]	***	***	******
HAN 2020 [30]	***	***	******
JEONG 2020 [31]	***	***	******
WANG L 2020 [32]	***	***	******
WANG R 2020 [33]	***	***	******
KANG 2020 [34]	***	***	******
KSID 2020 [35]	***	***	******
CHU 2020 [36]	***	***	******
LESCURE 2020 [37]	***	***	******
GUO 2020 [38]	***	***	******
LIU K 2020 [39]	***	***	******
ZHANG 2020 [40]	***	***	******
CHEN 2020 [41]	***	***	******
LIAN 2020 [42]	***	***	******
SHI 2020 [43]	***	***	******
SUN 2020 [44]	***	***	******
JIN 2020 [45]	***	***	******
DENG 2020 [46]	***	***	******
DING 2020 [47]	***	***	******
YE 2020 [48]	***	***	******
ARENTZ 2020 [49]	***	***	******
CHEN 2020 [50]	***	***	******
GAO 2020 [51]	***	***	******
QIAN 2020 [52]	***	***	******
HAN 2020 [53]	***	***	******
WANG Z 2020 [54]	***	***	******
XU 2020 [55]	***	***	******
CHENG Z 2020 [56]	***	***	******
WU C 2020 [57]	***	***	******
ZHU 2020 [58]	***	***	******
LIU KC 2020 [59]	***	***	******
CHEN Q 2020 [60]	***	***	******
ZHOU 2020 [61]	***	***	******
HU 2020 [62]	***	***	******
RUAN 2020 [63]	***	***	******

GAUTRET 2020 [64]	***	***	******
ZHENG 2020 [65]	***	***	******
SPITERI 2020 [66]	***	***	******
WU J 2020 [67]	***	***	******
GUAN 2020 [68]	***	***	******
XU X 2020 [69]	***	***	******

Supplementary Table 2: The Newcastle-Ottawa Quality Assessment Scale of included studies.

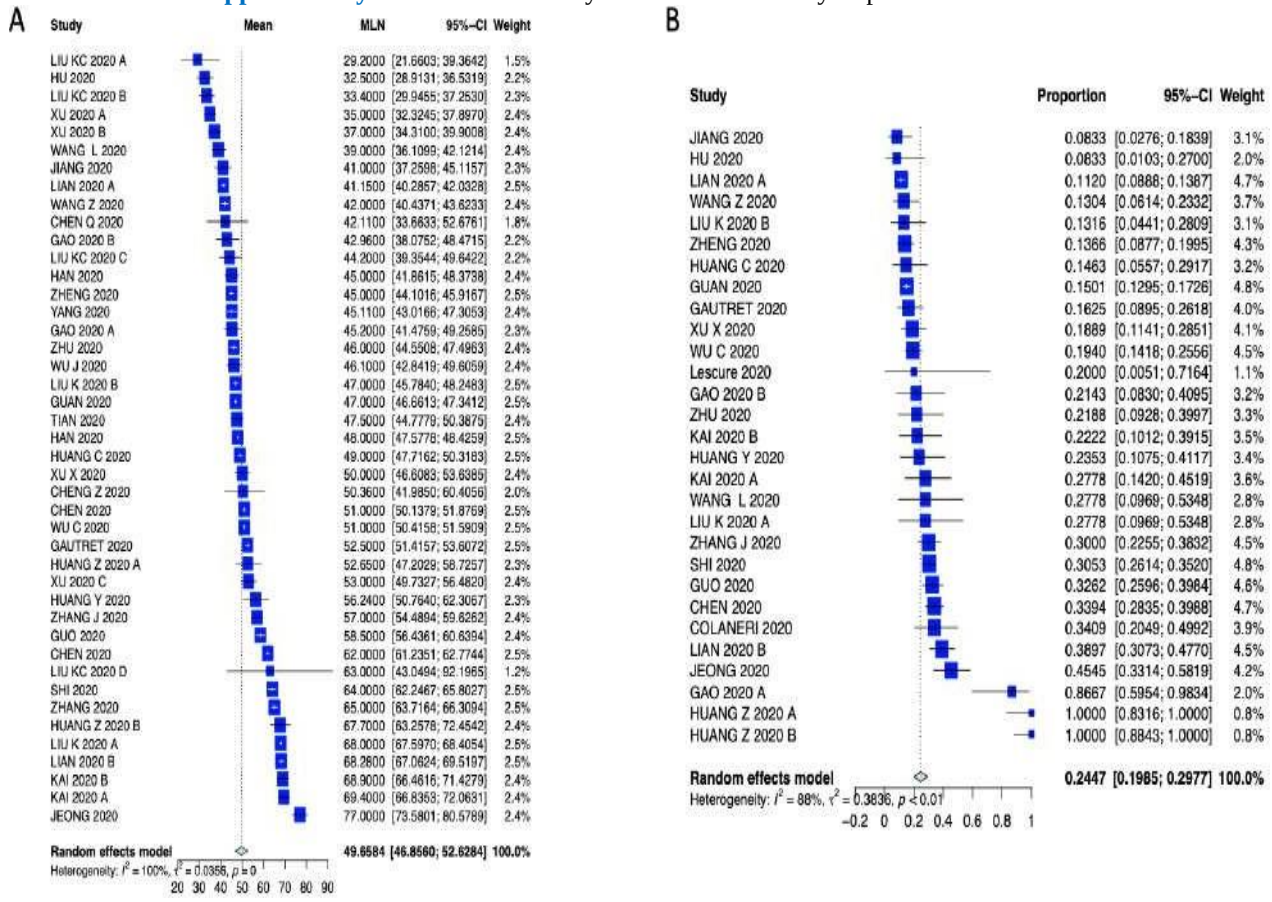


Supplementary Figure 2: Leave-one-out analysis.

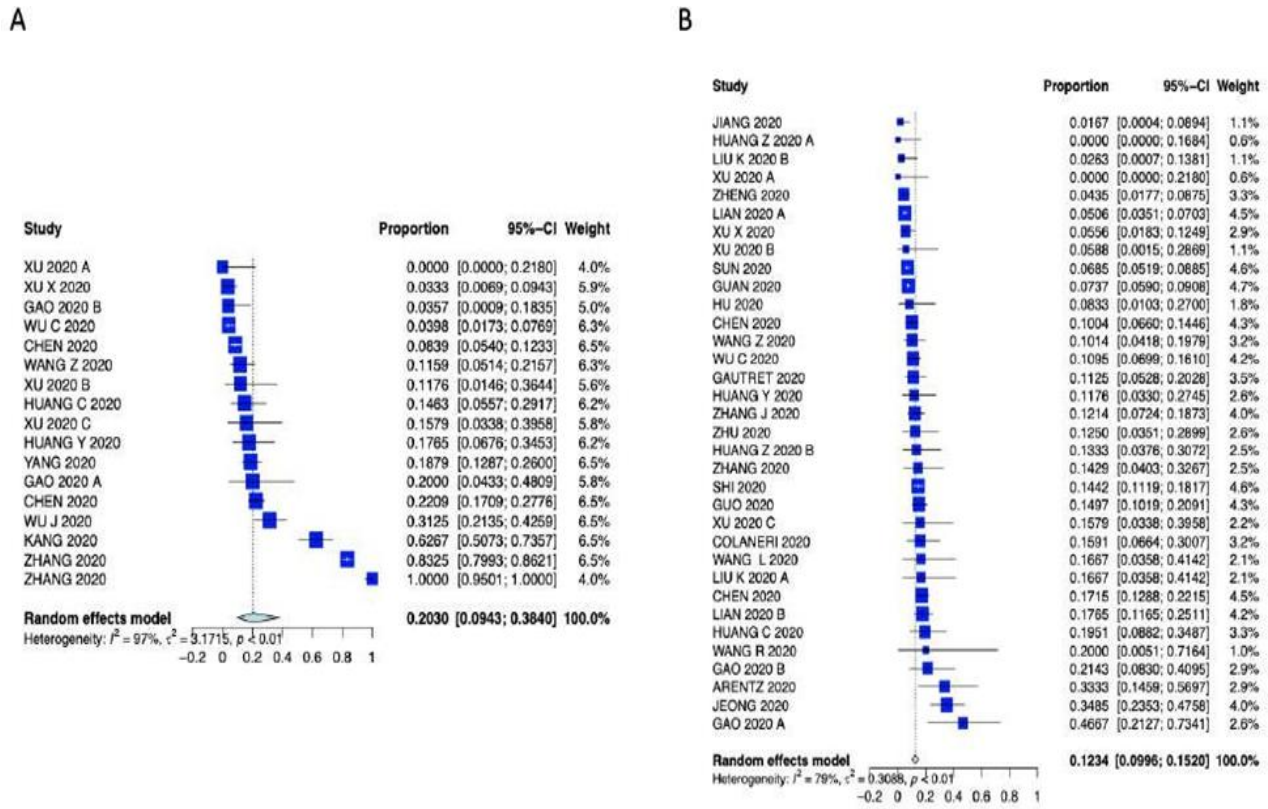
Outcome	**N. of Studies**	**Effect**	**95% CI**	**Heterogeneity: I^2, p-value**
Age	43	49.65 yrs	46.85 – 52.62 yrs	99.7%, p=0
Female gender	50	46.79%	44.48% - 49.11%	56.6%, p<0.0001
Smoking	12	10.96%	7.35% - 16.02%	82.0%, p<0.0001
Hypertension	29	24.47%	19.85% - 29.77%	88.4%, p<0.0001
Cardiac comorbidity	17	20.30%	9.43% - 38.40%	97.5%, p<0.0001
Diabetes	34	12.34%	9.96% - 15.20%	79.1%, p<0.0001
CAD	18	5.44%	3.50% - 8.38%	83.6%, p<0.0001
COPD	22	3.69%	2.09% - 6.42%	85.8%, p<0.0001
Liver disease	16	3.08%	2.12% - 4.47%	40.2%, p=0.0488
History of cancer	21	3.75%	2.17% - 6.41%	84.0%, p<0.0001

CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease; yrs = years

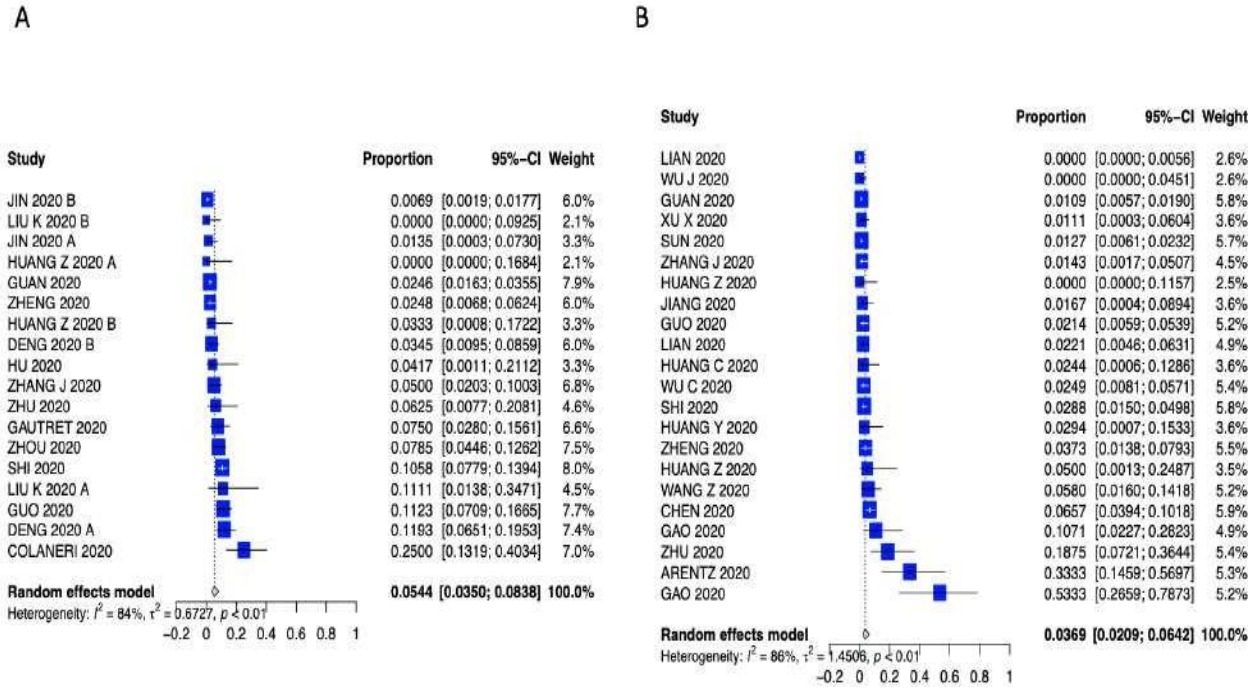
Supplementary Table 3: Meta-analysis outcome summary of patient characteristics.



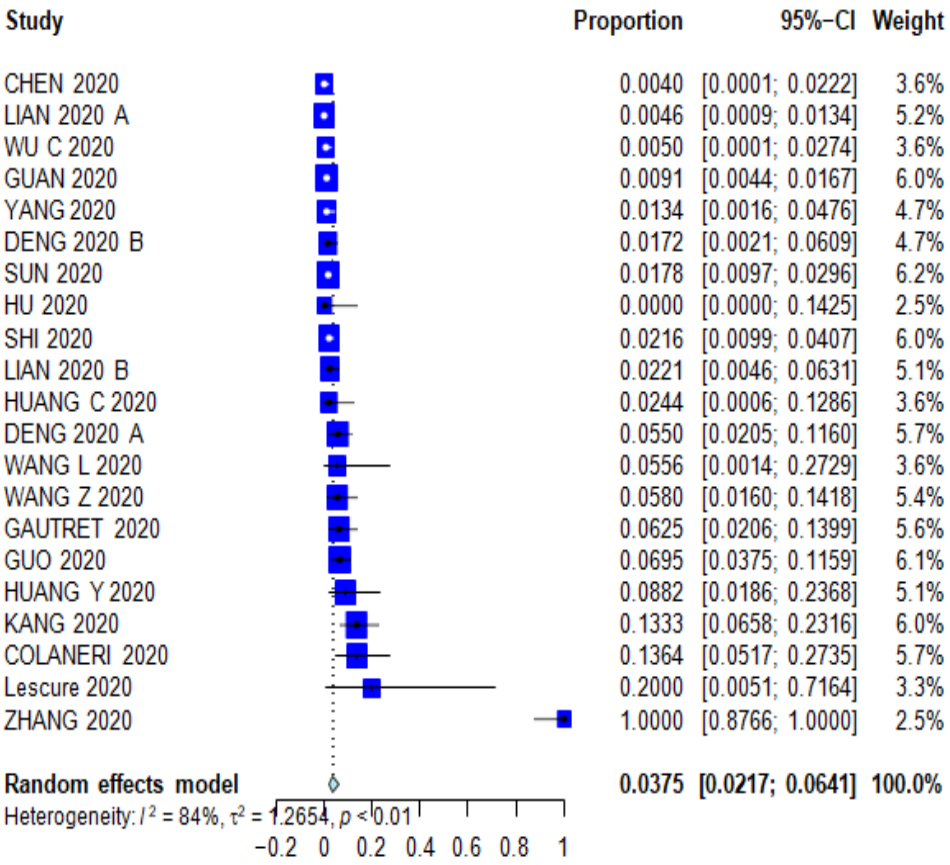
Supplementary Figure 3: Forest plot for A) Age and B) Hypertension.



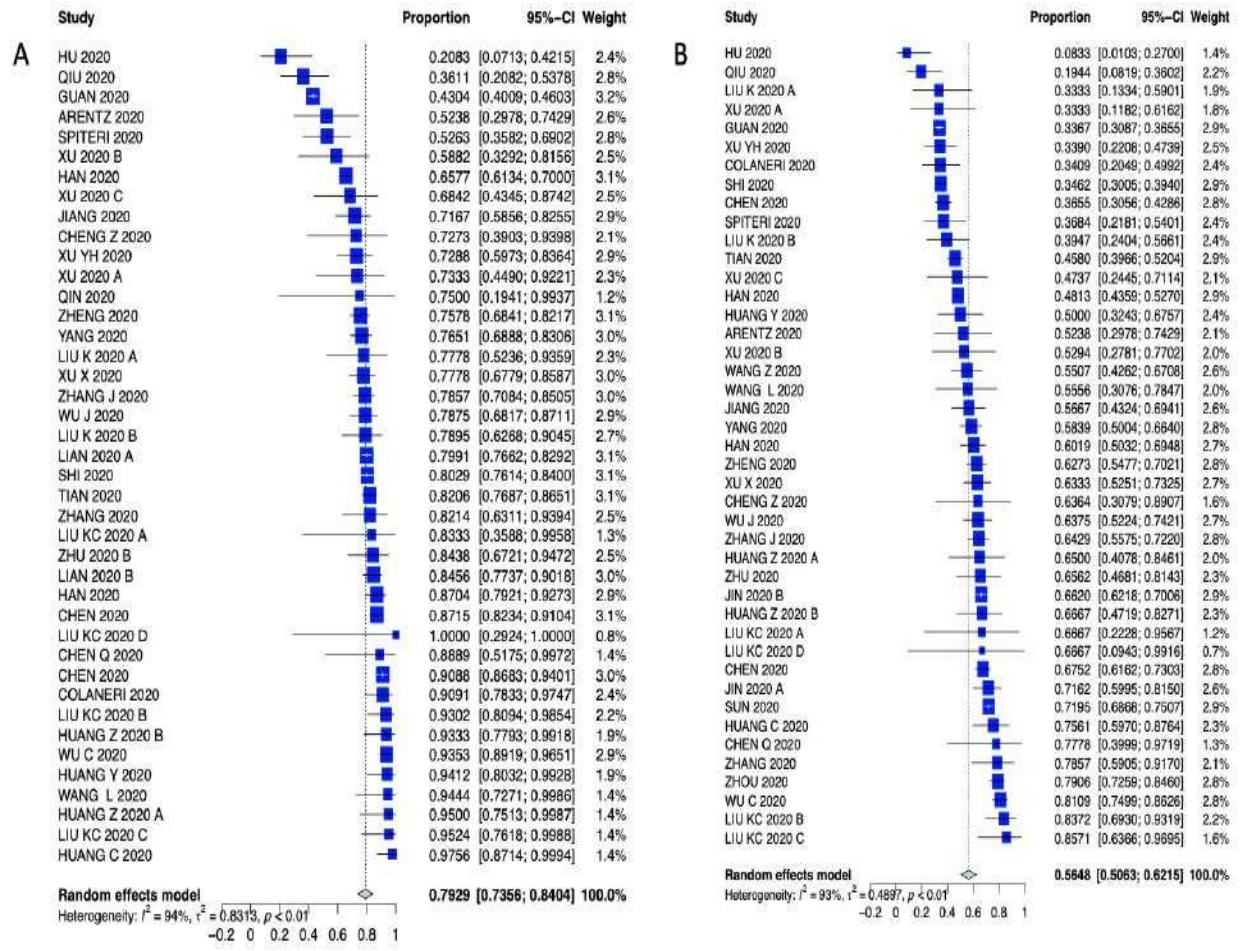
Supplementary Figure 4: Forest plot for A) Cardiac comorbidity and B) Diabetes.



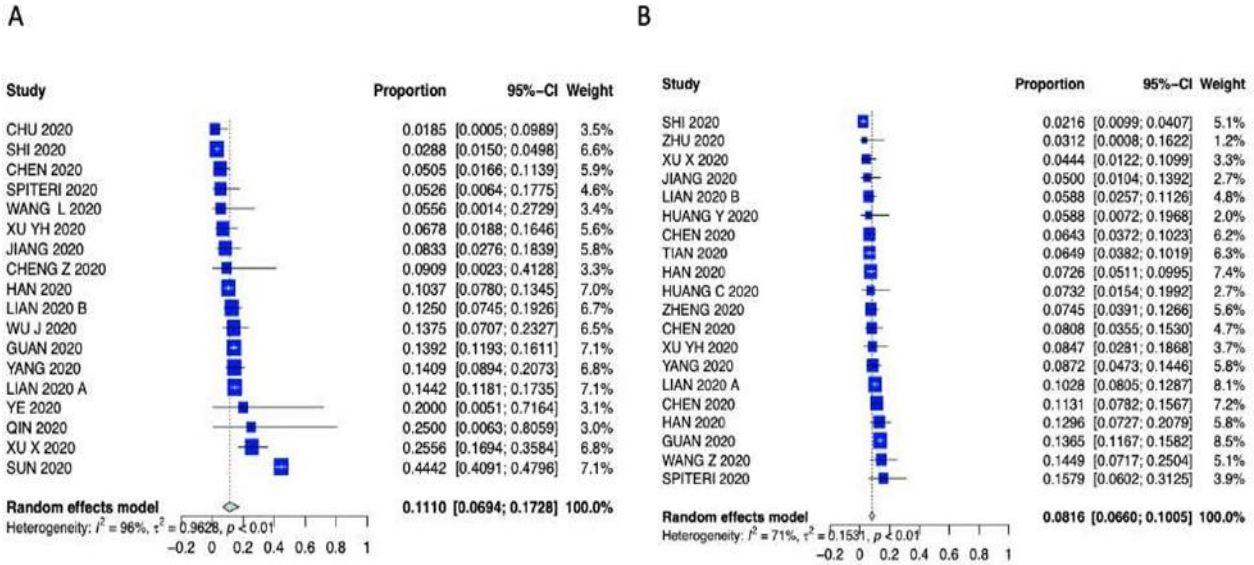
Supplementary Figure 5: Forest plot for A) Coronary Artery Disease and B) Chronic Obstructive Pulmonary Disease.



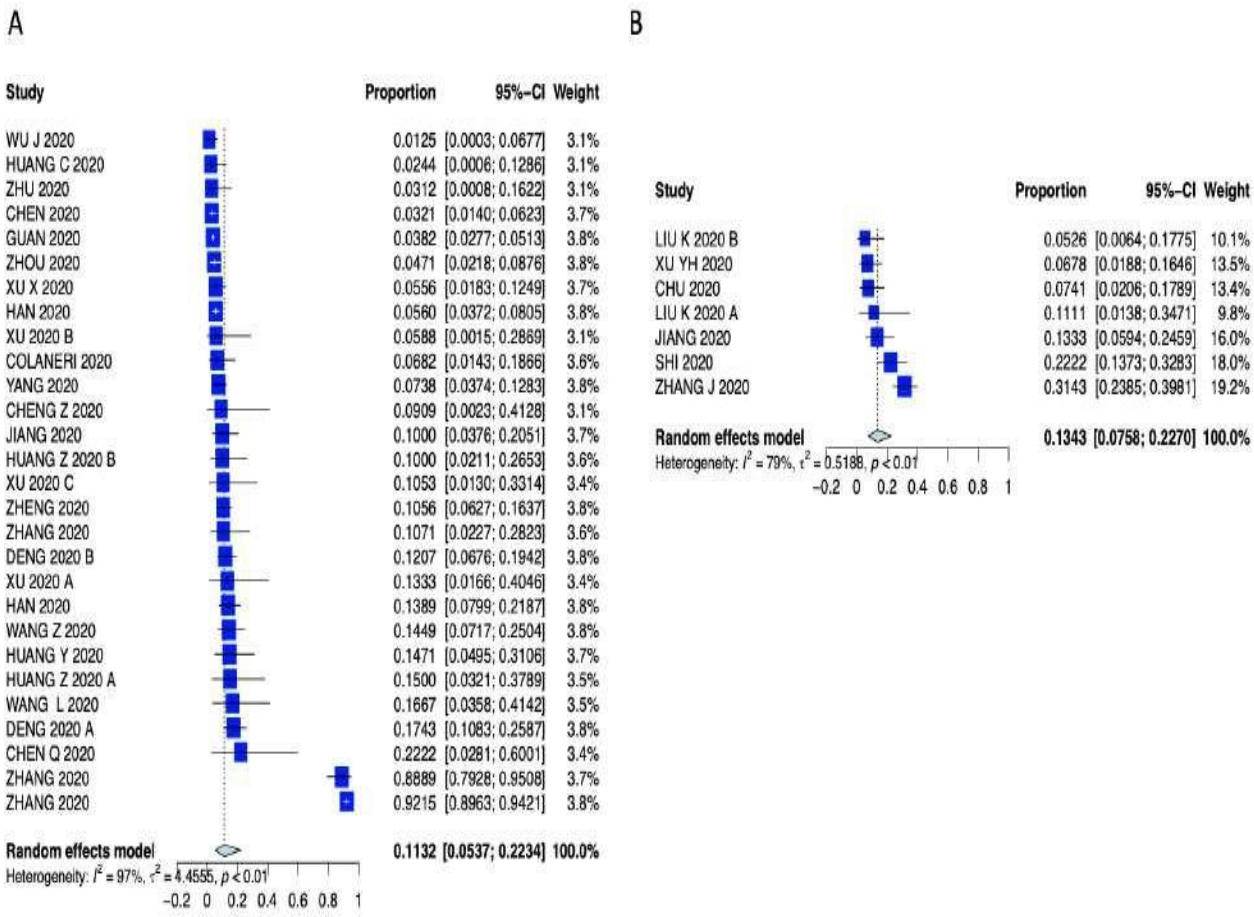
Supplementary Figure 6: Forest plot for History of Cancer.



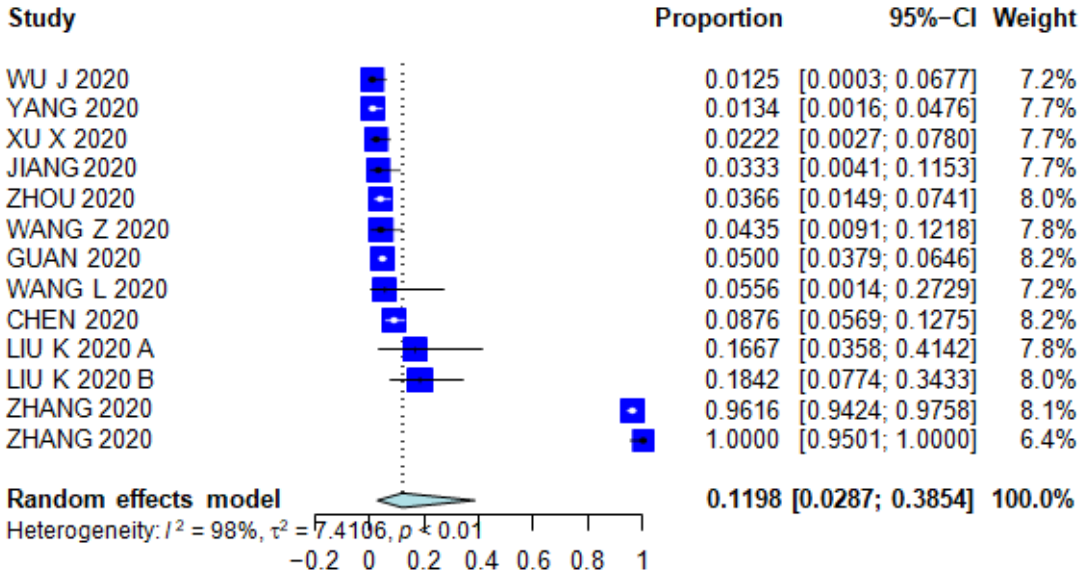
Supplementary Figure 7: Forest plot of A) Fever and B) Cough.



Supplementary Figure 8: Forest plot of A) Sore throat and B) Headache.



Supplementary Figure 9: Forest plot of A) Diarrhea and B) Chest Pain.



Supplementary Figure 10: Forest plot for Vomiting.

First Author/ year	Studies	Outcome	Type of Effect	Results
PARVEEN 2020 [79]	7	Comorbidities	odds ratio (severe vs. nonsevere; ICU care vs non-ICU care; survivor vs non-survivors)	Diabetes was lower in the survivors (OR: 0.56; p = 0.017) and non-severe (OR: 1.66; p = 0.002) patients. No association of diabetes was found with ICU care. Hypertension was positively associated with death (OR: 0.49; p<0.001; I2: 0.0%), ICU care (OR: 0.42; p = 0.009) and severity (OR: 2.69; p = 0.01)
KOH 2020 [80]	29	Symptoms, comorbidities	pooled prevalence/effect estimate	The most common symptoms at admission were fever, cough and fatigue, with a pooled prevalence of 90% (95% CI: 81–97%), 58% (95% CI: 47–68%), and 50% (95% CI: 29–71%), respectively. Myalgia, shortness of breath, headache, diarrhea and sore throat were less common with pooled prevalence of 27% (95% CI: 20– 36%), hypertension (17%, 95% CI: 7–28%), diabetes (10%, 95% CI: 6–15%), and cardiovascular disease (12%, 95% CI: 3–23%)
ESPINOSA 2020 [81]	39	Comorbidities	pooled prevalence/effect estimate	Hypertension was the most prevalent in 32% (95% CI: 31-33; weight 6.54%), followed by diabetes 22% (95% CI: 21-23; weight 6.57%), heart disease 13% (95% CI: 13-14; weight 6.62%), and COPD 8% (95% CI: 7-8; weight 6.65%)
SINGH 2020 [19]	18	Comorbidities	pooled prevalence/ effect estimate	22.9% (95% CI: 15.8 to 29.9) for hypertension; 11.5% (9.7 to 13.4) for diabetes; and 9.7% (6.8 to 12.6) for CVD
LI 2020 [82]	12	Comorbidities	odds ratio (severe vs. nonsevere)	Including chronic obstructive pulmonary disease (OR = 5.08, 95% CI: 2.68-9.63), diabetes (OR = 3.17, 95% CI: 2.26-4.45), hypertension (OR = 2.40, 95% CI: 1.47-3.90), coronary heart disease (OR = 2.66, 95% CI: 1.71-4.15), malignancy (OR = 2.21, 95% CI: 1.04-4.72), chronic liver disease (P = .192)

COPD: Chronic Obstructive Pulmonary Disease, CVD: cardiovascular disease, ICU: Intensive care unit, OR: Odds Ratio.

Supplementary Table 4: Results from the latest COVID-19 related published meta-analysis.

Study	Meta-regression Variable	Meta-regression Outcome
PRANATA 2020 [22]	Hypertension/Mortality	Hypertension was associated with increased composite poor outcome (risk ratio (RR) 2.11 (95% confidence interval (CI) 1.85, 2.40), p < 0.001; I2, 44%) and its sub-group, including mortality (RR 2.21 (1.74, 2.81)), severe COVID-19 (RR 2.04 (1.69, 2.47))
HUANG 2020 [23]	Diabetes/Mortality	Diabetes was associated with composite poor outcome (RR 2.38 [1.88, 3.03]) and its subgroup which comprised of mortality (RR 2.12 [1.44, 3.11]), severe COVID-19 (RR 2.45 [1.79, 3.35])
PRANATA 2020 [24]	Cardiovascular Disease and Cerebrovascular Disease/ Mortality	Cardiovascular disease was associated with increased composite poor outcome (RR 2.23 [1.71,2.91]), mortality (RR 2.25 [1.53,3.29], p<0.001; I2: 33%) and severe COVID-19 (RR 2.25 [1.51,3.36]). Cerebrovascular disease was associated with an increased composite poor outcome (RR 2.04 [1.43,2.91]). Subgroup analysis revealed that cerebrovascular disease was associated with mortality (RR 2.38 [1.92,2.96]) and showed borderline significance for severe COVID-19 (RR 1.88 [1.00,3.51]).

Supplementary Table 5: Prior meta-analysis meta-regression.