Impact of Asthma on Severity and Outcomes in COVID-19

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BACKGROUND: We conducted this systematic review to evaluate whether asthma increases the risk of severe disease and adverse outcomes among subjects with COVID-19. METHODS: We queried the PubMed and Embase databases for studies indexed through December 2020. We included studies providing data on severe disease, hospitalization, ICU care, need for mechanical ventilation, or mortality among subjects with COVID-19 with and without asthma. We calculated the relative risk for each reported outcome of interest and used random effects modeling to summarize the data. RESULTS: We retrieved 1,832 citations, and included 90 studies, in our review. Most publications reported data retrieved from electronic records of retrospective subject cohorts. Only 25 studies were judged to be of high quality. Subjects with asthma and COVID-19 had a marginally higher risk of hospitalization (summary relative risk 1.13, 95% CI 1.03–1.24) but not for severe disease (summary relative risk 1.17, 95% CI 0.62–2.20), ICU admission (summary relative risk 1.13, 95% CI 0.96–1.32), mechanical ventilation (summary relative risk 1.05, 95% CI 0.85–1.29), or mortality (summary relative risk 0.92, 95% CI 0.82–1.04) as compared to subjects with COVID-19 without asthma. CONCLUSIONS: Comorbid asthma increases risk of COVID-19-related hospitalization but not severe disease or other adverse outcomes in subjects with COVID-19. *Key words: asthma; COVID-19; mortality; risk; severity; systematic review.* [Respir Care 2021;66(12):1912–1923. © 2021 Daedalus Enterprises]

Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected nearly 185 million people worldwide. In contrast to some other common respiratory viral infections, COVID-19 often manifests as severe pneumonia. COVID-19 is associated with worse outcomes in the elderly population and those with comorbid health conditions such as obesity, diabetes mellitus, hypertension, and cardiovascular disorders.[1-8]

Viral and other respiratory infections are an important cause of recurrent disease exacerbations in asthma.[9] Individuals with asthma are, therefore, widely perceived to be at a higher risk of acquiring and of progressing to more severe COVID-19 disease. A few early reports suggested greater COVID-19 prevalence and severity among subjects with severe asthma.[7] However, subsequent data have remained conflicting.[10] Whereas the proportion of patients with asthma among patients with COVID-19 has been recorded to be higher than the general population prevalence of asthma in the United States of America and United Kingdom, the same was not noted in most Asian and European studies.[11-13] The proportion of asthma among patients with COVID-19 is also much lower than that observed during the 2009 influenza pandemic.[14] Pooled analyses of previous data in subjects with COVID-19 have suggested an overall impact ranging from protective effect to a marginal increase in mortality among those with asthma.[11,15-21] Patients with more severe asthma may be at a relatively greater risk of death.[7] Other patient outcomes are less well studied but show similar variability in results.[11,17,20-22] We therefore felt a need to perform a

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detailed analysis to clarify some of these issues. We conducted this review to evaluate if comorbid asthma increases the risk of severe disease, hospitalization, ICU care, need for mechanical ventilation, or mortality among subjects with COVID-19.

Methods

We preregistered our study protocol with the PROSPERO database (registration number CRD42021230263). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-analysis of Observational Studies in Epidemiology guidelines for this review.[23,24] An approval from our institutional review board was not necessary as we extracted only summary information from previously published articles.

Search Strategy

We conducted an online search for publications indexed till December 31, 2020, in the PubMed and Embase databases, without any linguistic restrictions. We used the following free-text search terms: (asthma, asthmatic) and (COVID19, COVID-19, COVID 19, nCoV, 2019nCoV, 2019-nCoV, CoV-2, CoV 2, SARS-CoV-2, SARSCoV2) for this purpose. We also examined the bibliographies of selected articles and recent reviews. In addition, we searched our files for any relevant publications.

Study Selection

After removing duplicate citations, 2 authors (ANA and RA) screened all titles and abstracts. We omitted publications not reporting on asthma or COVID-19. We also excluded experimental, radiological, or autopsy studies; case reports; letters to editor not describing original observations; conference abstracts; preprints; narrative and systematic reviews; guidelines; study protocols; and editorials. The full texts of citations considered potentially eligible by either reviewer were further assessed.

We included a study for data synthesis if it (1) included subjects with COVID-19 confirmed by detection of SARS-CoV2 RNA in respiratory specimens or strongly suspected on clinical or radiological assessment if a confirmatory test was not available; (2) assessed one or more of the following outcomes: severe COVID-19, hospital admission, transfer to ICU, need for mechanical ventilation, mortality, or a combination of these; and (3) provided numerical data (or information from which this could be extracted) on the number of subjects with and without asthma in the study population as well as the number of subjects experiencing outcome(s) of interest in either subject category. If the same (or substantially overlapping) subject cohort was studied for any particular outcome in more than one publication, only the one describing the largest subject population was selected. In case of any disagreement, study inclusion was decided by consensus between the 2 investigators.

Data Extraction and Study Quality

We extracted the following data from the eligible studies: lead author, study design, location and health care setting where the study was carried out, participant inclusion and exclusion criteria, the period of patient enrollment, the source of subject information, the method of ascertaining asthma diagnosis, the outcomes reported, the number of subjects with COVID-19 with and without asthma, and the number of events of interest in subjects with COVID-19 with and without asthma. We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of all studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. *Accessed February 22, 2021*). We considered a study to be of good quality if the NOS score was ≥ 7 (out of a maximum possible score of 9).

Statistical Analysis

We computed the relative risk, and the corresponding 95% CI, for each predefined outcome from each study.[25] We used a continuity correction of 0.5 for studies with zero cell frequencies prior to all calculations.

We constructed forest plots to graphically evaluate the spectrum of relative risks from individual studies for every explored outcome of interest. We pooled our data using the DerSimonian and Laird random effects model to generate summary estimates for relative risk.[26] Between-study heterogeneity was expressed using Higgins inconsistency index (I^2) and considered high for values > 0.75.[27] We attempted to explore reasons for heterogeneity only if data from 15 or more studies were summarized for any outcome. For this, we undertook subgroup analyses and meta-regression for predefined covariates that included continent where the study was conducted, study design, subject inclusion criteria, asthma definition criteria, and the overall study quality. Publication bias was assessed through Egger test.[28] We used the statistical software package Stata (intercooled edition 12.0, StataCorp, College Station, Texas) for data analysis.

Results

We identified 1,832 publications from our search (Fig. 1) and finally selected 90 articles for data synthesis.[29-118] The included studies were spread across 24 countries in 4 continents, with maximum contribution from the United States of America (39 studies). There were 21 publications from Asia, 26 from Europe, 42 from North America, and one from South America (Table S1 of online supplement, see the supplementary materials at http://www.rcjournal.com).

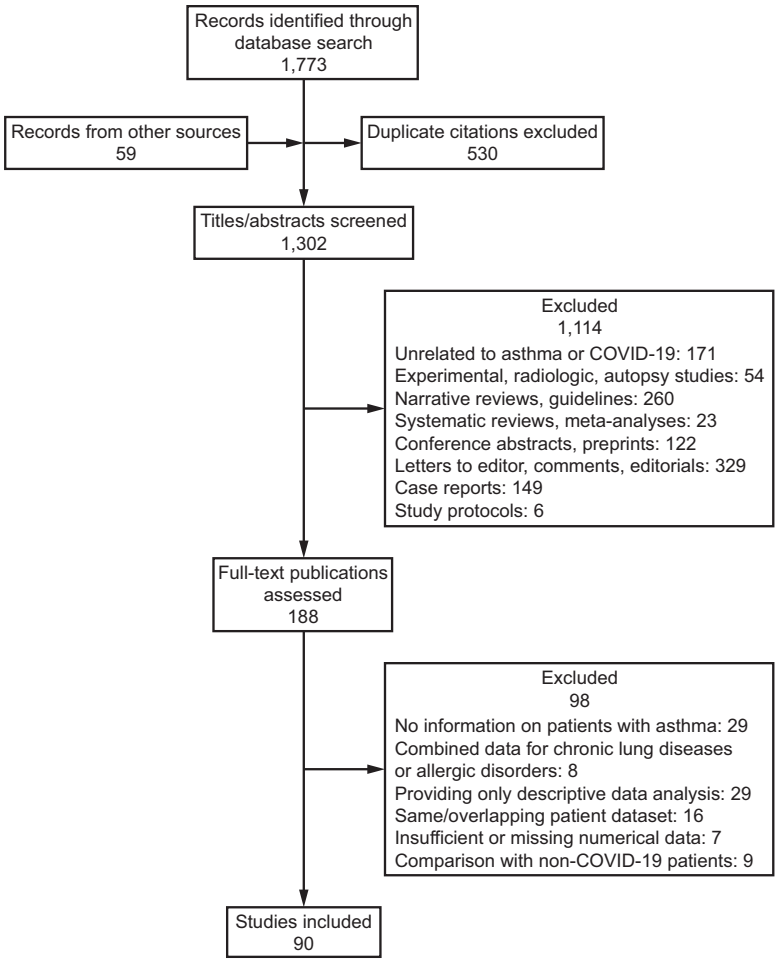

Fig. 1. Flow chart.

All studies reported data from retrospective subject cohorts, except for 8 (8.9%) that collected the information prospectively.[30,39,51,54,70,75,89,92] Only one study specifically evaluated children and adolescents; others included only adults or described a mixed population.[46] The period of data collection variably ranged between December 2019 and July 2020, although 4 (4.4%) studies did not provide this information. Subject information was retrieved mainly from medical records at participating health care facilities or from multi-center, regional, or national COVID-19 registries (Table S1 of online supplement, see the supplementary materials at http://www.rcjournal.com). Three (3.9%) studies queried insurance claims databases, 1 (1.3%) used telephone interview, and 5 (5.6%) did not provide specific information.[30,32,38,41,49,81,109,111,116] Five (5.6%) studies also included subjects with COVID-19 based on high clinical or radiological suspicion.[30,39,44,56,95] All others only studied subjects with disease confirmed by detection of SARS-CoV2 RNA in respiratory specimens. Most investigators reviewed medical records or used asthma-related diagnostic (or medication) codes in databases to identify subjects with asthma. However, 33 (36.7%) studies did not explicitly specify the process for defining asthma. The NOS score was 5 or higher for all studies; however, only 25 (27.8%) studies were of high quality (Table S1 of online supplement, see the supplementary materials at http://www.rcjournal.com).

Severe COVID-19

Twelve studies with 3,997 subjects with COVID-19, of whom 183 (4.6%) had asthma, provided information on severe COVID-19. All studies included subjects with laboratory-confirmed COVID-19. Only 1 (8.3%) had a prospective study design.[56] Three (25.0%) studies were considered high quality.[47,56,77] Of the 1,051 subjects with severe disease in the included cohorts, 45 (4.3%) had underlying asthma. Only 2 studies reported a relative risk for severe COVID-19 that significantly exceeded 1.0, and the confidence limits for all studies were wide (Fig S1 of online supplement, see the supplementary materials at http://www.rcjournal.com). The summary relative risk for severe disease was 1.17 (95%

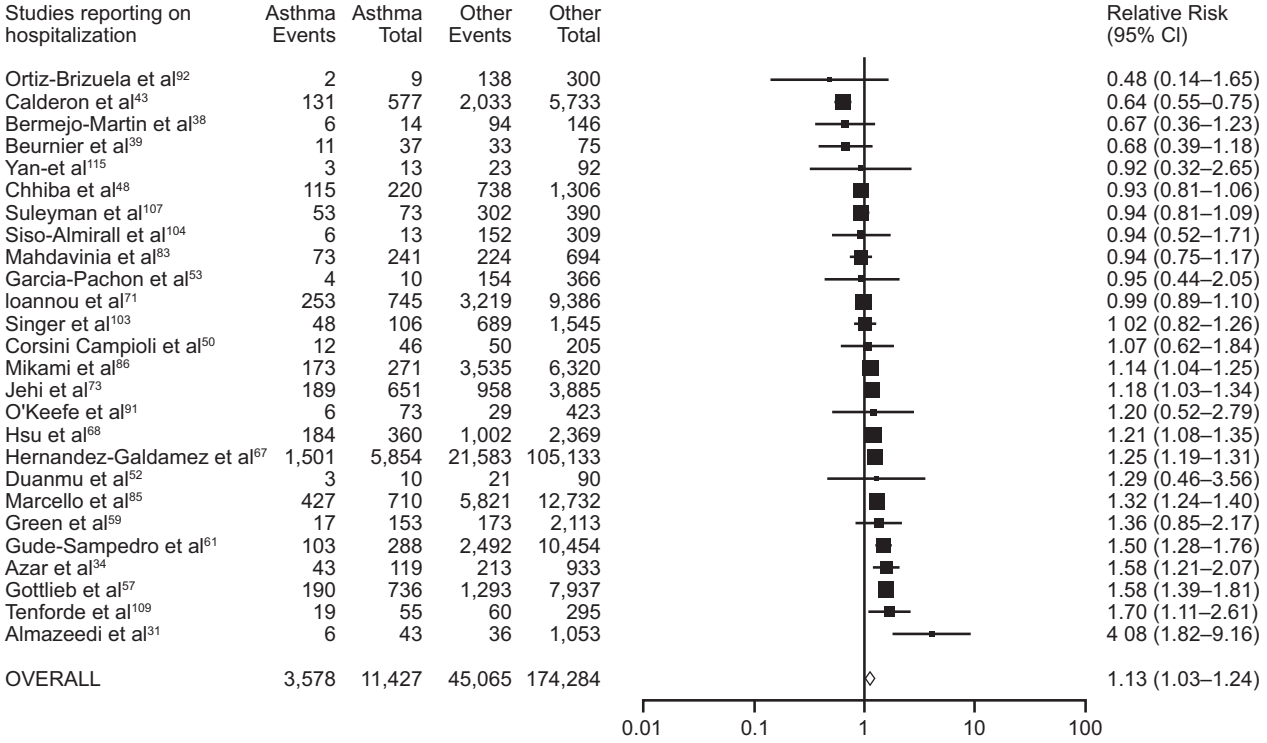

Fig. 2. Relative risk, and corresponding 95% CI, of need for hospitalization among subjects with COVID-19 with asthma.

CI 0.62–2.20), indicating that subjects with asthma were not predisposed to severe COVID-19.

There was considerable heterogeneity between the studies (I^2 80.9%). A subgroup analysis was not undertaken due to the small number of studies. There was no significant publication bias.

Need for Hospitalization

Twenty-six studies with 185,711 subjects with COVID-19, of whom 11,427 (6.2%) had asthma, provided information on hospitalization due to COVID-19. All except 2 (7.7%) studies included subjects with laboratory-confirmed COVID-19.[31,34] Only 2 (7.7%) studies had a prospective study design.[31,71] Nine (34.6%) studies were of high quality.[31,34,48,53,59,68,86,104,115] Overall, 26.1% of subjects were hospitalized. Of the 48,643 subjects who required hospitalization in the included cohorts, 3,578 (7.4%) had underlying asthma. Ten studies reported a relative risk for hospitalization that statistically significantly exceeded 1.0 (Fig. 2). Only one study reported a relative risk value clearly < 1.0.[43] Confidence limits for most studies were quite narrow (Fig. 2). The summary relative risk for hospitalization was 1.13 (95% CI 1.03–1.24), suggesting significantly higher risk of hospitalization among subjects with asthma.

There was considerable heterogeneity between the studies (I^2 85.5%). Studies conducted in Asia, however, were associated with negligible heterogeneity (Table S2 of online supplement, see the supplementary materials at http://www.rcjournal.com). On subgroup analysis, studies conducted in Asia or North America, those with a retrospective study design, those including only laboratory-confirmed COVID-19 cases, those where details regarding asthma definition were not specified, and relatively high-quality studies (NOS score ≥ 7) showed a summary relative risk clearly > 1.0, suggestive of significantly higher summary risk for hospitalization (Table S2 of online supplement, see the supplementary materials at http://www.rcjournal.com). Meta-regression indicated that subject inclusion criteria significantly influenced the risk for hospitalization. These differences were, however, not significant on multivariate analysis. There was no significant publication bias.

Need for ICU Admission

Twenty-four studies with 142,053 subjects with COVID-19, of whom 7,570 (5.3%) had asthma, provided information on the need for admission to ICU due to COVID-19. All but 2 (8.3%) studies included subjects with laboratory-confirmed COVID-19.[33,34] Only 1 (4.2%) study had a prospective study design.[76] Six (25.0%) studies were considered high quality (NOS score ≥ 7).[33,34,41,45,70,72] Overall, 3.1% of subjects required ICU care. Of the 4,444 subjects who were admitted to ICU in the included cohorts,

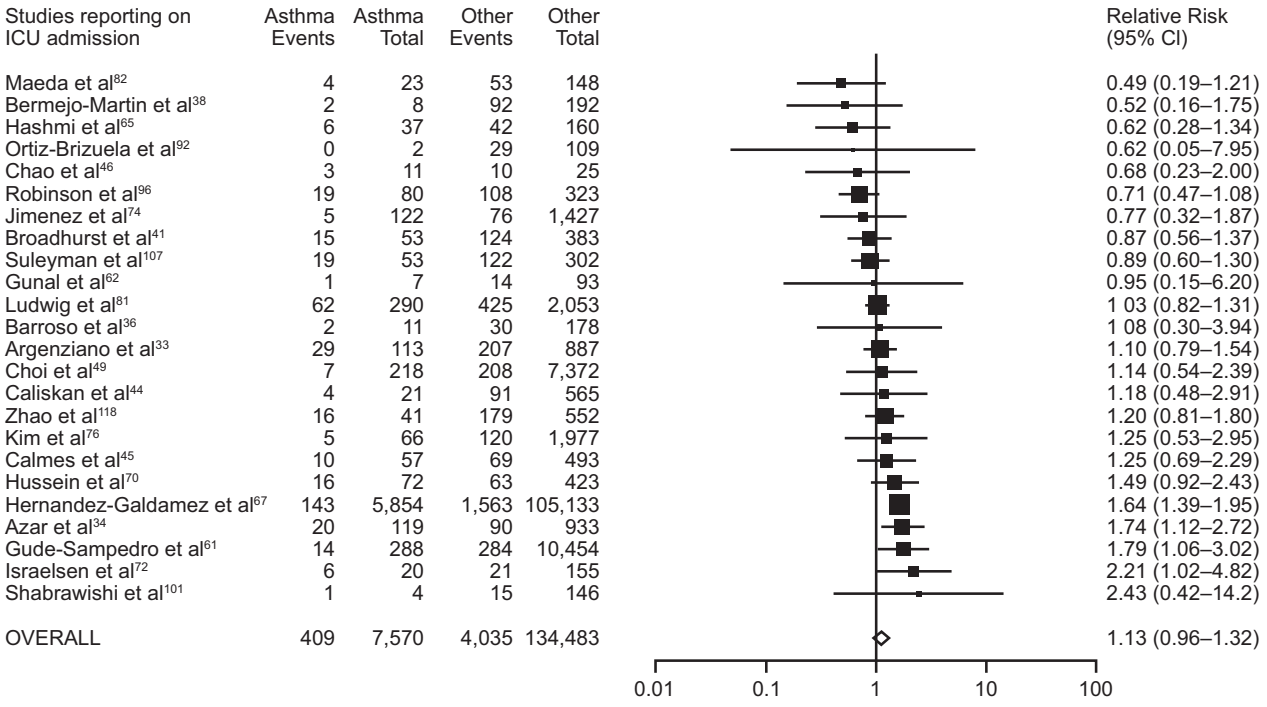

Fig. 3. Relative risk, and corresponding 95% CI, of need for admission to ICU among subjects with COVID-19 with asthma.

409 (9.2%) had underlying asthma. Only 4 studies reported a relative risk for admission to ICU that clearly exceeded 1.0, and confidence limits for most studies were wide (Fig. 3).[34,61,67,72] The summary relative risk for ICU admission was 1.13 (95% CI 0.96–1.32), denoting that subjects with asthma did not have a significantly increased risk of ICU admission.

There was only moderate heterogeneity between the studies (I^2 48.4%). Studies conducted in Asia and relatively high-quality studies (NOS score $\geq$ 7) were associated with negligible heterogeneity. On subgroup analysis, studies conducted in Asia, those where details regarding asthma definition were not specified, studies simultaneously reporting multiple subject outcomes (hospitalization, ICU admission, and mortality), and relatively high-quality studies showed a summary relative risk clearly $>$ 1.0, suggestive of significantly higher summary risk for ICU admission (Table S2 of online supplement, see the supplementary materials at http://www.rcjournal.com). Meta-regression indicated that studies simultaneously reporting on hospitalization, ICU admission, and mortality showed significantly higher risk for ICU admission. These differences were, however, not significant on multivariate analysis. There was no significant publication bias.

Need for Mechanical Ventilation

Eleven studies with 18,355 subjects with COVID-19, of whom 1,487 (8.1%) had asthma, provided information on the need for mechanical ventilation due to COVID-19. All studies included subjects with laboratory-confirmed COVID-19. Two (18.2%) studies had a prospective study design.[71,76] Only 2 (18.2%) studies were of high quality.[41,70] Overall, 11.6% of subjects was mechanically ventilated. Of the 2,131 subjects requiring mechanical ventilation in the included cohorts, 209 (9.8%) had underlying asthma. Two studies reported a relative risk for need for mechanical ventilation that statistically significantly exceeded 1.0, whereas another study showed a clear protective effect for subjects with asthma (Fig. 4).[70,76,96] The summary relative risk for mechanical ventilation was 1.05 (95% CI 0.85–1.29), indicating the absence of significantly higher risk for need of mechanical ventilation among individuals with asthma.

There was only moderate heterogeneity between the studies (I^2 51.5%). A subgroup analysis was not undertaken due to small number of studies. There was no significant publication bias.

Mortality

Fifty-three studies with 587,444 subjects with COVID-19, of whom 25,468 (4.3%) had asthma, provided information on mortality due to COVID-19. All except 4 (7.5%) studies included subjects with laboratory-confirmed COVID-19.[30,31,34,35] Six (11.3%) studies had a prospective study design.[30,31,54,71,76,90] Sixteen (30.2%) studies were considered high quality.[31,34,35,37,45,47,48,51,68,70,78,86,93,98,104,112] The overall mortality rate was 11.3%. Of the 66,696 subjects who died in the included cohorts, 2,840 (4.3%) had underlying asthma. Only 5 studies reported a relative risk for mortality

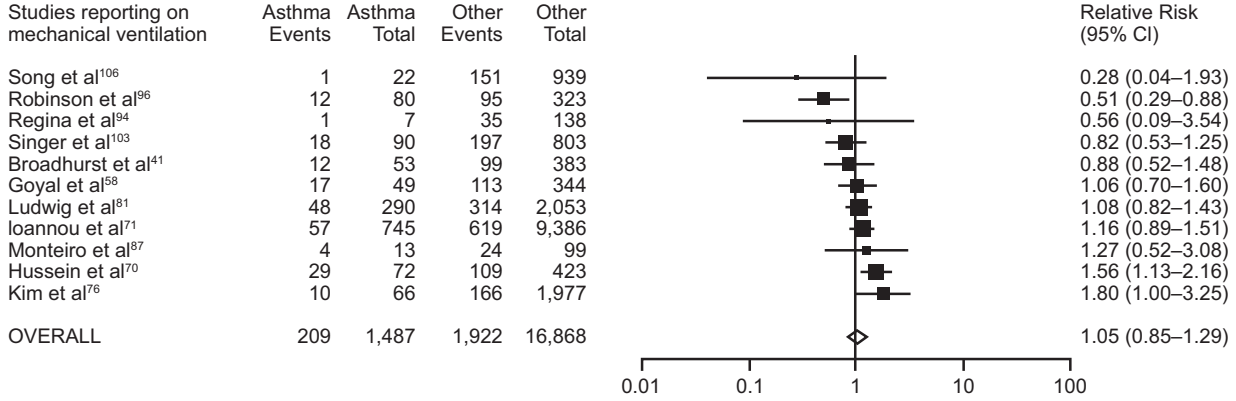

Fig. 4. Relative risk, and corresponding 95% CI, of need for mechanical ventilation among subjects with COVID-19 with asthma.

that clearly exceeded 1.0 (Fig. 5).[31,49,67,76,117] Another 6 studies suggested a clearly protective effect for asthma.[35,48,51,63,71,93] The confidence limits for most studies were wide (Fig. 5). The summary relative risk for mortality was 0.92 (95% CI 0.82–1.04), pointing to the absence of a statistically significant higher risk of death among subjects with asthma.

There was considerable heterogeneity between the studies (I^2 81.1%). No prespecified covariate influenced heterogeneity significantly. On subgroup analysis, the studies conducted in North America, those clearly specifying process for asthma definition, and high-quality studies showed a summary relative risk clearly < 1.0, suggestive of significantly reduced summary risk of death (Table S2 of online supplement, see the supplementary materials at http://www.rcjournal.com). No prespecified covariate significantly influenced summary relative risk on meta-regression. There was no significant publication bias.

Use of Inhaled Corticosteroids (ICS) and Subject Outcomes

An American study suggested no change in risk for hospitalization (relative risk 0.82, 95% CI 0.62–1.09) or risk for ICU admission (relative risk 0.88, 95% CI 0.75–1.04) for subjects with asthma using inhaled corticosteroids (ICS).[48] A French study similarly found a nonsignificant increase in risk for ICU admission for subjects on ICS (relative risk 2.16, 95% CI 0.55–8.49).[39] A Belgian study reported no significant change in odds of mortality for those using ICS (odds ratio 1.70, 95% CI 0.79–3.40).[45]

Discussion

We found that subjects with asthma had an overall higher risk of need for hospitalization (summary relative risk 1.13, 95% CI 1.03–1.24) among subjects with COVID-19. However, there was no increase in the risk for severe COVID-19 (summary relative risk 1.17, 95% CI 0.62–2.20), the need for ICU care (summary relative risk 1.13, 95% CI 0.96–1.32), mechanical ventilation (summary relative risk 1.05, 95% CI 0.85–1.29), or mortality (summary relative risk 0.92, 95% CI 0.82–1.04).

Only a few systematic reviews have focused specifically on COVID-19 outcomes in subjects with asthma.[11,17-22] Some of them summarized information from a few studies on asthma as one of the several comorbidities and risk factors evaluated.[1,4,15,16] Most reviews included < 15 studies. One review summarized data from 64 studies, several of which were available only as preprints without peer review.[11] A more recent meta-analysis summarized subject outcome data from 82 publications indexed in PubMed database ($n = 64$) or available on the medRxiv preprint server ($n = 18$) till December 22, 2020.[21] This meta-analysis reported no clear evidence of increased risk of hospitalization (summary relative risk 1.06, 95% CI 0.94–1.19), ICU admission (summary relative risk 1.18, 95% CI 0.98–1.42), or mortality (summary relative risk 0.85, 95% CI 0.71–1.01) due to asthma. This meta-analysis had a time frame similar to our review but reported on a few different studies. This was primarily because we specifically excluded publications available solely as preprints that had not been peer reviewed. Despite this and other minor methodological differences, our summary estimates largely mirror those reported in this meta-analysis.[21] We also provide additional information regarding severe COVID-19 and need for mechanical ventilation among these subjects. Both the number of studies as well as the number of outcomes studied are key strengths of our review.

Even when individuals with asthma contract COVID-19, the comorbidity does not appear to be associated with substantially greater COVID-19 severity or worse outcomes. This apparent paradox is indeed intriguing for a disease whose control is known to be negatively affected by respiratory viral infections.[9] This is in stark contrast to COPD, another important obstructive airway disorder, which is associated with significantly poorer prognosis in patients

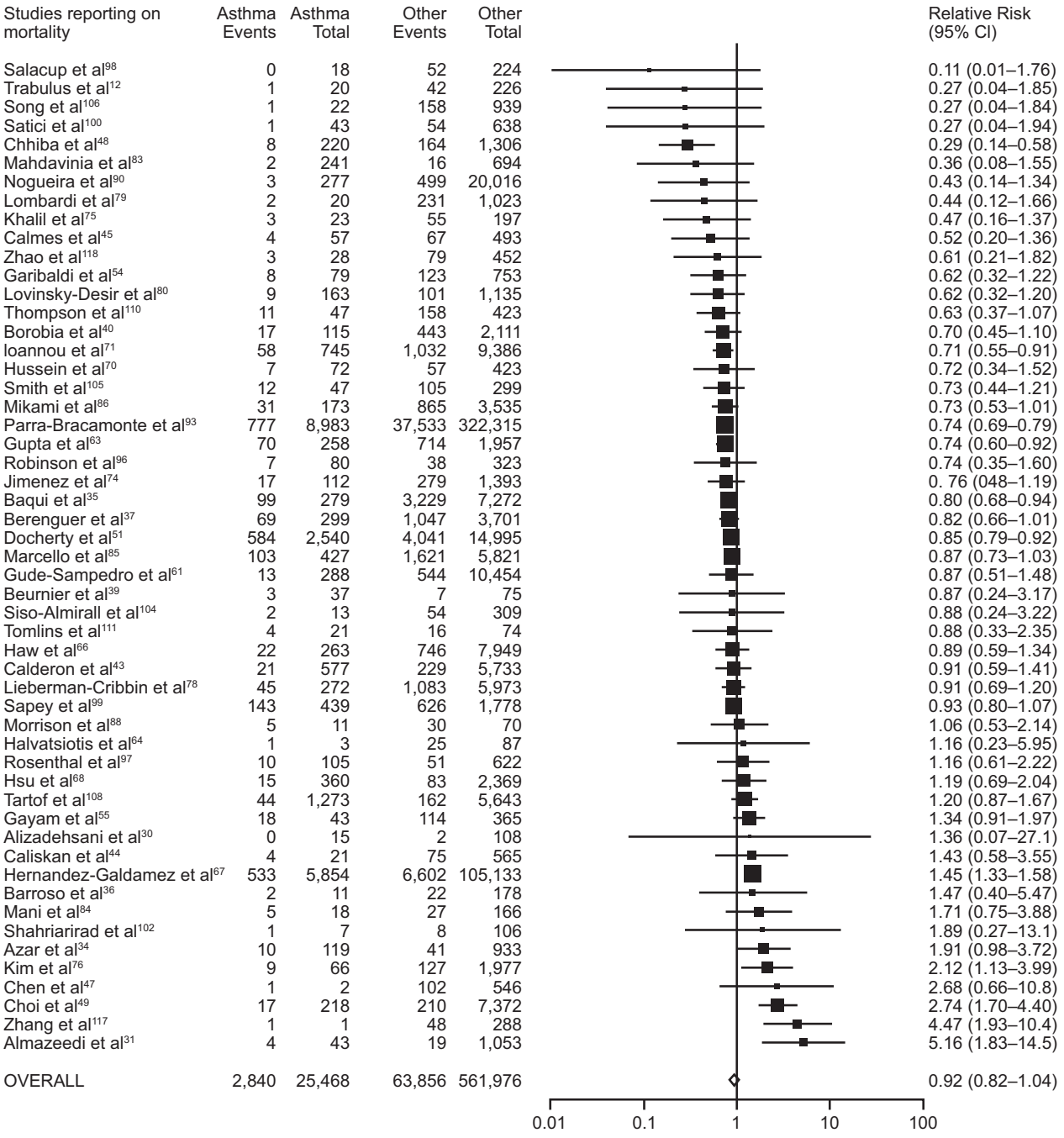

Fig. 5. Relative risk, and corresponding 95% CI, of mortality among subjects with COVID-19 with asthma.

with COVID-19.[119,120] This could be attributed to several factors. Patients with asthma are generally younger with lower prevalence of other comorbidities as compared to COPD. Enhanced T-helper-2 inflammation, commonly encountered among those with atopic asthma, may reduce angiotensin-converting enzyme 2 (ACE-2) expression in airway epithelium.[121] On the contrary, in COPD, ACE-2 expression is generally upregulated, primarily because of smoking. The routine use of ICS to control asthma could be an additional modifier. Ciclesonide suppressed SARS-CoV-2 replication in cultured human airway epithelial cells.[122] Expression of ACE-2 and transmembrane protease serine 2 (TMPRSS2) in sputum samples has also been observed to be much lower among subjects with asthma using ICS than those not using.[123] Since both ACE-2 and TMPRSS2 are involved in SARS-CoV-2 entry into cells,

these observations could explain the reduced susceptibility to COVID-19, and less severe disease, among subjects with asthma, especially the more common atopic variant.[13] Indeed, there are some data to suggest that patients with nonallergic asthma alone may be at a higher risk of more severe clinical outcomes related to COVID-19.[116] Finally, most patients with asthma remain relatively well controlled on therapy, especially if they are compliant with ICS and other agents appropriate to their disease stage. Use of ICS did not significantly influence subject outcomes in 3 of the studies reviewed by us.[39,45,48] None of the included studies provided additional analysis based on asthma severity or phenotypes. Hence, we cannot speculate if any specific subject subgroups experienced worse outcomes. These remain an area of future research.

Our systematic review has a few limitations. Due to the dynamic nature of the pandemic, and the lag between data collection and publication of results, most studies provided information from the first 6 months of 2020 and from regions that were severely afflicted earlier. Thus, the figures may not be truly representative of subject data from all the geographic locations. Nearly all the included studies had a retrospective design and collated data from review of electronic health records that were likely completed in an overwhelmed health system. This may have resulted in both underreporting as well as misclassification of preexisting comorbid diseases. Several studies reported only on in-patients (who even otherwise have a higher probability of adverse outcomes compared to other subjects) rather than milder cases in the community, and outcome data were not available for all subjects at the time of analysis in many instances. Only 30.3% of the included studies were of sufficiently high quality. There were differences in health care strategies regarding SARS-CoV-2 testing and admission/transfer criteria and variability in institutional practices in the timing of investigations and other evaluations and level and extent of medical intervention available to subjects. This is reflected in the wide variations in relative risk for all outcomes. Such heterogeneity can restrict the generalizability of our results. We cannot rule out an overestimation from lack of adjustment for potential confounders (eg, age, gender, other comorbid health conditions, asthma control and therapy, or other subject characteristics) as we focused on univariate relative risk estimates.

Our findings should provide assurance to patients with asthma. Also, our data synthesis from many studies should provide reasonable guidance to clinicians and policymakers regarding the risk stratification of patients with COVID-19 and formulation of algorithms for allocation and escalation of their acute care. They should also help administrators in modulating their practices and recommendations on prioritization of COVID-19 vaccination. In fact, the United Kingdom government recently decided to remove mild asthma as a priority category for COVID-19 vaccination.[124] However, there is still a need to conduct large well-designed studies to define if any patient characteristics or asthma phenotypes significantly worsen adverse COVID-19 outcomes or if patients with poorly controlled or severe asthma are at a higher risk.

Conclusions

In summary, the available evidence suggests that subjects with asthma with COVID-19 are at a higher risk of hospitalization. However, they do not appear to be at increased risk for severe COVID-19, need for ICU care, requirement for mechanical ventilation, or mortality, as compared to subjects with COVID-19 without asthma.

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