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Asthma and COVID-19; different entities, same outcome: a meta-analysis of 107,983 patients

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ABSTRACT

Objective: There are varying reports of the prevalence and effect of comorbid asthma in coronavirus disease-2019 (COVID-19) patients. We sought to conduct a meta-analysis comparing asthmatic and non-asthmatic patients to determine the clinical significance of preexisting asthma in COVID-19 patients.

Data Sources: Online databases PubMed, ScienceDirect, Web of Science, and Scopus, were searched up to July 15, 2020, for papers comparing asthma *versus* non-asthma COVID-19 patients.

Study Selection: According to prespecified inclusion criteria, this analysis included eleven retrospective studies with 107,983 COVID-19 patients. Subgroup analysis was performed based on age groups.

Results: The mean age of the patients was 59.9 years (95%CI = 51.9–67.9). Across studies, the prevalence of asthma was 11.2% (95%CI: 9.1%–13.3%) among COVID-19 patients who attended the hospitals. Asthma patients were more likely to be younger (SMD = −0.36, 95%CI = −0.61 to −0.10, $p=0.005$), and obese (OR = 1.98, 95%CI = 1.54–2.55, $p<0.001$), there was no differential risk of hospitalization rate, ICU admission, or development of acute respiratory distress syndrome (ARDS) between asthmatic and non-asthmatic cohorts. However, asthmatic patients had increased risk of endotracheal intubation (RR = 1.27, 95%CI = 1.02–1.58, $p=0.030$) especially patients aged <50 years (RR = 6.68, 95%CI = 1.76–11.13, $p=0.009$). Despite this result, asthmatic patients had better recovery with a higher liability of being discharged and were less likely to die (RR = 0.80, 95%CI = 0.65–0.97, $p=0.026$).

Conclusion: To our knowledge, our meta-analysis is the largest to shed light on preexisting asthma as a predictor of intubation in COVID-19, especially in young and obese patients. Identifying high-risk groups is crucial for designing more effective intervention plans and optimization of efficient resource allocation.

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Introduction

Since the emergence of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in late 2019, there has been a rapid global spread of COVID-19, quickly overwhelming many health care systems (1). As of July 15, the Centers for Disease Control and Prevention has recorded a total of 3,416,428 cases and 135,991 total deaths in the United States (2). Coronavirus disease 2019 (COVID-19) primarily presents with respiratory symptoms ranging in severity from asymptomatic to severe, with patients developing ARDS and requiring mechanical ventilation (3).

Older age and patients with comorbidities, particularly hypertension and diabetes, have been identified as significant risk factors for poor prognosis (4). However, there have been varying reports of the prevalence and effect of comorbid asthma in COVID-19 patients (5). Although initial reports of 140 COVID-19 patients in Wuhan, China, indicated no self-reported asthma cases (6), another study from the UK Biobank of 605 hospitalized COVID-19 patients reported a 17.9% prevalence of asthma (7).

Respiratory viral infections have long been established as the most common trigger for asthma exacerbations in adults and children. Infections with rhinoviruses, influenza,

adenovirus, and coronaviruses have been identified as risk factors for the development of asthma exacerbation in both adults and children (8). Notably, not all viruses affect asthma patients equally. Rhinoviruses are associated with more severe exacerbations than other respiratory viruses (9).

Studies in recent months have identified angiotensin-converting enzyme 2 (ACE2) is a key receptor in SARS-Cov-2 entry into host cells (10,11). Jackson et al. reported significant reductions in the expression of the ACE2 receptor in asthmatics with high levels of allergic sensitization. However, individuals with nonatopic asthma did not have significantly reduced ACE2 expression (12). Another study also found that T2 inflammation in asthma and atopy was associated with suppressed expression of ACE2 in nasal and airway epithelial cells (13). This is consistent with the Camiolo et al. study reporting the higher expression of ACE2 in the T2-low subset of asthma patients; these patients were found to display characteristics (male sex and higher diastolic blood pressure) that are risk factors for severe COVID-19 disease (11). Although more work is required to determine the direct implications of ACE2 expression in COVID-19 patients, this suggests a possible protective factor for asthma patients. Indeed, a recent study found that asthma was not associated with increased rates of hospitalization or ARDS. However, asthma was associated with prolonged intubation duration in COVID-19 patients younger than 65 (5).

Given that the surge in critically ill patients has imposed a significant burden on hospital capacity in some outbreak regions, there is a compelling need to identify clinical predictors of severe COVID-19 disease to assist in risk stratification and optimization of efficient resource allocation. Here, we have conducted a meta-analysis comparing the course of illness between asthmatic and non-asthmatic patients to determine the clinical significance of preexisting asthma in COVID-19 patients. The results will add to the current body of research on COVID-19 and aid in the prevention and management of COVID-19 in asthma patients.

Methods

Systematic search

We performed a systematic literature search according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement in PubMed, ScienceDirect, Web of Science, and Scopus up to July 15, 2020, on papers comparing asthma *versus* non-asthma COVID-19 patients. The following keywords were used; “Asthma/asthmatic/pneumonia” combined with “COVID-19/SARS-COV-2/2019-ncov/novel coronavirus 2019.” We manually screened out the relevant potential article in the references selected. This process was performed

independently by two participants. Also, we performed a precise searching within the medrxiv database for the pre-print articles to enrich this work and increase the sample size using the same keywords.

Study selection

No time or language restriction was applied. Inclusion criteria were as follows: (1) Types of Studies: retrospective, prospective, observational, descriptive, or case-control studies reporting COVID-19 patients with asthma; (2) Subjects: diagnosed patients with COVID-19; (3) Exposure intervention: COVID-19 patients diagnosed with Real-Time polymerase chain reaction, radiological imaging, or both with asthma; and (4) Outcome indicator: the standardized mean difference (SMD), relative risk (RR) or odds ratio (OR) for hospitalization rate and period, ICU admission, intubation rate, and duration, as well as mortality. The following exclusion criteria were considered: (1) Case reports, reviews, editorial materials, conference abstracts; (2) Insufficient reported data information; or (3) *In vitro* or *in vivo* studies.

Data extraction

Two investigators separately conducted literature screening (RME, EAT) followed by data abstraction in a pre-designed excel sheet by two investigators (MHH, RME). Any disagreement was resolved by another investigator (EAT). Study characteristics (author name, publication date, journal name, geographical region, study design, and sample size) and the patients' demographics (age and sex) were collected. Comorbidities, laboratory findings, complications, and outcomes of COVID-19 disease were extracted.

Statistical analysis

Meta-analysis was performed using OpenMeta[Analyst] and comprehensive meta-analysis software version 3.0 (14). The SMD, RR or OR, and 95% confidence intervals (CI) were applied to estimate pooled results using the Random-effects model (15). Subgroup analysis was performed based on three age groups defined by the Centers for Disease Control and Prevention (CDC)-reported grouping of COVID-19 patients (16). Heterogeneity was evaluated using Cochran's Q statistic and quantified using Higgin's I^2 statistics (17).

Results

Characteristics of included studies

The workflow of the search process is shown in Figure 1. Eleven retrospective articles published after March 6, 2020,

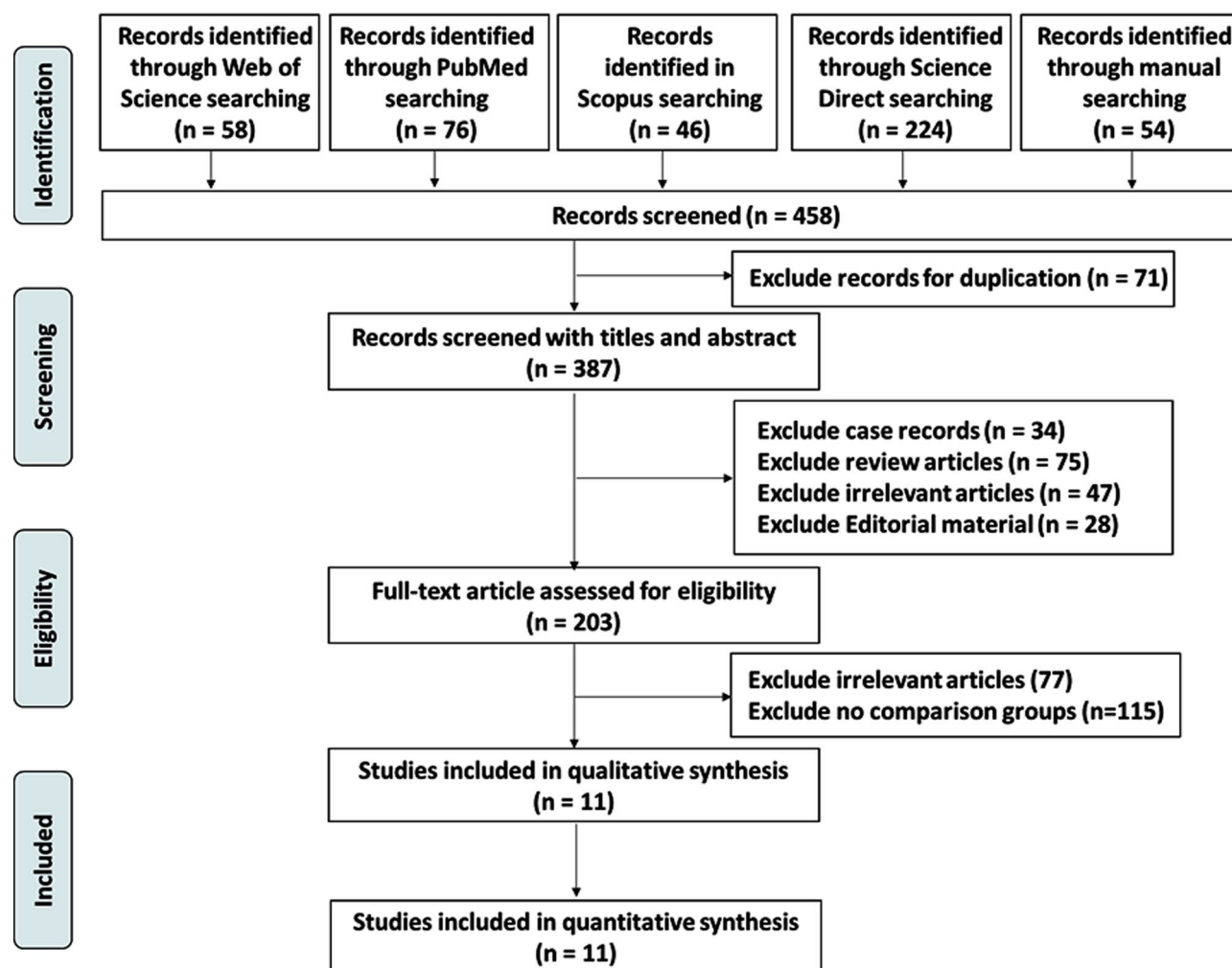


Figure 1. A systematic search on the comparison between asthma and non-asthma COVID-19 patients. The workflow in the search process. The search was performed in PubMed, ScienceDirect, Web of Science, and Scopus up to July 6. A total of 387 records were addressed in the first screening, and 203 reports were identified for article eligibility. Of these, 115 papers were excluded due to the absence of comparison groups, and 77 articles were eliminated for being irrelevant, resulting in 11 eligible articles. Pairwise comparison between asthma and non-asthma COVID-19 patients was performed in the current analysis.

were eligible (5,18–27). They included 107,983 COVID-19 patients, 3,946 with comorbid asthma disease, and 104,037 without asthma. Of these, females accounted for 46% (95%CI: 40.5%–51.5%). The mean age of the patients was 59.9 years (95%CI: 51.9–67.9). Across studies, the prevalence of asthma presented to the hospital was 11.2% (95%CI: 9.1%–13.3%). On comparison according to the geographical region of COVID-19 patients, the USA had the highest incidence (proportion = 12.8%, 95%CI: 9.3%–16.3%), followed by Europe (proportion = 12.7%, 95%CI: 2.7%–22.8%), and Mexico represented the least proportion of 2.9% (95%CI: 2.8%–3.0). The hospitalization rate among COVID-19 patients was 78% (95%CI: 72.7%–83.3%), with an average length of hospital stays of 10.2 days (95%CI: 7.75–12.6). The prevalence of COVID-19 patients who required ventilatory support was 21.2% (95%CI: 7.4%–35.0%). Case-fatality rate was 10.6% (95%CI:

6.2%–15%). The main characteristics of the included studies are summarized in Table 1.

Pooled summary of the pairwise comparison between asthma and non-asthma patients

As shown in Table 2, asthma patients were more likely to be younger (SMD = -0.36 , 95%CI: -0.61 to -0.10 , $p=0.005$), females (OR = 1.83, 95%CI = 1.31 to 2.56, $p<0.001$) and obese (OR = 1.98, 95%CI = 1.54 to 2.55, $p<0.001$), and less likely to have of Asian background (OR = 0.53, 95%CI = 0.35 to 0.80, $p=0.003$). There was no significant difference between asthmatic and non-asthmatic patients regarding the frequencies of comorbidities or results of laboratory tests. Moreover, there was no differential risk of hospitalization rate, ICU admission, or development of acute respiratory distress

Table 1. Characteristics of the included studies.

First author	DOP	Journal name	City	Country	Sample Size	Mean age (SD), years	Female (%)	Number of asthmatics patients	Asthma (%)	Hosp. rate (%)	Intubation rate (%)	Mean LOS (SD), days	Survival rate (%)	Ref.
Dreher Mahdavinia	17-Apr 14-May	Dtsch Arztebl Int J Allergy Clin Immunol Pract	Aachen Chicago, Illinois	Germany USA	50 935	66.3 (13.3) NA	34.0 55.4	6 241	12.0 25.8	100 31.8	NA 8.44%	NA 7.9 (5.4)	86.00 98.07	(20) (5)
Goyal Chhiba	11-Jun 15-Jun	NEJM J of Allergy & Clinical Immunol	New York Chicago, Illinois	USA USA	393 1,526	61.5 (18.5) NA	39.4 52.9	49 220	12.5 14.4	100 55.9	33.07% NA	NA NA	NA 95.28	(22) (19)
Barroso	18-Jun	J Investig Allergol Clin Immunol	Madrid	Spain	189	67.5 (13.7)	42.3	11	5.8	100	NA	10.8 (9.6)	87.30	(18)
Lieberman Grandbastien	6-Jun 27-Jun	Chest J of Allergy & Clinical Immunol	New York Strasbourg	USA France	6,245 106	NA 63.2 (13.1)	NA 37.7	227 23	3.6 21.7	100 100	NA 14.15%	NA NA	81.94 NA	(24) (23)
Nguyen Giannouchos Wang Hussein	NA 30-Jul NA NA	medRxiv Eur Respir J medRxiv Respiratory Medicine	Chicago NA New York Louisiana	USA Mexico USA USA	689 89,756 7,592 502	54.3 (20.7) 46.2 (16.0) NA 60.8 (15.4)	57.0 43.6 45.1 52.0	105 2,603 344 72	17.3 2.9 4.5 14.3	51.7 34.8 76.2 74.9	NA NA NA 29.28%	NA NA NA 12.0 (10.9)	87.35 NA 89.40 87.25	(25) (21) (26) (27)
Pooled summary					107,983	59.9 years (51.9–67.9)	46% (40.5–51.5)	3,901	11.2% (9.1–13.3)	78% (72.7–83.3)	21.2% (7.4–35.0)	10.2 days (7.75–12.6)	89.4% (85–93.8)	

All articles were published in 2020 and retrospective study design. NA: not applicable, DOP: Date of publication, SD: standard deviation, Hosp. rate: hospitalization rate, LOS: length of hospital stay, Ref. reference. The pooled summary is presented as an effect estimate and 95% confidence interval. Categorical variables are presented as untransformed proportions, while quantitative data are presented as means. The total sample size included 3,946 asthma and 104,037 non-asthma adult patients.

syndrome (ARDS) between asthmatic and non-asthmatic cohorts (all $p > 0.05$). However, pooled summary of COVID-19 outcomes showed a 27% increased risk of requiring intubation ($RR = 1.27$, $95\%CI = 1.02$ to 1.58 , $p = 0.030$) and more prolonged duration of intubation ($SMD = 0.575$, $95\%CI = 0.147$ – 1.004 , $p = 0.008$) in asthmatic group. Despite this result, asthmatic patients had better recovery with less likely to die ($RR = 0.80$, $95\%CI = 0.65$ to 0.97 , $p = 0.026$) (Table 2).

Subgroup analysis

As depicted in Figure 2, stratification by age groups revealed prolonged duration of endotracheal intubation among asthmatic patients below 50 years ($RR = 6.68$, $95\%CI = 1.76$ – 11.13 , $p = 0.009$) and those aged 50–64 years ($RR = 3.56$, $95\%CI = 2.19$ – 5.78 , $p < 0.001$). Asthma patients aged 50–64 also had higher risk of endotracheal intubation ($RR = 1.56$, $95\%CI = 1.02$ – 2.37 , $p = 0.038$), and was associated with prolonged length of hospitalization ($RR = 2.13$, $95\%CI = 1.40$ – 3.22 , $p < 0.001$). In contrast elder group did not show an impact of having asthma comorbidity on the outcomes of COVID-19 disease.

Discussion

To the best of our knowledge, this is the first meta-analysis to study the role of preexisting bronchial asthma on the outcomes of COVID-19 disease. Eleven articles, from Europe and North America with 107,983 COVID-19 patients, were included in the study. For COVID-19 patients, the hospitalization rate was 78%, and those requiring ventilatory support were 21.2%, which was in line with prior COVID-19 related reports (28). The overall prevalence rate of asthma in COVID-19 patients (11.2%) was above the national average asthma rate in adults, 7.7% (29). One possible explanation could be that patients with a history of asthma reached out for COVID-19 testing more than others because of their concern and overlapping symptoms.

Pooled analysis showed that asthma patients were more likely to be younger, females, and obese. The prevalence of asthma in hospitalized cases was more common in the Black race and less likely to be of Asian background. This is consistent with the CDC reports that women have a higher rate of asthma (9.8%) compared to men (5.4%), and African Americans were three times more likely to be hospitalized and to die from asthma than any other races or ethnicities (30). Obesity is considered a risk factor and disease modifier in asthma. A high prevalence of obesity was previously reported in COVID-19 and non-COVID19 asthma cohorts (26,30). Obesity may lead to severe exacerbations, a more difficult-to-control phenotype, and reduced therapeutic response (31,32).

Table 2. Pooled summary for outcomes in COVID-19 patients.

Characteristics	# studies	Sample size		Test of association			Effect size		Heterogeneity		Egger's <i>p</i> -value		
		Total	Asthma	Non-asthma	Method	Effect measure	Analysis Model	Estimate	95% CI	<i>p</i> -value		<i>I</i> ²	
Demographic data													
Age	3	797	106	691	IV	SMD	Random	−0.36	−0.61, −0.10	0.005	19.98%	0.28	0.15
Sex (female)	5	3,258	567	2,691	MH	OR	Random	1.83	1.31, 2.56	<0.001	53.23%	0.073	0.77
Body mass index	3	1,626	324	1,302	IV	SMD	Random	0.27	0.14, 0.39	<0.001	0.0%	0.80	0.51
Obesity	3	2,217	303	1,914	MH	OR	Random	1.98	1.54, 2.55	<0.001	0.0%	0.84	0.22
Race: AA	3	2,963	533	2,430	MH	OR	Random	1.39	0.87, 2.24	0.16	79.85%	0.007	0.25
Race: Asian	2	2,461	461	2,000	MH	OR	Random	0.53	0.35, 0.80	0.003	0.0%	0.57	NA
Race: White	3	2,963	533	2,430	MH	OR	Random	1.10	0.78, 1.54	0.58	56.90%	0.098	0.43
Smoking status	4	2,323	326	1,997	MH	OR	Random	1.42	0.91, 2.24	0.12	0.0%	0.92	0.54
Laboratory data													
Lymphocyte count	3	797	106	691	IV	SMD	Random	0.03	−0.28, 0.35	0.83	43.4%	0.17	0.56
C-reactive protein	2	691	83	608	IV	SMD	Random	4.13	−0.58, 8.85	0.08	99.01%	<0.001	NA
Ferritin	2	691	83	608	IV	SMD	Random	0.18	−0.18, 0.55	0.33	37.07%	0.20	NA
Comorbidities													
Hypertension	4	2,323	326	1,997	MH	OR	Random	1.01	0.55, 1.88	0.95	71.18%	0.015	0.031
Diabetes	4	2,323	326	1,997	MH	OR	Random	0.96	0.73, 1.24	0.75	0.0%	0.53	0.95
COPD	3	2,217	303	1,914	MH	OR	Random	1.92	0.69, 5.32	0.21	63.74%	0.06	0.51
Coronary artery disease	3	2,217	303	1,914	MH	OR	Random	0.74	0.23, 2.34	0.61	61.73%	0.07	0.36
Chronic kidney disease	3	797	106	691	MH	OR	Random	0.68	0.33, 1.39	0.29	0.0%	0.97	0.65
Cancer	2	691	83	608	MH	OR	Random	0.95	0.44, 2.06	0.91	0.0%	0.56	NA
Outcomes													
Outpatient	3	2,963	533	2,430	MH	RR	Random	1.04	0.96, 1.13	0.27	0.0%	0.60	0.69
Hospitalization rate	6	101,000	3,585	97,415	MH	RR	Random	0.94	0.84, 1.04	0.074	83.22%	<0.001	0.80
Discharge alive	4	3,152	544	2,608	MH	RR	Random	1.02	0.95, 1.09	0.536	0.0%	0.547	0.30
Intubation rate	4	1,936	385	1,551	MH	RR	Random	1.27	1.02, 1.58	0.030	0.0%	0.64	0.71
ARDS	3	1,487	319	1,168	MH	RR	Random	1.73	0.76, 3.98	0.19	83.7%	0.002	0.37
ICU admission	4	91,973	2,906	89,067	MH	RR	Random	1.64	0.67, 3.97	0.27	86.5%	<0.001	0.14
Case-fatality rate	7	17,678	1,265	16,413	MH	RR	Random	0.80	0.65, 0.97	0.026	0.0%	0.43	0.22
Prolonged intubation	2	1,437	313	1,124	IV	SMD	Random	0.57	0.14, 1.00	0.008	88.3%	0.003	NA
Prolonged length of stay	3	1,626	324	1,302	IV	SMD	Random	0.16	−0.03, 0.35	0.10	38.47%	0.19	0.97

AA: African American, IV: inverse variance, MH: Mantel-Haenszel, SMD: standardized mean difference, OR: odds ratio, RR: relative risk, CI: confidence interval, *I*²: the ratio of true heterogeneity to total observed variation, NA: not applicable, COPD: chronic obstructive pulmonary disease, ARDS: acute respiratory distress syndrome, ICU: intensive care unit.

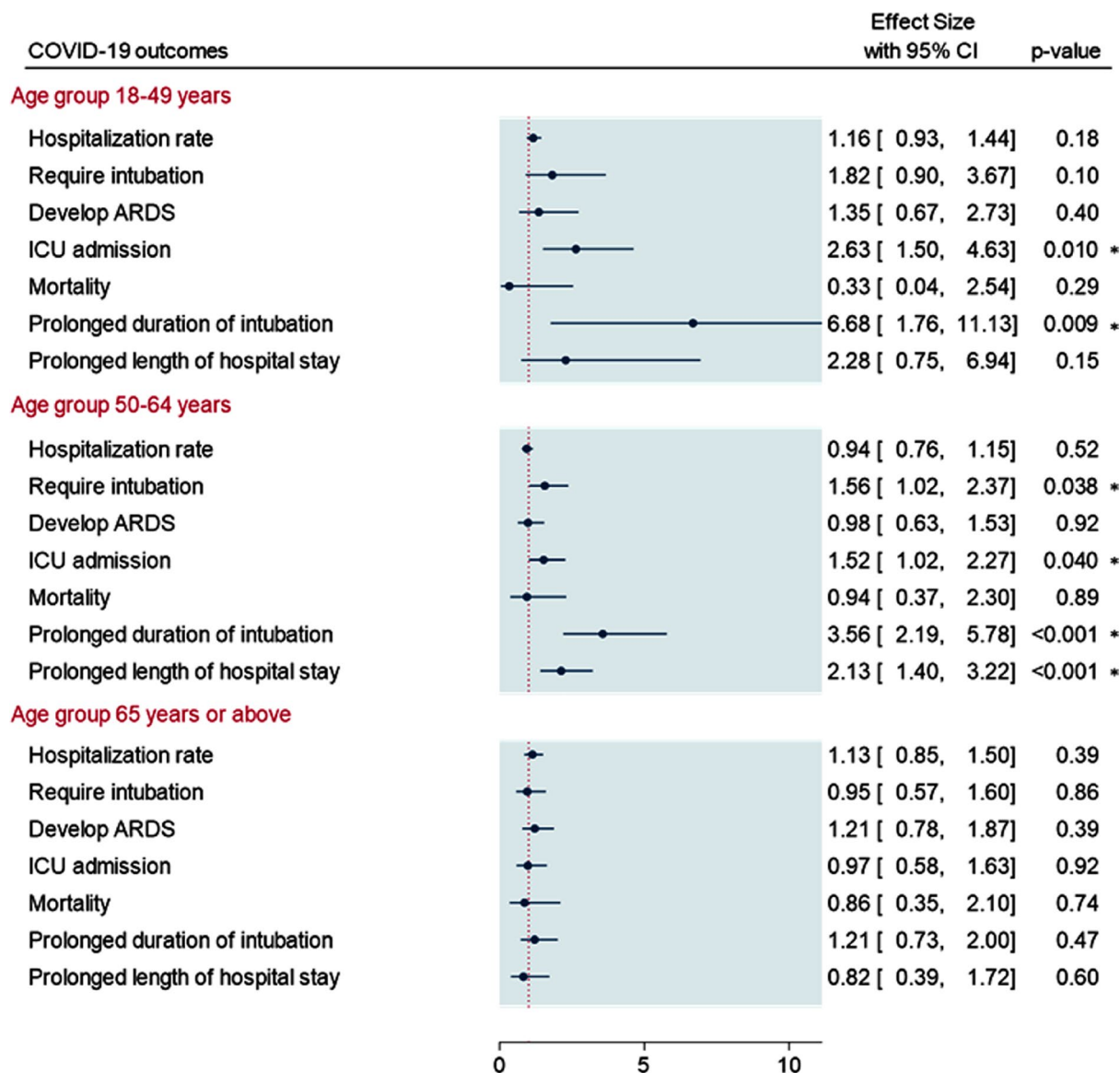


Figure 2. The risk of poor outcomes stratified by age groups. Pairwise meta-analysis comparison of asthma vs. non-asthma in COVID-19 patients aged 18–49 years, aged 50–64 years, and aged 65 years or above, according to the Centers for Disease Control and Prevention (CDC) categorization of age in COVID-19 disease. *Significant *p* values.

In our results, there was no significant difference between asthmatic and non-asthmatic groups regarding comorbidities, laboratory tests, or hospitalization rates. Asthma patients aged 50–64 years had a higher risk of endotracheal intubation, and those below 65 years were associated with prolonged intubation time and length of hospital stay, but not in the age group of 65 years or above. Deep dive into these studies showed higher body mass index and obesity rates among asthmatic patients in this middle age group. Longer hospitalization time may be related to prolonged dependence on mechanical ventilation.

Despite this trend, asthma was not associated with a higher rate of death, ICU admission, nor ARDS among COVID-19 patients. In contrast, asthma cohorts showed recovery better than expected; they had a significantly higher discharge rate

and less mortality risk. The lower expression of ACE2 receptors in the nasal epithelia and alveoli of asthma patients and those with inhaled corticosteroids could explain this issue. Hence, a putative, less viral load in host cells (11,33,34).

As the past months have demonstrated, we expect the number of new COVID-19 cases to continue waxing and waning. During peaks of the disease, when health care resources are spread thin, practitioners should expect COVID-19 patients with comorbid asthma to have a higher likelihood of requiring intubation and a longer course of mechanical ventilation. Despite this, we found that asthmatic patients had better outcomes than other cohorts. Compared with non-asthmatics, patients with comorbid asthma had a higher likelihood of being discharged and had a lower mortality rate. Our study will help

guide providers in their risk stratification of asthmatic COVID-19 patients to more confidently allocate scarce resources, namely mechanical ventilators.

A limitation of our study is that one study, which reported the lowest prevalence of asthma, contributed to the majority of cases in our meta-analysis. This may limit the generalizability of our findings. Second, the studies included in the current meta-analysis did not cover Asian and African geographic regions; therefore, more caution is warranted during the results' extrapolation. Third, heterogeneity was evident in some analyses, particularly sub-group analysis, as the number of underlying studies was limited. In this sense, the related results should be interpreted with caution as the potential for false-negative results could be of concern when testing many dependent variables. Fourth, it should be noted that two of the included studies (25,26) were not peer-reviewed at the time of reanalysis. Lastly, as there was limited data concerning the allergic asthmatic patients in the enrolled studies, a subgroup analysis between asthma allergic vs. asthma non-allergic or non-asthmatic groups was not feasible. Further analysis of this issue regarding comorbidities, laboratory tests, or hospitalization rates is recommended in future metanalyses. Various SARS-CoV-2 strains have been genotyped worldwide; the influence of each subtype on genotype-phenotype consequences remains unclear.

Conclusion

In conclusion, our results suggest that adult patients with underlying asthma disease do not have an increased risk of severe illness or mortality from COVID-19 disease. However, obese individuals with asthma may require extra attention because they might require prolonged mechanical ventilation. This needs to be considered by all health care providers when triaging COVID-19 patients.

Data availability statement

All data generated from this analysis were supplied in the text and the tables.

Declaration of interest

The authors report no conflict of interest.

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