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ORIGINAL ARTICLE

Effect of chronic obstructive pulmonary disease and smoking on the outcome of COVID-19

R. Pranata,[1] A. Y. Soeroto,[2] I. Huang,[1,3] M. A. Lim,[1] P. Santoso,[2] H. Permana,[4] A. A. Lukito[1,5]

[1]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia [2]Division of Respirology and Critical Illness, Department of Internal Medicine, and [3]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia, [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia, [5]Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village, Tangerang, Indonesia

Correspondence to: Raymond Pranata, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Banten, Indonesia. e-mail: raymond_pranata@hotmail.com

Running head: COPD and smoking in COVID-19

RP and AYS contributed equally to this work.

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SUMMARY

OBJECTIVE: To investigate the association between chronic obstructive pulmonary disease (COPD) and smoking with outcomes in patients with COVID-19.

METHODS: A systematic literature search was performed using PubMed, EuropePMC, SCOPUS and the Cochrane Central Database. The outcomes of interest were: a composite of poor outcome mortality, severe COVID-19, the need for treatment in an intensive care unit (ICU) and disease progression.

RESULTS: Data on 4603 patients were pooled from 21 studies. COPD was associated with an increased risk for composite poor outcome (OR 5.01, 95% CI 3.06–8.22; $P < 0.001$; I^2 0%); mortality (OR 4.36, 95% CI 1.45–13.10; $P = 0.009$; I^2 0%); severe COVID-19 (OR 4.62, 95% CI 2.49–8.56; $P < 0.001$; I^2 0%); ICU care (OR 8.33, 95% CI 1.27–54.56; $P = 0.03$; I^2 0%); and disease progression (OR 8.42, 95% CI 1.60–44.27; $P = 0.01$; I^2 0%). Smoking was found to increase the risk of composite poor outcome (OR 1.52, 95% CI 1.16–2.00; $P = 0.005$; I^2 12%), and subgroup analysis showed that smoking was significant for increased risk of severe COVID-19 (OR 1.65, 95% CI 1.17–2.34; $P = 0.004$; I^2 11%). Current smokers were at a higher risk of composite poor outcome (OR 1.58, 95% CI 1.10–2.27; $P = 0.01$; I^2 0%) than former or non-smokers.

CONCLUSION: Our systematic review and meta-analysis revealed that COPD and smoking were associated with poor outcomes in patients with COVID-19.

KEY WORDS: coronavirus; chronic obstructive pulmonary disease; COVID-19; pneumonia; smoking

The COVID-19 pandemic has continued to spread worldwide,[1] and although most people are asymptomatic or only display a mild, flu-like illness, a significant proportion develop a severe response. Severe COVID-19 can lead to fatal complications, including acute respiratory distress syndrome, multi-organ failure and death.[2] The question as to why some individuals become critically ill, while others do not, remains a puzzle to be solved. It is therefore of great importance to find risk factors or comorbidities associated with severe COVID-19 to protect the vulnerable and allow for prudent resource allocation.[3–5]

In 2015, over 1.1 billion people smoked tobacco products, which remains one of the leading causes of preventable death worldwide.[6,7] One study has shown smoking to be an independent predictor of disease progression in COVID-19,[8] but this has been disputed.[9,10] Due

to the large number of smokers, a slight increase in risk would have a significant impact at the level of public health. Meanwhile, chronic obstructive pulmonary disease (COPD) has been shown to increase the severity of COVID-19 and tobacco smoking is one of the leading causes of COPD.[11]

In this systematic review and meta-analysis, we aimed to investigate the association between COPD, smoking, and the potential for poor outcome in patients with COVID-19.

METHODS

Search strategy and study selection

A systematic literature search was performed, using PubMed, EuropePMC, SCOPUS and the Cochrane Central Database with the search terms 1) "COVID-19" OR "Coronavirus 2019" OR "SARS-CoV-2" AND "Smoking"; 2) "COVID-19" OR "Coronavirus 2019" OR "SARS-CoV-2" AND "Smoker"; 3) "COVID-19" OR "Coronavirus 2019" OR "SARS-CoV-2" AND "Chronic Obstructive Pulmonary Disease"; 4) "COVID-19" OR "Coronavirus 2019" OR "SARS-CoV-2" AND "Characteristic". After removal of duplicates, the abstract for each article was independently screened by two authors (IH and RP). After eliminating any irrelevant articles, the full texts were then thoroughly assessed according to the criteria for inclusion or exclusion given below. The search was finalised on 1 April 2020. This systematic review and meta-analysis is compliant with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Inclusion and exclusion criteria

All research articles that described adult patients diagnosed with COVID-19, together with information on smoking, COPD, and the specific outcome of interest (mortality, severe COVID-19 and ICU care) were included in this study. These included cohort studies, case control, cross-sectional and large case series. We excluded articles other than original research, case series with samples below 20, case reports, articles on research in paediatric populations (age ≤17 years) and non-English language articles.

Data extraction

Data were extracted separately by two authors (MAL and RP) using a standardised method to identify the relevant study characteristics and the outcome of interest. Study characteristics included author, year, study design, age, sex, cardiovascular diseases, hypertension, diabetes mellitus, COPD and smoking (former and current). COPD was defined as "the presence of

COPD as comorbidity", and reports of non-specific pulmonary conditions, such as chronic lung disease/respiratory illness/respiratory comorbidities, were not considered as COPD. Smoking, in this study, was defined as "any information on smoking history; current, former or both".

As outcomes of interest, we extracted mortality, severity, need for ICU care, and COVID-19 disease progression. Mortality was defined as "death" and ICU care as admittance to an ICU during in-hospital care. Severe COVID-19 was defined as the outcome for patients who had any of the following features at the time of, or after, admission: 1) respiratory rate ≥30 breaths per min; 2) oxygen saturation ≤93% (at rest); 3) ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air (PaO_2:fiO_2) ≤300 mmHg; or 4) specific complications, such as septic shock, respiratory failure and/or multiple organ dysfunction.[12] Disease progression was defined as the clinical progression from mild or asymptomatic to severe COVID-19 and/or the need for escalation of treatment for COVID-19 pneumonia, but the exact definition may have differed across studies.

The primary outcome for the analysis was a "composite poor outcome", which included mortality, severe COVID-19, need for ICU care or disease progression. The secondary outcomes were the individual components. These outcomes were reported in groups of COPD (+) vs. COPD (–), smoking (+) vs. smoking (–), and current smoker vs. former/non-smoker in the figures.

Statistical analysis

Review Manager 5.3 (Cochrane Collaboration, London, UK) and Stata v.16 (StataCorp, College Station, TX, USA) were used for statistical analysis. The Mantel-Haenszel formula with a random-effects model was used to calculate dichotomous variables, regardless of heterogeneity. Odds ratios (ORs) are reported for the effect estimate, along with 95% confidence intervals (CIs) for continuous and dichotomous variables. *P* value was two-tailed, and the statistical significance set at <0.05. Meta-regression analysis was performed using restricted-maximum likelihood for age, sex, cardiovascular disease, hypertension and diabetes mellitus. Funnel-plot analysis was performed to assess the risk of publication bias. To assess the small-study effect, we performed regression-based Harbord's test for binary outcome.

RESULTS

Study selection and characteristics

We found a total of 265 records, of which 174 remained after the removal of duplicates; 139 records were excluded after screening the title/abstracts. After assessing 38 full texts for

eligibility, we excluded 17 for the following reasons: 1) no COPD or smoking variable (n = 11); 2) referred to specific groups (i.e., myocarditis, cardiac injury) (n = 5); and 3) variable present, but discrepancy in the outcome grouping (n = 1). We included 21 studies in the qualitative synthesis and in the meta-analysis (Supplementary Figure S1; http://dx.doi.org/10.6084/m9.figshare.12240965), which included a total of 4603 patients.[8–11,13–29] There were a cumulative total of 44 missing data in the study. The characteristics of the included studies are displayed in the Table. Full characteristics of the included studies can be accessed at: http://dx.doi.org/10.6084/m9.figshare.12240965.

Chronic obstructive pulmonary disease

COPD showed higher risk for composite poor outcome (OR 5.01, 95% CI 3.06–8.22; $P < 0.001$; I^2 0%, $P = 0.98$) (Figure 1). Subgroup analysis of COPD patients showed a higher mortality (OR 4.36, 95% CI 1.45–13.10; $P = 0.009$; I^2 0%, $P = 0.88$), greater likelihood of having severe COVID-19 (OR 4.62, 95% CI 2.49–8.56; $P < 0.001$; I^2 0%, $P = 0.78$), ICU care (OR 8.33, 95% CI 1.27–54.56; $P = 0.03$; I^2 0%, $P = 0.89$) and disease progression (OR 8.42, 95% CI 1.60–44.27; $P = 0.01$; I^2 0%, $P = 0.84$).

Smoking

Meta-analysis showed that smoking was associated with higher risk for composite poor outcomes (OR 1.52, 95% CI 1.16–2.00; $P = 0.005$; I^2 12%, $P = 0.30$) (Figure 2). Subgroup analysis showed that smoking increased the risk of severe COVID-19 (OR 1.65, 95% CI 1.17–2.34; $P = 0.004$; I^2 11%, $P = 0.34$). However, smoking was not associated with the risk of mortality (OR 1.30, 95% CI 0.87–1.95; $P = 0.20$; I^2 0%, $P = 0.55$), ICU care (OR 0.63, 95% CI 0.11–3.54; $P = 0.60$; I^2 0%, $P = 0.50$) and disease progression (OR 2.98, 95% CI 0.12–76.54; $P = 0.51$; I^2 71%, $P = 0.06$). Nevertheless, the majority of subgroups showed a trend towards higher risk in smokers.

Current smokers

Current smokers were at higher risk for composite poor outcomes than former/non-smokers (OR 1.58, 95% CI 1.10–2.27, $P = 0.01$; I^2 0%; Supplementary Figure S2; http://dx.doi.org/10.6084/m9.figshare.12240965]. Subgroup analysis showed that being a current smoker was not associated with risk of mortality (OR 1.93, 95% CI 0.87–4.26; $P = 0.10$; I^2 0%, $P = 0.80$), severity (OR 1.56, 95% CI 0.91–2.69; $P = 0.10$; I^2 7 %, $P = 0.37$) or ICU care

(OR 0.27, 95% CI 0.01–5.62; *P* = 0.40). However, the majority of subgroups showed a trend towards increased risk in current smokers.

Meta-regression

Meta-regression showed that the association between COPD and composite poor outcomes did not vary significantly with age (coefficient: –0.029, *P* = 0.492), sex (coefficient: 0.022, *P* = 0.615), hypertension (coefficient: –0.026, *P* = 0.421), cardiovascular diseases (coefficient: 0.01, *P* = 0.931) and diabetes (coefficient: –0.041, *P* = 0.447). Furthermore, the association between smoking and composite poor outcome did not vary significantly with age (coefficient: –0.022, *P* = 0.285), sex (coefficient: 0.007, *P* = 0.728), hypertension (coefficient: –0.011, *P* = 0.395), COPD (coefficient: 0.081, *P* = 0.166), cardiovascular diseases (coefficient: –0.05, *P* = 0.318), or diabetes (coefficient: 0.005, *P* = 0.833).

Publication bias

Funnel-plot analysis showed a qualitatively asymmetrical shape for "COPD and smoker". Regression-based Harbord's test indicated small-study effects for COPD and composite poor outcome (*P* = 0.005). There was no indication of small-study effects for smoking and composite poor outcome (*P* = 0.837).

DISCUSSION

This meta-analysis showed that COPD was associated with increased mortality, severe COVID-19, need for ICU care and disease progression in patients with COVID-19 pneumonia. Smoking was associated with an increased risk of composite poor outcome and severe COVID-19. This analysis corroborates the findings of a previous meta-analysis which demonstrated an increased risk of poor outcomes in smokers and in COPD patients.[30] The current meta-analysis displayed outcomes consistent with previous work, with almost two-fold and three-fold sample sizes for COPD and smoking, respectively. Furthermore, this meta-analysis provides additional analysis for "current smokers", which had not been adequately addressed previously, presumably due to the lack of reporting studies.

Morbidity and mortality in patients with COPD are usually related to acute exacerbation. Although the usual cause of acute exacerbation is bacterial infection,[31] respiratory viruses are also notable precipitants.[32,33] Acute exacerbation of COPD may add burden to an already struggling respiratory capacity in COVID-19 patients. Furthermore, expression of angiotensin-converting enzyme 2 (ACE2) is shown to be elevated in patients with COPD.[34] Viral surface

spike (S) protein of SARS-CoV-2 binds to ACE2 in order to enter susceptible cells.[35] Increased ACE2 expression may thus lead to increased susceptibility of COPD patients to COVID-19. Clinical relevance has been demonstrated by this meta-analysis, which showed that COPD is associated with mortality, severe COVID-19, the need for ICU care and disease progression, which might be due to increased susceptibility and concomitant acute exacerbation. Moreover, the heterogeneity across the analysis was 0%, indicating the consistency of the association.

ACE2 expression in the pulmonary airways has also been found to be upregulated in current smokers.[34] Nicotine is postulated to be the underlying cause of dysregulation of the renin-angiotensin system (RAS), although the evidence remains inconclusive.[36] Inhalation and repetitive hand-to-mouth movements during smoking may also contribute to increased viral contamination.[37] These factors may increase susceptibility to COVID-19 infections. Smoking has been shown to increase hospitalisations and ICU admission in influenza patients.[38] The present analysis shows that smokers are at higher risk of severe COVID-19, but not mortality, than non-smokers. There were three studies that clearly demonstrate the harm associated with smoking in COVID-19 patients, namely Guan et al.,[11] Hu L et al.,[29] and Liu W et al.[8] The study by Guan et al.[11] has the largest sample size of the three studies, although the authors did not provide adjustment for smoking as a risk factor for severity. Hu L et al.[29] and Liu W et al.[8] respectively, showed that smoking was independently associated with increased COVID-19 severity and disease progression. Nevertheless, subgroup analyses for the association between smoking and mortality, and COVID-19 progression demonstrated a pooled effect estimate >1, and might be significant with a higher sample size.

A novel hypothesis proposed by Changeux et al.[39] suggested a protective effect for nicotine against COVID-19. The rationale for this is that SARS-CoV-2 might be a blocker of nicotinic acetylcholine receptors (nAChRs), which are present in the lung epithelium and are postulated to be the major regulators of pro-inflammatory cytokines secreted by macrophages, which appear to be dysregulated in COVID-19.[39,40] This hypothesis was based on the structural similarity between nicotine and SARS-CoV-2, which may cause competitive inhibition at the nAChRs, lowering susceptibility to COVID-19 or reducing the severity of clinical presentation.[39] Nevertheless, our study showed that smoking was associated with an increase in severity of COVID-19. In our subgroup analysis between smoking and ICU care, we found that the odds ratio is <1. However, this finding might be coincidental due to the small sample size.

Being a current smoker was associated with increased risk for composite poor outcome, but not for the individual components of the outcome. This might be because the small sample

size did not provide adequate statistical power. Unfortunately, subgroup analysis for this segment is not conclusive due to the small sample size. It is also difficult to assess the comorbidities of smokers/past-smokers/non-smokers, and it is possible that patients stopped smoking once they developed smoking-related complications. This would appear to increase the risk of the comparator group.

Although the evidence basis for the specific management of COVID-19 in patients with underlying COPD is lacking, the guidelines from the British Thoracic Society (BTS) and Global Initiative for COPD (GOLD) have recommended the use of the current COPD guidelines, with several specific directives.[41,42] Acute exacerbation of COPD presenting with respiratory failure type 2 is an indication for non-invasive ventilation (NIV), regardless of COVID-19 status. Several additional measures should be taken due to the nature of the aerosol-generating procedure, including the use of a non-vented mask and filter, with vented tubing.[42] As nebulisation is not considered to be an aerosol-generating procedure, its use is tolerated. The advice on the use of antibiotics, corticosteroids, bronchodilator and oxygen therapy remains unchanged, pending further evidence.[41]

One limitation of this systematic review and meta-analysis is the possibility of publication bias, which was reflected by the asymmetrical, inverted funnel-plot and significant small-study effects. Most of the articles included in the study were published on preprint servers and are not yet peer-reviewed. As most of the reports were from Wuhan (China), there might be some overlap of samples across the studies.[43] The design of most studies included in this review was retrospective. Only prospective-based cohort studies can accurately measure strength of association, while taking into account the many variables (personal characteristics, in-hospital medical treatments and types of ventilation supports) that could affect the outcome and become confounding factors. In the current meta-analysis, we could only make the assumption that all patients received comparable medical treatment and protocols. The duration of hospitalisation might influence the outcome, together with other variables that might be difficult to measure, such as overloading of hospital wards and equipment shortages. There were only a small number of events for analysis of ICU or disease progression, for both COPD and smoking; hence, the results should be interpreted with caution. Selection and referral bias may limit the generalisability of this meta-analysis, as the studies included appear to be conducted in referral centres. Lower risk patients tend to be placed in mobile hospitals or they self-isolated in their homes. Furthermore, the prevalence of poor outcome in the COPD group is high and the use of odds ratios may have led to an overestimation of the overall effect.

CONCLUSION

COPD was associated with increased risk for composite poor outcome, including individual components: mortality, severe COVID-19, ICU care and disease progression. Smoking increases the risk for composite poor outcome and its severe COVID-19 subgroup. Being a current smoker was also associated with composite poor outcome. This meta-analysis showed that the overall association with poor outcome was stronger for COPD than for smoking.

Conflicts of interest: none declared.

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Table Characteristics of the included studies*

Author, year	Study design	Outcome of interest	Samples	Male	Overall age (mean/median) (years)	Smoking (ever or current)	Current smoker	Former smoker	COPD
Chen, 2020	Observational, retrospective, case series	Mortality	31 vs. 92	22/31 vs. 39/92	72 vs. 53	7/31 vs. 10/92	N/A	N/A	3/31 vs. 3/92
Chen T, 2020	Observational, retrospective, case series	Mortality	113 vs. 161	83/113 vs. 88/161	68.0 vs. 51.0	9/113 vs. 10/161	7/113 vs. 5/161	2/113 vs. 5/161	11/113 vs. 7/161 (CLD)
Fu, 2020	Observational, retrospective, case series	Mortality	34 vs. 166)	16/34 vs. 83/166	<49: 2 vs. 47 50–59: 8 vs. 45 60–69: 7 vs. 52 >70: 17 vs. 22	16/34 vs. 73/ 166	N/A	N/A	4/34 vs. 4/166 (CLD)
Li, 2020	Observational, retrospective, case series	Mortality	15 vs. 87	11/15 vs. 48/87	69 vs. 55	1/15 vs. 6/87	1/15 vs. 6/87	N/A	1/15 vs. 1/87
Luo, 2020	Observational, retrospective, case series	Mortality	100 vs. 303	57/100 vs. 136/303	71 vs. 49	9/100 vs. 136/303	N/A	N/A	17/100 vs. 11/303 (CLD)
Zhou, 2020	Observational, retrospective cohort	Mortality	54 vs. 137	38/54 vs. 81/137	69.0 vs. 52.0	5/54 vs. 6/137	5/54 vs. 6/137	N/A	4/54 vs. 2/137
Guan, 2020	Observational retrospective, case series	Severe COVID-19	173 vs. 926	100/173 vs. 537/926	52.0 vs. 45.0	38 /172 vs. 120/913	29/172 vs. 108/913	9/172 vs. 12/913	6/173 vs. 6/926
Hu, 2020	Observational, retrospective, case series	Severe COVID-19	172 vs. 151	91/172 vs. 75/151	65 vs. 56	26/172 vs. 12/151	N/A	N/A	6/172 vs. 0/151
Liu, 2020	Observational, prospective, cohort	Severe COVID-19	17 vs. 44)	10/17 vs. 21/44	56 vs. 41	2/17 vs. 2/44	2/17 vs. 2/44	N/A	3/17 vs. 2/44
Qin, 2020	Observational retrospective, case series	Severe COVID-19	286 vs. 166	155/286 vs. 80/166	61 vs. 53	3/286 vs. 4/166	N/A	N/A	9/286 vs. 3/166
Tabata, 2020	Observational, retrospective cohort	Severe COVID-19	28 vs. 76	15/28 vs. 32/76	72.5 vs. 66.5	7/28 vs. 11/76	N/A	N/A	7/104 (CLD)

Wan, 2020	Observational, retrospective, case series	Severe COVID-19	40 vs. 95	21/40 vs. 52/95	56 vs. 44	1/40 vs. 8/95	1/40 vs. 8/95	N/A	4/40 vs. 0/95 (CLD)
Wang, 2020	Observational retrospective, case-series	Severe COVID-19	38 vs. 72	24/38 vs. 24/72	≤40: 3 vs. 50 41–60: 8 vs. 13 >60: 27 vs. 9	9/38 vs. 17/72	N/A	N/A	4/38 vs. 2/72
Xu, 2020	Observational, retrospective, case series	Severe COVID-19	25 vs. 44	13/25 vs. 22/44	67 vs. 49	3/25 vs. 2/44	3/25 vs. 2/44	N/A	N/A
Zhang, 2020	Observational retrospective, case series	Severe COVID-19	55 vs. 166	35/55 vs. 73/166	62 vs. 51	N/A	N/A	N/A	4/55 vs. 2/166
Zhang J, 2020	Observational retrospective, case series	Severe COVID-19	58 vs. 82	33/58 vs. 38/82	<30: 1 vs. 4 30–49: 9 vs. 28 50–69: 28 vs. 41 ≥70: 20 vs. 9	6/58 vs. 3/82	2/58 vs. 0/82	4/58 vs. 3/82	2/58 vs. 0/82
Cao 2020	Observational, retrospective, case series	ICU care	19 vs. 179	17/19 vs. 84/179	63.7 vs. 48.6	1/19 vs. 10/179	N/A	N/A	N/A
Huang 2020	Observational retrospective, case series	ICU care	13 vs. 28	11/13 vs. 19/28	49.0 vs. 49.0	0/13 vs. 3/28	0/13 vs. 3/28	N/A	1/13 vs. 0/28
Wang D, 2020	Observational retrospective, case series	ICU care	36 vs. 102	22/36 vs. 53/102	66 vs. 51	N/A	N/A	N/A	6/36 vs. 1/102
Feng 2020	Observational, retrospective, case series	Disease progression	15 vs. 126	7/15 vs. 65/126	58 vs. 41	0/15 vs. 7/126	N/A	N/A	2/15 vs. 2/126
Liu W 2020	Observational, retrospective, case series	Disease progression	11 vs. 67	7/11 vs. 32/67	55 vs. 37	3/11 vs. 2/67	N/A	N/A	1/11 vs. 1/67

* Data presented in each column relate to patients in the group with poor outcome vs. the group without poor outcome.

COPD = chronic obstructive pulmonary disease; N/A = not available; CLD = chronic lung disease; ICU = intensive care unit

Figure 1 Forest plot of the effect of COPD on outcome of COVID-19. COPD = chronic obstructive pulmonary disease; + = positive; - = negative; M-H = Mantel-Haenszel; CI = confidence interval; df = degree of freedom; ICU = intensive care unit.

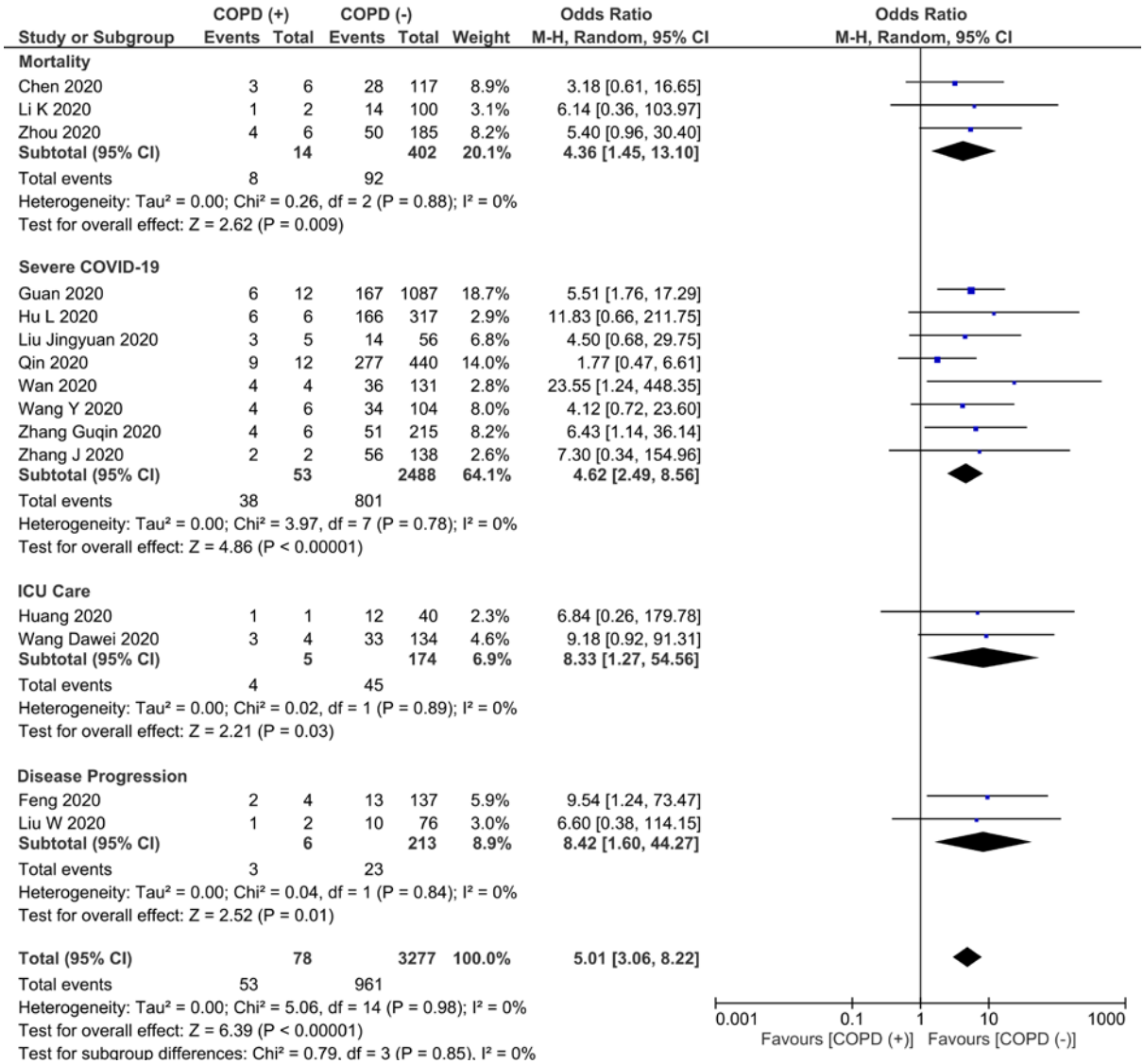

Figure 2 Forest plot of the effect of smoking on outcome of COVID-19. + = positive; - = negative; M-H = Mantel-Haenszel; CI = confidence interval; df = degree of freedom; ICU = intensive care unit.