Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Original Article

The Association of Asthma With COVID-19 Mortality: An Updated Meta-Analysis Based on Adjusted Effect Estimates

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What is already known about this topic? The pooled prevalence of asthma in COVID-19 patients has been reported to be similar to that in the general population. However, the association of asthma with the risk for COVID-19 mortality is less evident.

What does this article add to our knowledge? Asthma was significantly related to a reduced risk for COVID-19 mortality.

How does this study impact current management guidelines? Asthma was an independent protective factor for the mortality of COVID-19 patients. Routine interventions and treatment for asthma patients infected with severe acute respiratory syndrome coronavirus 2 should be continued.

BACKGROUND: The association of asthma with the risk for mortality among coronavirus disease 2019 (COVID-19) patients is not clear.
OBJECTIVE: To investigate the association between asthma and the risk for mortality among COVID-19 patients.
METHODS: We performed systematic searches through electronic databases including PubMed, EMBASE, and Web of Science to identify potential articles reporting adjusted effect estimates on the association of asthma with fatal COVID-19. A random-effects model was conducted to estimate pooled effects. Sensitivity analysis, subgroup analysis, meta-regression, Begg's test and Egger's test were also performed.
RESULTS: Based on 62 studies with 2,457,205 cases reporting adjusted effect estimates, COVID-19 patients with asthma had a significantly reduced risk for mortality compared with those without it (15 cohort studies: 829,670 patients, pooled hazard ratio [HR] = 0.88, 95% confidence interval [CI], 0.82-0.95, I^2 = 65.9%, P < .001; 34 cohort studies: 1,008,015 patients, pooled odds ratio [OR] = 0.88, 95% CI, 0.82-0.94, I^2 = 39.4%, P = .011; and 11 cross-sectional studies: 1,134,738 patients, pooled OR = 0.87, 95% CI, 0.78-0.97, I^2 = 41.1%, P = .075). Subgroup analysis based on types of adjusted factors indicated that COVID-19 patients with asthma had a significantly reduced risk for mortality among studies adjusting for demographic, clinical, and epidemiologic variables (pooled OR = 0.87, 95% CI, 0.83-0.92, I^2 = 36.3%, P = .013; pooled HR = 0.90, 95% CI, 0.83-0.97, I^2 = 69.2%, P < .001), but not among studies adjusting only for demographic variables (pooled OR = 0.88, 95% CI, 0.70-1.12, I^2 = 40.5%, P = .097; pooled HR = 0.82, 95% CI, 0.64-1.06, I^2 = 0%, P = .495). Sensitivity analysis proved that our results were stable and robust. Both Begg's test and Egger's test indicated that potential publication bias did not exist.
CONCLUSIONS: Our data based on adjusted effect estimates indicated that asthma was significantly related to a reduced risk for COVID-19 mortality. © 2021 American Academy of Allergy, Asthma & Immunology **(J Allergy Clin Immunol Pract 2021;9:3944-68)**

Key words: *Asthma; COVID-19; Mortality; Meta-analysis; Adjusted effect estimate*

INTRODUCTION

A recent systematic review by Liu et al[1] suggested that coronavirus disease 2019 (COVID-19) patients with asthma had a lower risk for death compared with those without it, based on crude effects from six studies. Another systematic review by Shi et al,[2] based on 12 eligible articles reporting adjusted effects, also indicated that asthma was associated with a significantly reduced risk for COVID-19 mortality. These two studies are interesting.

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Abbreviations used
COVID-19- Coronavirus disease 2019

However, these systematic reviews do not explore sources of heterogeneity; also, more recent primary studies with larger sample sizes have been published. Therefore, an updated meta-analysis based on risk factor-adjusted effects was performed to verify the relationship between asthma and COVID-19 mortality, considering that several factors (sex, age, and underlying comorbidities) significantly affected the clinical outcomes of COVID-19 patients.[3-7]

METHODS

This meta-analysis was conducted in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[8] Systematic searches were carried out in Web of Science, PubMed and EMBASE to identify potential articles as of June 25, 2021. Search terms used were "2019-nCoV" or "SARS-CoV-2" or "COVID-19" or "coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2" and "asthma." Full queries for each bibliographic database are available in Table E1 (in this article's Online Repository at www.jaci-inpractice.org). We included primary studies comparing COVID-19 patients with asthma versus those without asthma regarding mortality, and in which adjusted effect estimates on the association between asthma and COVID-19 mortality were reported. In the case of a study resulting in more than one publication, only the one with more complete data was included. Duplicated publications, reviews, errata, protocols, comments, case reports, and studies with incomplete data were excluded.

Two independent authors (H. Hou and Y. Li) screened articles and abstracted essential information from all included eligible studies. Any disagreement was resolved by discussion. An assessment of study quality using National Institutes of Health Study Quality Assessment tools was performed by two independent reviewers (Y. Wang and H.Yang). For all included articles, study quality was judged as good, fair, or poor (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Basic information, including the first author, study period, prevalence of asthma, county or region, number of cases, age (means and SDs or medians with interquartile ranges), percentage of males, study design, adjusted risk factors, and adjusted effects, was extracted from each eligible article.

We conducted statistical analyses using STATA (version 12.1, StataCorp LP, College Station, Tex) and R (version 3.6.3, The R Foundation,Vienna, Austria). The pooled effect (pooled odds ratio [OR] and/or hazard ratio [HR]) and its 95% confidence interval (CI) were estimated by a random-effects model. Moreover, we presented separate results for the pooled OR and pooled HR. Heterogeneity across studies was assessed by Higgins I^2 statistic and chi squared–based Q test. Publication bias was investigated by Begg's test and Egger's test. Sensitivity analysis was conducted to evaluate the stability of our results by omitting each eligible study one at a time. Meta-regression and subgroup analyses were performed to investigate potential sources of heterogeneity (such as age, sex, region, data collection period (number of months since the first COVID-19 case), hospitalization status, and the types of adjusted factors). Two-tailed P less than .05 was considered statistically significant.

RESULTS

A total of 62 studies[9-70] with 2,457,205 patients were included. Basic characteristics of the included studies are presented in Table I. A flowchart of the study search and selection is shown in Figure 1. Sample sizes across the included studies ranged from 132 to 654,858. There were 30 studies conducted in North America (21 in the United States, eight in Mexico, and one in Canada), 15 in Europe (eight in the United Kingdom, two in Spain, and one each in Ireland, Italy, France, Belgium, and Sweden), 11 in Asia (six in Korea and one each in China, Turkey, Iran, Kuwait, and Saudi Arabia), and six in other regions (three in Brazil, one in Nigeria, one in Libya, and one from an international center). There were 39 retrospective cohort studies, 11 cross-sectional studies, nine prospective cohort studies, two case-control studies, and one case series.

Overall results based on adjusted effect estimates demonstrated that COVID-19 patients with asthma had a significantly reduced risk for mortality compared with those without it (15 cohort studies: 829,670 patients, pooled HR = 0.88, 95% CI, 0.82-0.95, $I^2 = 65.9\%$, $P < .001$; 34 cohort studies: 1,008,015 patients, pooled OR = 0.88, 95% CI, 0.82-0.94, $I^2 = 39.4\%$, $P = .011$; 11 cross-sectional studies: 1,134,738 patients, pooled OR = 0.87, 95% CI, 0.78-0.97, $I^2 = 41.1\%$, $P = .075$) (Figure 2). The results of subgroup analysis based on hospitalization status showed that asthma was associated with a significantly reduced risk for mortality in COVID-19 patients when we restricted the analysis to studies that included only hospitalized patients (20 studies: 751,644 patients, pooled OR = 0.87, 95% CI, 0.79-0.95, $I^2 = 44.0\%$, $P = .019$; 11 studies: 811,941 patients, pooled HR = 0.87, 95% CI, 0.81-0.94, $I^2 = 68.7\%$, $P < .001$) (Figure 3). The significant association was observed in studies reporting ORs but not in those reporting HRs in subgroups that included all laboratory-confirmed patients (36 studies: 1,391,631 patients, pooled OR = 0.88, 95% CI, 0.82-0.94, $I^2 = 31.5\%$, $P = .064$; six studies: 24,156 patients, pooled HR = 1.10, 95% CI, 0.80-1.50, $I^2 = 66.2\%$, $P = .011$) (Figure 3). The inconsistency of results may be a result of the difference in the number of studies in each subgroup; subgroups with fewer studies tended to conclude more often that asthma was not associated with mortality in COVID-19 patients. Subgroup analysis based on types of adjusted factors indicated that COVID-19 patients with asthma had a significantly reduced risk for mortality among studies adjusting for demographic, clinical, and epidemiologic variables (39 studies: 2,078,426 patients, pooled OR = 0.87, 95% CI, 0.83-0.92, $I^2 = 36.3\%$, $P = .013$; 16 studies: 835,345 patients, pooled HR = 0.90, 95% CI, 0.83-0.97, $I^2 = 69.2\%$, $P < .001$) (Figure 4), but not among studies adjusting only for demographic variables (nine studies: 97,434 patients, pooled OR = 0.88, 95% CI, 0.70-1.12, $I^2 = 40.5\%$, $P = .097$; two studies: 10,883 patients, pooled HR = 0.82, 95% CI, 0.64-1.06, $I^2 = 0\%$, $P = .495$) (Figure 4). Further subgroup analysis by region revealed that COVID-19 patients with asthma had a significantly reduced risk for mortality

TABLE I. Main characteristics of studies included in this meta-analysis

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
Shah[9]	March 2 to May 6, 2020	United States	68 (13.0)	522	All hospitalized patients with confirmed COVID-19	41.8	63 (50-72)	Case-control study	OR: 0.74 (0.33-1.64)	Age, BMI, sex, race, all baseline comorbidities
Arshad[10]	March 10 to May 2, 2020	United States	251 (9.9)	2541	All hospitalized adult patients with confirmed COVID-19	51.1	63.7 ± 16.5	Retrospective cohort study	HR: 0.916 (0.632-1.327)	Hydroxychloroquine alone, azithromycin alone, hydroxychloroquine plus azithromycin, age, sex, race, BMI, lung comorbidity, immunodeficiency comorbidity, cardiovascular comorbidity, CKD, COPD, HTN, cancer comorbidity, DM, percent O_2 saturation <95, admitted to ICU, ventilator, given steroid, given tocilizumab
Mato[11]	February 17 to April 30, 2020	International center	12 (6.1)	198	All patients diagnosed with confirmed COVID-19	63	63 (35-92)	Retrospective cohort study	HR: 2.5 (1.1-5.8)	Age, CIRS score, DM, chronic renal disease
Poblador-Plou[12]	March 4 to May 17, 2020	Spain	NR	4412	All individuals with laboratory-confirmed infection by SARS-CoV-2	41.2	67.7 ± 20.7	Retrospective cohort study	OR: 0.45 (0.18-1.11) OR: 0.68 (0.40-1.17)	Age
van Gerwen[13]	March 1 to May 13, 2020	United States	430 (11.6)	3703	All adult patients with laboratory-confirmed diagnosis of COVID-19	55.3	56.8 ± 18.2	Retrospective cohort study	OR: 0.89 (0.64-1.25)	Age group, sex, race, BMI, smoking status, comorbidities (HTN, CAD, AF, CHF, PVD, CVA/TIA, dementia, DM, hypothyroidism, CKD, malignancy, COPD, and prior VTE)

Hernandez-Galdamez[14]	Up to June 27, 2020	Mexico	5854 (2.77)	211,003	Laboratory-confirmed COVID-19 cases	54.71	45.7 ± 16.3	Cross-sectional study	OR: 0.82 (0.74-0.90)	Age, sex, CKD, immunosuppression, DM, COPD, HTN, CVD, obesity and smoking
Hernandez-Vasquez[15]	Up to May 18, 2020	Mexico	1590 (3.1)	51,053	Patients with confirmed COVID-19	57.6	46.6 ± 15.8	Cross-sectional study	OR: 1.02 (0.84-1.23)	Age, gender, smoking
Almazeedi[16]	February 24 to April 20, 2020	Kuwait	43 (3.9)	1096	All patients with confirmed COVID-19	81	41 (25-75)	Retrospective cohort study	OR: 4.92 (1.03-23.44)	Age, obesity, DM, HTN, chronic renal disease, smoker, qSOFA score, elevated procalcitonin, and elevated CRP
Perez-Guzman[17]	February 25 to May 1, 2020	United Kingdom	56 (9.1)	614	Patients admitted for COVID-19	62.21	69 ± 25	Retrospective cohort study	OR: 0.42 (0.19-0.91)	Age
Tartof[18]	February 13 to May 23, 2020	United States	1273 (18.4)	6916	Members diagnosed with COVID-19	44.98	49.1 ± 16.6	Retrospective cohort study	Risk ratio: 0.81 (0.54-1.21)	BMI, age, sex, race and ethnicity, smoking, metastatic tumor/cancer, MI, other immune condition, organ transplant, CHF, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, HTN, DM status, and time
Parra-Bracamonte[19]	January 13 to June 13, 2020	Mexico	4028 (2.8)	142,690	All cases positive for COVID-19	56	45 (34.0-57.0)	Cross-sectional study	OR: 0.949 (0.832-1.082)	Age, sex, smoking habits, hospitalization, and comorbidity traits
Fox[20]	March 1 to April 24, 2020	United States	27 (7.6)	355	All hospitalized adult patients with confirmed COVID-19	49	66.21 ± 14.21	Retrospective cohort study	OR: 0.714 (0.076-6.670)	Age, BMI, sex, ethnicity, COPD, heart failure, HTN, CAD, AF, and CKD

(continued)

TABLE I. *(Continued)*

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
Yehia[21]	February 19 to June 25, 2020	United States	628 (5.6)	11,210	All hospitalized adult patients with confirmed COVID-19	49.8	61 (46-74)	Retrospective cohort study	HR: 0.91 (0.74-1.12)	Race, age, sex, insurance, Agency for Healthcare Research and Quality Elixhauser Comorbidity Index scores, neighborhood deprivation index scores, cancer, CKD, COPD, CHF, CAD, DM, and obesity
Emami[22]	February 20 to March 1, 2020	Iran	25 (2.0)	1239	All hospitalized patients with confirmed COVID-19	55.9	51.48 ± 19.54	Retrospective cohort study	HR: 1.04 (0.53-2.02)	Age, DM, CVD, chronic liver disease, CKD, cancer, human immunodeficiency virus, smoking, and immunodeficiency disease
Trabulus[23]	March 15 to June 1, 2020	Turkey	20 (6.0)	336	All hospitalized adult patients with confirmed COVID-19	57.1	55.0 ± 16.0	Retrospective cohort study	OR: 3.087 (0.382-24.965)	Age
Santos[24]	February 20 to June 2, 2020	Brazil	488 (5.7)	80,102	All hospitalized patients with confirmed COVID-19	57.3	NR	Retrospective cohort study	HR: 0.71 (0.61-0.81)	ICU, DM, neurological, kidney disease, cardiopathy, race, and pneumopathy
Ioannou[25]	February 28 to June 22, 2020	United States	745 (7.4)	10,131	Patients with confirmed COVID-19	91	63.6 ± 16.2	Retrospective cohort study	HR: 0.80 (0.60-1.05)	All sociodemographic characteristics, comorbid conditions, and symptoms
									HR: 0.85 (0.65-0.11)	Age
Gutierrez[26]	Through September 16, 2020	Mexico	17,026 (2.6)	654,858	Adult (age ≥20 y) patients with confirmed COVID-19	52.21	46.1 (45.8-46.3)	Cross-sectional study	OR: 0.90 (0.84-0.96) OR: 0.96 (0.75-1.24) OR: 1.07 (0.86-1.34) OR: 0.44 (0.29-0.68)	Sex, age, indigenous speaker, obese, smoking, COPD, chronic renal disease, CVD, ministry of health, social security, private health provider, and quintiles of share poverty

Clift[27]	January 24 to April 30, 2020	United Kingdom	825,422 (13.57)	10,776	All adult patients with laboratory-confirmed diagnosis of COVID-19	55.33	69.6 ± 17.9	Prospective cohort study	HR: 0.84 (0.73-0.97) HR: 1.03 (0.91-1.17)	Age, BMI, Townsend score (linear), ethnic group, domicile (residential care, homeless, neither), and range of conditions and treatments
Kim[28]	March 1 to May 12, 2020	United States	903 (8.3)	10,861	All hospitalized adult patients with confirmed COVID-19	59.6	65 (54-77)	Prospective cohort study	OR: 0.81 (0.67-0.98)	Age, sex, race and ethnicity, presence of comorbidities, smoking status, hospital type, and BMI groups
Tang[29]	March 1 to June 16, 2020	United States	54 (7.2)	752	All individuals with laboratory-confirmed infection by SARS-CoV-2	39.9	72.1 ± 11.9	Retrospective cohort study	HR: 0.64 (0.30-1.40)	Age, sex, race, and facility
Ken-Dror[30]	March to April, 2020	United Kingdom	42 (12.8)	429	All hospitalized adult patients with confirmed COVID-19	56.4	70 ± 18	Prospective cohort study	OR: 3.22 (1.16-8.92)	Age, CRP, respiratory rate, diastolic blood pressure, dementia, Akaike information criterion, area under the curve, and sensitivity/ specificity
Choi[31]	NR	Korea	96 (2.3)	4057	Hospitalized patients with mild to critical COVID-19 nationwide	42.5	NR	Prospective cohort study	HR: 2.20 (1.02-4.76)	Age, sex, obesity, systolic blood pressure, diastolic blood pressure, heart rate, temperature, DM, HTN, heart failure, chronic heart disease, COPD, CKD, cancer, chronic liver disease, rheumatic or autoimmune disease, and dementia
Nyabera[32]	February 1 to April 30, 2020	United States	18 (6.2)	290	Older adult inpatients (≥65 y) with laboratory-confirmed COVID- 19 infection	51.7	77.6 ± 8.3	Retrospective cohort study	OR: 0.66 (0.24-1.83)	BMI, age, CAD, COPD, DM, end-stage renal disease, and HTN

(continued)

TABLE I. *(Continued)*

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
Lee[33]	January 20 to May 27, 2020	Korea	686 (9.4)	7272	Adult COVID-19 patients	40.3	NR	Retrospective cohort study	OR: 1.06 (0.71-1.59)	Age, sex, and CCI
Murillo-Zamora[34]	March 4 to August 15, 2020	Mexico	NR	66,123	All hospitalized adult patients with confirmed COVID-19	60.7	NR	Retrospective cohort study	HR: 0.92 (0.85-0.99)	Sex, age, clinically diagnosed pneumonia at hospital admission, tobacco use, obesity, COPD, type 2 DM arterial HTN, immunosuppression, and CKD
Ling[35]	January 27 to August 7, 2020	United Kingdom	52 (11.7)	444	All hospitalized adult patients with confirmed COVID-19	55.1	74 (63-83)	Cross-sectional study	OR: 0.31 (0.13-0.71)	Age, sex, obesity, ethnicity, and presence of DM (types 1 and 2 combined)
Izurieta[36]	April 1 to May 8, 2020	United States	962,666 (3.8)	27,961	All elderly patients (ages $\geq$65 y) with confirmed COVID-19	48.8	75 (70-85)	Retrospective cohort study	OR: 0.93 (0.85-1.03)	Sex, age, area deprivation index national rank, circulation rate, population density, vaccination, presence of medical conditions, frailty conditions, immune compromised status, and race
Lundon[37]	March 28 to April 26, 2020	United States	403 (4.5)	8928	All individuals with laboratory-confirmed infection by SARS-CoV-2	46.2	58.0 $\pm$ 18.8	Cross-sectional study	OR: 0.68 (0.51-0.91)	Age, sex, race and ethnicity, New York City borough, English as preferred language, smoking status, COPD, HTN, obesity, DM, CKD, human immunodeficiency virus, and cancer

Schwartz[38]	January 21 to September 30, 2020	Canada	2655 (4.7)	56,606	All individuals with laboratory-confirmed infection by SARS-CoV-2	48.4	NR	Cross-sectional study	OR: 0.85 (0.66-1.09)	Sex (male vs female), age (<30 y, 30-44 y, 60-4 y, or ≥75 y, compared with 45-59 y), comorbidities (COPD, renal disease, cardiac disease, DM, immune compromised or cancer, obesity, or other comorbidities, compared with no comorbidities), working or residing in long-term care home (yes vs no), and symptoms (fever and/or cough, other symptoms, or missing symptoms compared with asymptomatic)
Martos-Benítez[39]	January 1 to May 13, 2020	Mexico	NR	38,324	All individuals with laboratory-confirmed infection by SARS-CoV-2	58.3	46.9 ± 15.7	Retrospective cohort study	OR: 0.86 (0.64-1.16)	Age, sex, smoking habit, time from symptoms onset to medical contact, COPD, high blood pressure, CVD, DM, obesity, CKD, and other comorbidities
Oh[40]	January 1 to June 4, 2020	Korea	NR	7780	Adult (age ≥20 y) patients with confirmed COVID-19	NR	NR	Retrospective cohort study	OR: 1.03 (0.76-1.41)	COPD, interstitial lung disease, lung cancer, lung disease d/t external agent, obstructive sleep apnea, tuberculosis of lung, age, income level, sex, residence, underlying disability, CCI, HTN, DM, peripheral vascular disease, renal

(continued)

TABLE I. *(Continued)*

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
										disease, rheumatic disease, dementia, peptic ulcer paraplegia, hemiplegia or paraplegia, moderate or severe liver disease, mild liver disease, cerebrovascular disease, CHF, MI, malignancy, metastatic solid tumor, and acquired immunodeficiency syndrome/human immunodeficiency virus
Park[41]	February 15 to April 24, 2020	Korea	NR	2269	Patients hospitalized with COVID-19	35.9	55.5 ± 20.2	Retrospective cohort study	OR: 2.13 (0.74-6.13)	Age, male, respiratory rate, fever, altered consciousness, hemoptysis, sore throat, malaise, COPD, CKD, malignancy, chronic neurological disorder, and preexisting cardiovascular risk factor/CVD
Ahlstrom[42]	March 6 to May 27, 2020	Sweden	261 (2.6)	1981	All adult patients with laboratory-confirmed diagnosis of COVID-19	74	61 (52-69)	Case-control study	HR: 1.52 (1.04-2.22)	Simplified acute physiology score 3, age, sex, ischemic heart disease, nonischemic heart disease, HTN, type 1 DM, type 2 DM, stroke, chronic renal disease, COPD, immunosuppressed, and cancer

Lopez Zuniga[43]	February 4 to April 30, 2020	Spain	NR	318	All adult patients with laboratory-confirmed diagnosis of COVID-19	58.5	64.9 ± 14.1	Prospective cohort study	HR: 2.235 (0.554-9.02)	Age, sex, HTN, COPD, immunosuppression, chronic heart disease, AF, obesity, tumor, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, needed high oxygen volume, DM, qSOFA, hydroxychloroquine azithromycin, lopinavir/ritonavir, interferon, corticosteroids, tocilizumab, vitamin D supplementation, and anticoagulation therapy
Mollalo[44]	January 22 to November 22,2020	United States	NR	NR	All individuals with laboratory-confirmed infection by SARS-CoV-2	NR	NR	Cross-sectional study	OR: 4.584 (2.583-8.137) OR: 0.818 (0.461-1.452)	NR
Lohia[45]	March 10 to June 30, 2020	United States	134 (7.2)	1871	All adult patients with laboratory-confirmed diagnosis of COVID-19	51.6	64.1 ± 16	Retrospective cohort study	OR: 0.98 (0.61-1.58)	Age, sex, race, BMI, and comorbidities including HTN, CAD, DM, CKD, ESRD on dialysis, CHF, any cancer, any liver disease, hyperlipidemia, and history of stroke
Cedano[46]	March 3 to April 22, 2020	United States	7 (5)	132	All adult patients admitted to ICU with severe COVID-19 infection	59	63 (53-71)	Retrospective cohort study	OR: 2.13 (0.10-45.4)	Age, male sex, arterial HTN, DM, COPD, CAD, systolic heart failure, diastolic heart failure, CKD, end-stage kidney disease, BMI, and mechanical ventilation

(continued)

TABLE I. *(Continued)*

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
Girardin[47]	March 2 to May 24, 2020	United States	493 (11.7)	4446	All hospitalized patients with confirmed COVID-19	58.1	62 ± 18	Case series	HR: 0.83 (0.67-1.04)	Age, ethnic minority, male sex, low income, smoking, obesity, COPD, sleep apnea, HTN, DM, peripheral artery disease, CAD, autoimmune disease, and cancer
Cao[48]	March to September 2020	United States	72 (21.0)	343	All adult patients with laboratory-confirmed diagnosis of COVID-19	56	60.7 ± 15.9	Prospective cohort study	OR: 0.72 (0.31-1.57)	Age, race (Black or not Black), sex, COPD, and obesity
Ho[49]	March 7 to June 7, 2020	United States	468 (4.4)	10,523	All adult patients with laboratory-confirmed diagnosis of COVID-19	54.2	58.4 ± 18.8	Retrospective cohort study	OR: 0.64 (0.53-0.77)	Age, sex, BMI, race, COVID-19 disease severity, CCI, COPD, CRP (>150), interleukin-6 (>80), ferritin (>2000), D-dimer (>2.0 μg/L), use of anticoagulation, use of corticosteroids, and smoking (current and former)
Guan[50]	December 2019 to May 6th, 2020	China	830 (2.1)	39,420	All hospitalized patients with confirmed COVID-19	49.9	55.7	Retrospective cohort study	OR: 0.84 (0.48-1.48)	Presence of any other systemic comorbidities, female sex, and age
Bloom[51]	January 17 to August 17, 2020	United Kingdom	7859 (10.4)	75,463	All hospitalized patients with confirmed COVID-19	55.4	NR	Prospective cohort study	HR: 1.17 (0.73-1.86) HR: 0.99 (0.61-1.58) HR: 0.94 (0.62-1.43) HR: 1.02 (0.67-1.54) HR: 1.96 (1.25-3.08) HR: 0.97 (0.89-1.05) HR: 0.86 (0.80-0.92) HR: 1.13 (1.01-1.28) HR: 0.97 (0.89-1.06)	Age, sex, ethnicity, deprivation, obesity, smoking, chronic cardiac disease, CKD, and malignancy
Osibogun[52]	February 27 to July 6, 2020	Nigeria	45 (2.1)	2184	All hospitalized patients with confirmed COVID-19	65.8	43 (33-55)	Retrospective cohort study	OR: 1.52 (0.41-5.57)	Age and sex

de Souza[53]	February 26 to August 10, 2020	Brazil	4566 (7.15)	44,128	All hospitalized patients with confirmed COVID-19	54.2	NR	Retrospective cohort study	HR: 0.79 (0.73-0.85)	Male sex, age, fever, cough, dyspnea, respiratory distress, blood oxygen saturation <95%, diarrhea, other symptom, cardiac disease, liver disease, immunodepression, DM, neuropathy, pneumopathy, kidney disease, other comorbidity, flu vaccine, ICU admission, invasive mechanical ventilation, and noninvasive ventilation
Mulhem[54]	March 13 to April 29, 2020	United States	429 (13.3)	3219	All hospitalized patients with confirmed COVID-19	49	65.2 (52.6-77.2)	Retrospective cohort study	OR: 1.14 (0.84-1.55)	Gender, age, race, current smoking and comorbidities
Topless[55]	March 16 to August 24, 2020	United Kingdom	40,898 (8.6)	2118	All individuals with laboratory-confirmed infection by SARS-CoV-2	NR	NR	Retrospective cohort study	OR: 1.11 (0.80-1.53)	Current age, sex, ethnicity, Townsend deprivation index, BMI, and smoking status
Bennett[56]	March 2 to September 14, 2020	Ireland	467 (2.4)	19,789	All individuals with laboratory-confirmed infection by SARS-CoV-2	43.6	NR	Retrospective cohort study	OR: 0.82 (0.50-1.35)	Age (linear, quadratic, and cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, and CKD

(continued)

TABLE I. *(Continued)*

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
										Chronic liver disease, immunodeficiency, DM, BMI ≥40, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility, and route of transmission
									OR: 0.82 (0.53-1.26)	Age
Lieberman-Cribbin[57]	February 29 to April 24, 2020	United States	272 (4.4)	6250	All individuals with laboratory-confirmed infection by SARS-CoV-2	NR	NR	Cross-sectional study	OR: 0.94 (0.66-1.34)	Age, sex, and race
Calmes[58]	March 18 to April 17, 2020	Belgium	57 (9.6)	596	All hospitalized adult patients with confirmed COVID-19	49.3	58.8 ± 18.9	Retrospective cohort study	OR: 0.74 (0.24-2.3)	Age, sex, cardiopathy, immunosuppressive disease, and COPD
									OR: 0.59 (0.20-1.8)	Age and sex
Choi[59]	Up to May 15, 2020	Korea	218 (2.9)	7590	All individuals with laboratory-confirmed infection by SARS-CoV-2	40.8	NR	Retrospective cohort study	OR: 1.317 (0.708−2.451)	Age, sex, and underlying diseases
Kim[60]	February to May 2020	Korea	70 (3.2)	2200	All hospitalized adult patients with confirmed COVID-19	35.7	56.7 ± 19.0	Cross-sectional study	OR: 1.762 (0.813-3.822)	Age and sex

									OR: 1.656 (0.624-4.395)	Age, sex, BMI, smoking history, underlying comorbidity (COPD, DM, HTN, heart failure, other heart disease, CKD, chronic liver disease, cancer, autoimmune disease, dementia, and other psychological disorder), and medication (antiretroviral, hydroxy chloroquine, systemic steroid, and azithromycin)
Alwafi[61]	March 15 to August 15, 2020	Saudi Arabia	28 (4.0)	706	All hospitalized patients with confirmed COVID-19	68.5	48.0 ± 15.6	Cross-sectional study	OR: 0.80 (0.07-8.82)	Age, sex, and comorbidities
Vera-Zertuche[62]	February 24 to April 26, 2020	Mexico	542 (3.5)	15,529	All individuals with laboratory-confirmed infection by SARS-CoV-2	57.8	46.6 ± 15.5	Retrospective cohort study	OR: 0.63 (0.24-1.70)	Sex, age, and time from symptom onset to care, social lag index, aging index, afro-descendant/100 inhabitants, indigenous language-speaking/ 100 inhabitants, affiliation to health services/100 inhabitants, members per household, hospitals/10,000 inhabitants, and hospital beds/10,000 inhabitants

(continued)

TABLE I. *(Continued)*

First author	Study period	Country	Prevalence of asthma, n (%)	Patients, n	Population	Male (%)	Age, y	Study design	Adjusted-effect (95% confidence interval)	Confounders
Elhadi[63]	May 29 to December 30, 2020	Libya	51 (11)	465	All adult COVID-19 patients admitted to ICUs	51.6	69 (56.5-75)	Prospective cohort study	HR: 0.66 (0.40−1.10)	Age, BMI, comorbidities, laboratory findings during admission, qSOFA score, type of intubation during admission, developed sepsis/ septic shock at during ICU admission, inotropes/ vasopressor, antibiotic, and major complications or events
Cummins[64]	February 1 to June 30, 2020	United Kingdom	244 (13.7)	1781	All adult (age ≥16 y) patients with laboratory-confirmed diagnosis of COVID-19	55.2	NR	Retrospective cohort study	OR: 1.03 (0.70-1.50)	Age, sex, ethnicity, top 30% most deprived areas, obese, smoker (current), AF, cancer, chronic heart disease, CKD, COPD, dementia, depression, type 1 DM, type 2 DM, epilepsy, heart failure, HTN, learning disability, severe mental illness, peripheral arterial disease, and stroke
Castro[65]	By 14 December 2020	Brazil	14,567 (2.8)	522,167	All hospitalized patients with confirmed COVID-19	56.0	61 (47-73)	Retrospective cohort study	OR: 0.81 (0.77-0.86)	Age, sex, ethno-racial self-classification, region, ICU, obesity, DM, chronic liver disease, chronic neurological disease, chronic lung disease, immunodeficiency, and CKD
									HR: 0.88 (0.84-0.92)	

Beltramo[66]	March 1 to April 30, 2020	France	3273 (3.7)	89,530	All hospitalized patients with confirmed COVID-19	53.1	65 ± 20	Retrospective cohort study	OR: 0.82 (0.71-0.94)	Lung cancer, COPD, pulmonary sarcoidosis, ILD, emphysema, sleep apnea, chronic respiratory failure, and pulmonary HTN
Robles-Pérez[67]	March to December 2020	Mexico	2403 (3.2)	75,595	All Social Security workers with confirmed COVID-19	42.4	NR	Retrospective cohort study	OR: 0.96 (0.51-1.79)	Age, sex, and presence of comorbidities
De Rosa[68]	February 27 to June 15, 2020	Italy	23 (1.5)	1538	Hospitalized adult patients with confirmed COVID-19	58	74 (61-83)	Retrospective cohort study	OR: 1.45 (0.44-4.78)	Age, sex, smoking, DM, HTN, CVD, COPD, immunodepression, P/F, lymphocytopenia, LDH, eGFR, D-dimer, and CRP
Marciniak[69]	January 17, 2020 to February 15, 2021	United Kingdom	NR	73,832	Hospitalized adult patients with confirmed COVID-19	NR	NR	Prospective cohort study	OR: 0.90 (0.85-0.96)	Age, sex, and comorbidities
Kelly[70]	March 2 to October 31, 2020	United States	1487 (5.4)	27,640	All veterans with confirmed COVID-19	88.6	57.2 ± 16.6	Retrospective cohort study	OR: 0.88 (0.65-1.19)	Age, sex, race, ethnicity, marital status, clinical factors, health care facility, and month of COVID-19 diagnosis

AF, atrial fibrillation; *BMI*, body mass index; *CAD*, coronary artery disease; *CCI*, Charlson comorbidity index; *CHF*, congestive heart failure; *CIRS*, cumulative illness rating scale score; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease comorbidity; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration rate; *HR*, hazard ratio; *HTN*, hypertension; *ICU*, intensive care unit; *IQR*, interquartile range; *LDH*, lactate dehydrogenase; *MI*, myocardial infarction; *NR*, not reported; *OR*, odds ratio; *P/F*, arterial oxygen tension/inspired oxygen fraction; *qSOFA*, quick sequential organ failure assessment.
Values of age are presented as means ± SDs or medians (IQRs).

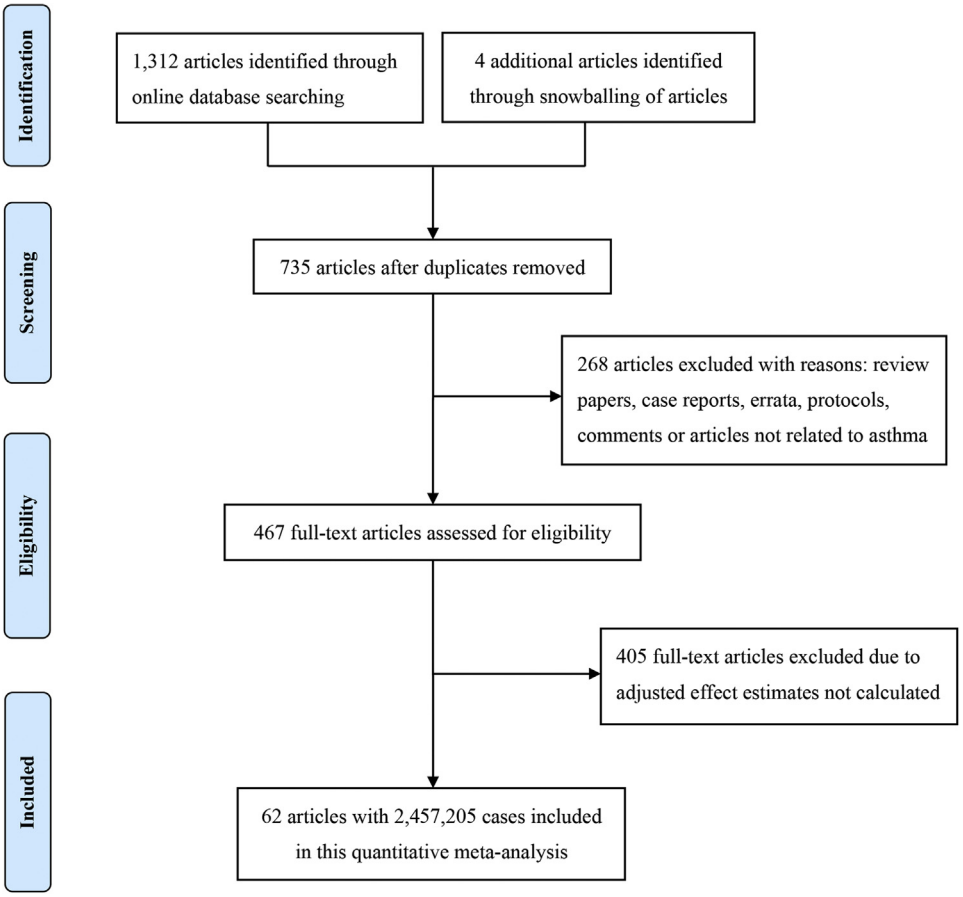

FIGURE 1. Flowchart of study search and selection.

compared with patients without asthma among North American patients (24 studies: 1,355,172 patients, pooled OR = 0.87, 95% CI, 0.82-0.92, I^2 = 15.8%, P = .243; six studies: 95,203 patients, pooled HR = 0.90, 95% CI, 0.84-0.96, I^2 = 0%, P = .808 (Figure 5) and South American patients (3 studies: 646,397 patients, pooled HR = 0.80, 95% CI, 0.72-0.90, I^2 = 83.1%, P = .003) (Figure 5), but not among Asian patients (9 studies: 68,669 patients, pooled OR = 1.13, 95% CI, 0.92-1.38, I^2 = 1.0%, P = .426; 2 studies: 5296 patients, pooled HR = 1.47, 95% CI, 0.71-3.07, I^2 = 51.7%, P = .150) (Figure 5) or European patients (11 studies: 195,083 patients, pooled OR = 0.86, 95% CI, 0.73-1.01, I^2 = 56.0%, P = .012; 4 studies: 88,538 patients, pooled HR = 1.07, 95% CI, 0.89-1.29, I^2 = 52.1%, P = .099) (Figure 5). Age (OR: tau^2 = 0.010, t = −0.62, P = .542; HR: tau^2 = 0.008, t = −0.63, P = .540) (Figure 6, *A* and *B*), sex (OR: tau^2 = 0.007, t = −0.14, P = .889; HR: tau^2 = 0.016, t = 0.33, P = .743) (Figure 6, *C* and *D*), and data collection periods (OR: tau^2 = 0.007, t = −0.28, P = .777; HR: tau^2 = 0.017, t = −0.82, P = .428) (Figure 6, *E* and *F*) could not explain potential sources of heterogeneity by meta-regression. We did not observe potential publication bias in Begg's test (OR: P = .394; HR: P = .343) (Figure 7, *A* and *B*) or Egger's test (OR: P = .142, HR: P = .265) (Figure 7, *C* and *D*). Sensitivity analysis proved that our results were stable.

DISCUSSION

This meta-analysis on the basis of adjusted effects estimates found that COVID-19 patients with asthma had a significantly reduced risk for mortality compared with those without asthma, which suggests that asthma might be an independent protective factor for developing fatal outcomes among COVID-19 patients. Meta-regression and subgroup analyses showed that none of these factors (such as age, sex, region, hospitalization status, data collection period, and the types of adjusted factors) could explain the potential sources of heterogeneity. Although the detailed mechanisms underlying the association between asthma and the reduced risk for COVID-19 mortality are unclear, several possibilities exist: (1) COVID-19 patients with asthma may receive more medical care in clinical practice; (2) the use of inhaled corticosteroids, allergen immunotherapy, and biological agents might be beneficial through suppressing viral replication and alleviating inflammation[71]; and (3) type 2 immune response in patients with asthma might counteract the severe acute respiratory syndrome coronavirus 2 infection-induced inflammatory process.[72] Further studies should focus on underlying mechanisms of preexisting asthma reducing the risk for fatal COVID-19. The association between having asthma and lower COVID-19 mortality may also have resulted from study bias, including selection bias (eg, a lack of representativeness), information bias (asthma underreporting or overreporting), and

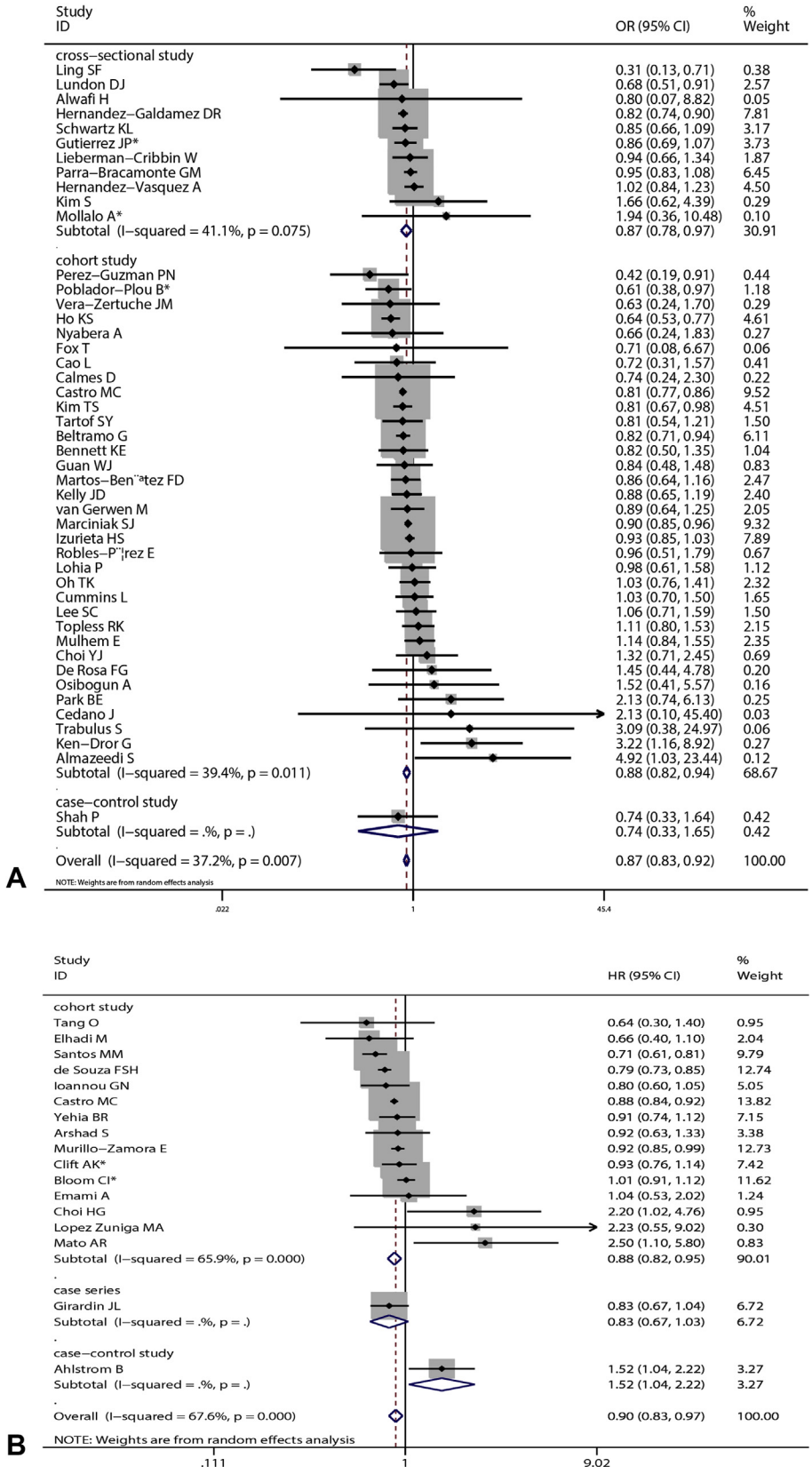

FIGURE 2. Forest plots indicating that coronavirus disease 2019 (COVID-19) patients with asthma had a significantly reduced risk for mortality compared with those without it. Arrow indicates that the 95% confidence interval (CI) for effect size in the study was equal to or greater than the x-axis value. Sizes of the shaded area reflect the study-specific statistical weights. (**A**) Pooled odds ratio (OR). (**B**) Pooled hazard ratio (HR). *Combined effects based on subgroups.

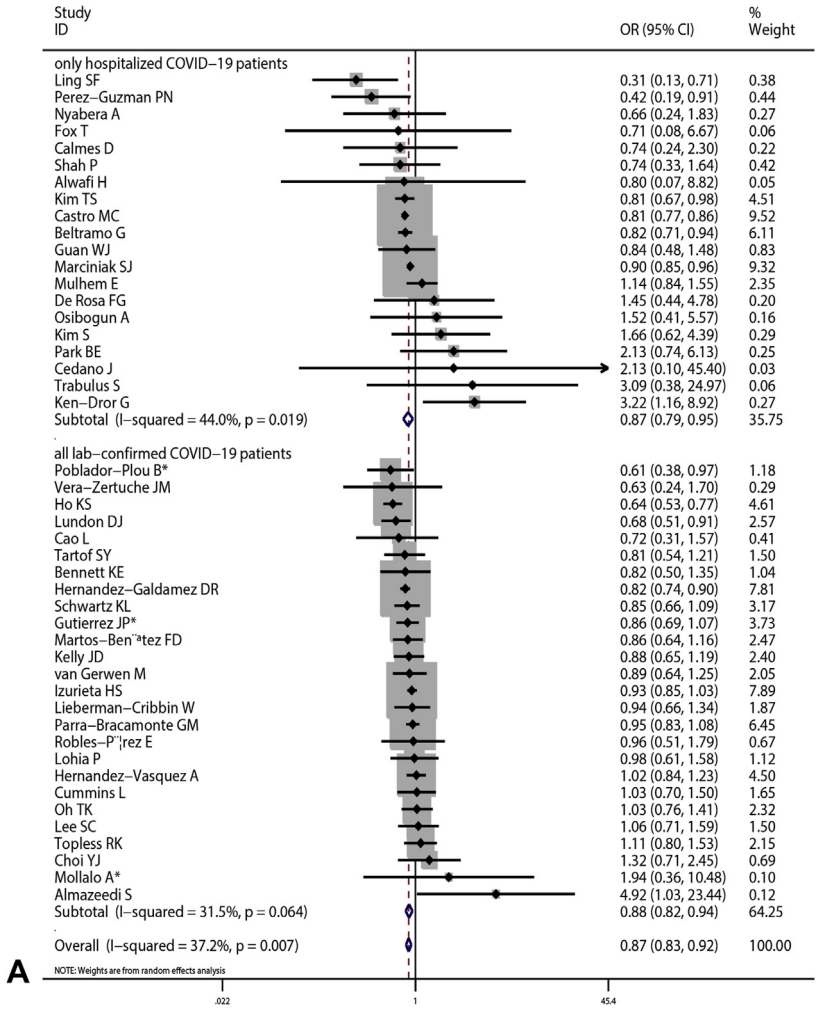

FIGURE 3. Subgroup analysis by hospitalization status: (**A**) pooled odds ratio (OR) and (**B**) pooled hazard ratio (HR). *Combined effects based on subgroups. *CI*, confidence interval.

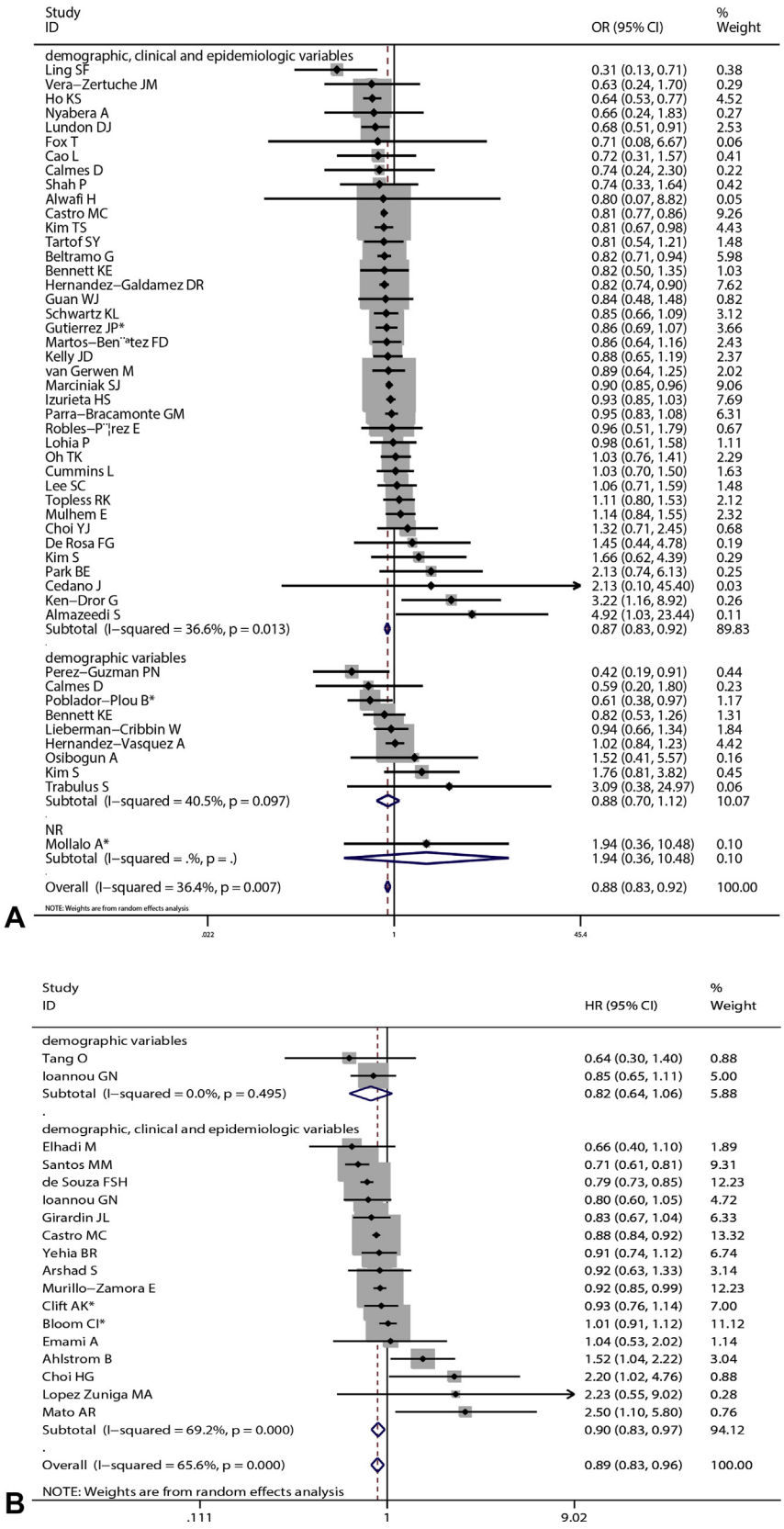

FIGURE 4. Subgroup analysis by type of adjusted factors: (**A**) pooled odds ratio (OR) and (**B**) pooled hazard ratio (HR). *Combined effects based on subgroups. *CI*, confidence interval.

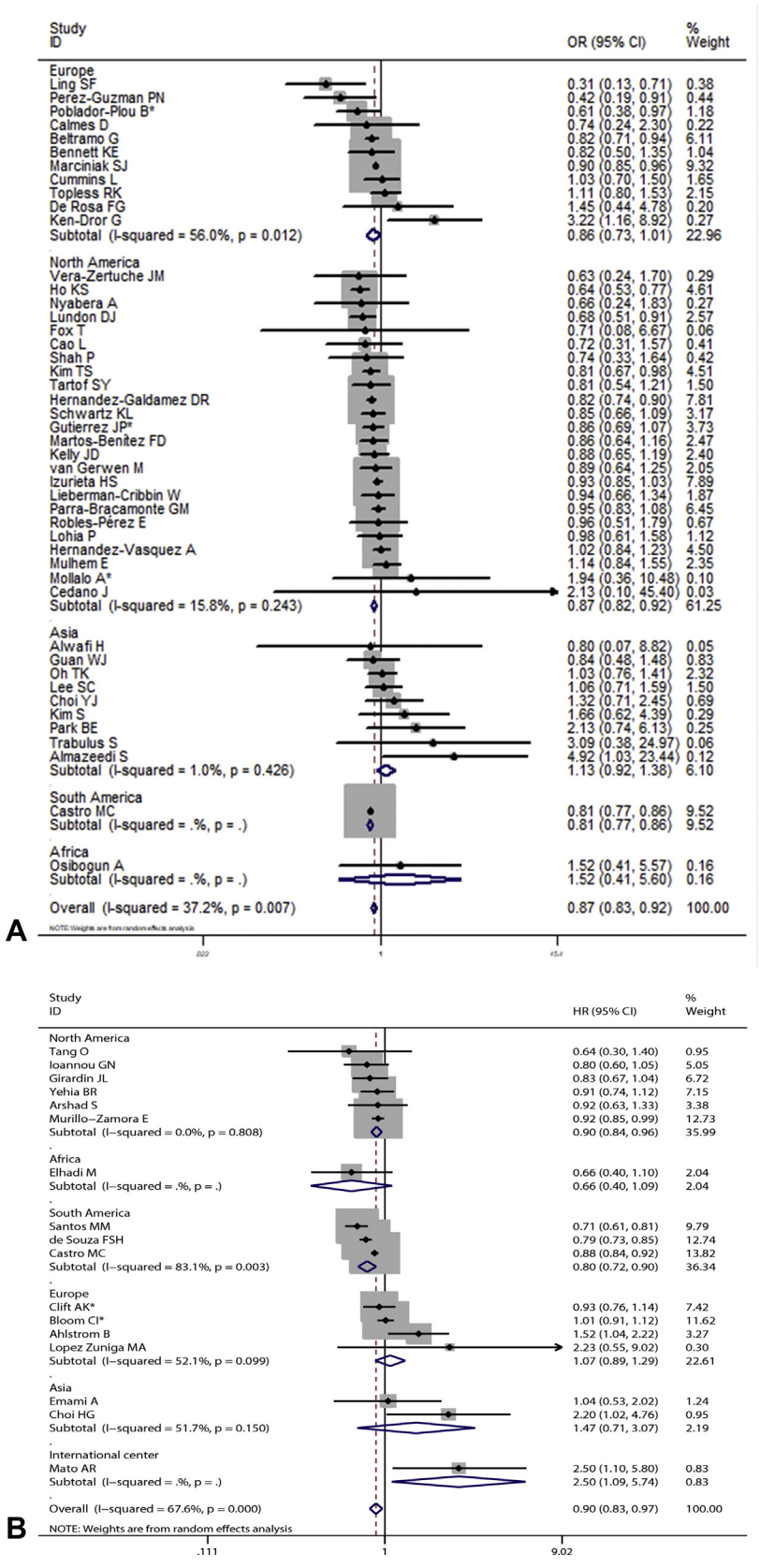

FIGURE 5. Subgroup analysis based on region: (**A**) pooled odds ratio (OR) and (**B**) pooled hazard ratio (HR). *Combined effects based on subgroups. *CI*, confidence interval.

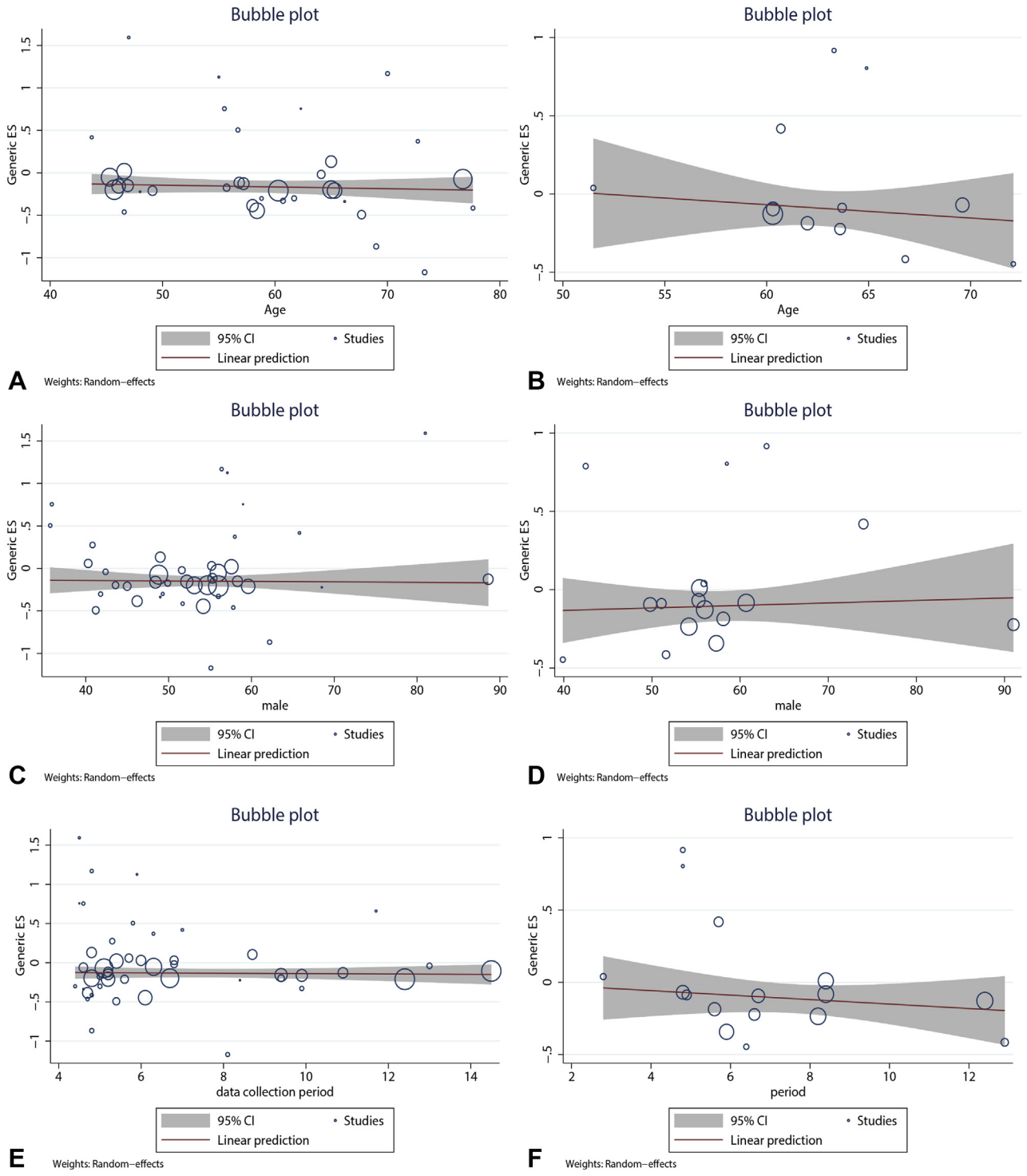

FIGURE 6. Meta-regression for age to evaluate association between asthma and mortality of COVID-19 patients: (**A**) pooled odds ratio [OR]; (**B**) pooled hazard ratio (HR) and sex; (**C**) pooled OR; (**D**) pooled HR and data collection period; (**E**) pooled OR; and (**F**) pooled HR. *CI*, confidence interval.

confounding bias (eg, asthma may have been relatively underrepresented among patients with other comorbidities that predispose more often to COVID-19 mortality, such as diabetes, obesity, or smoking, because asthma is common among younger patients).

A strength of this study was the large number of included studies (62 eligible articles) with 2,457,205 cases reporting adjusted effect estimates, which consider the influences of confounding factors such as age, sex, and underlying diseases on the association between asthma and mortality among COVID-19

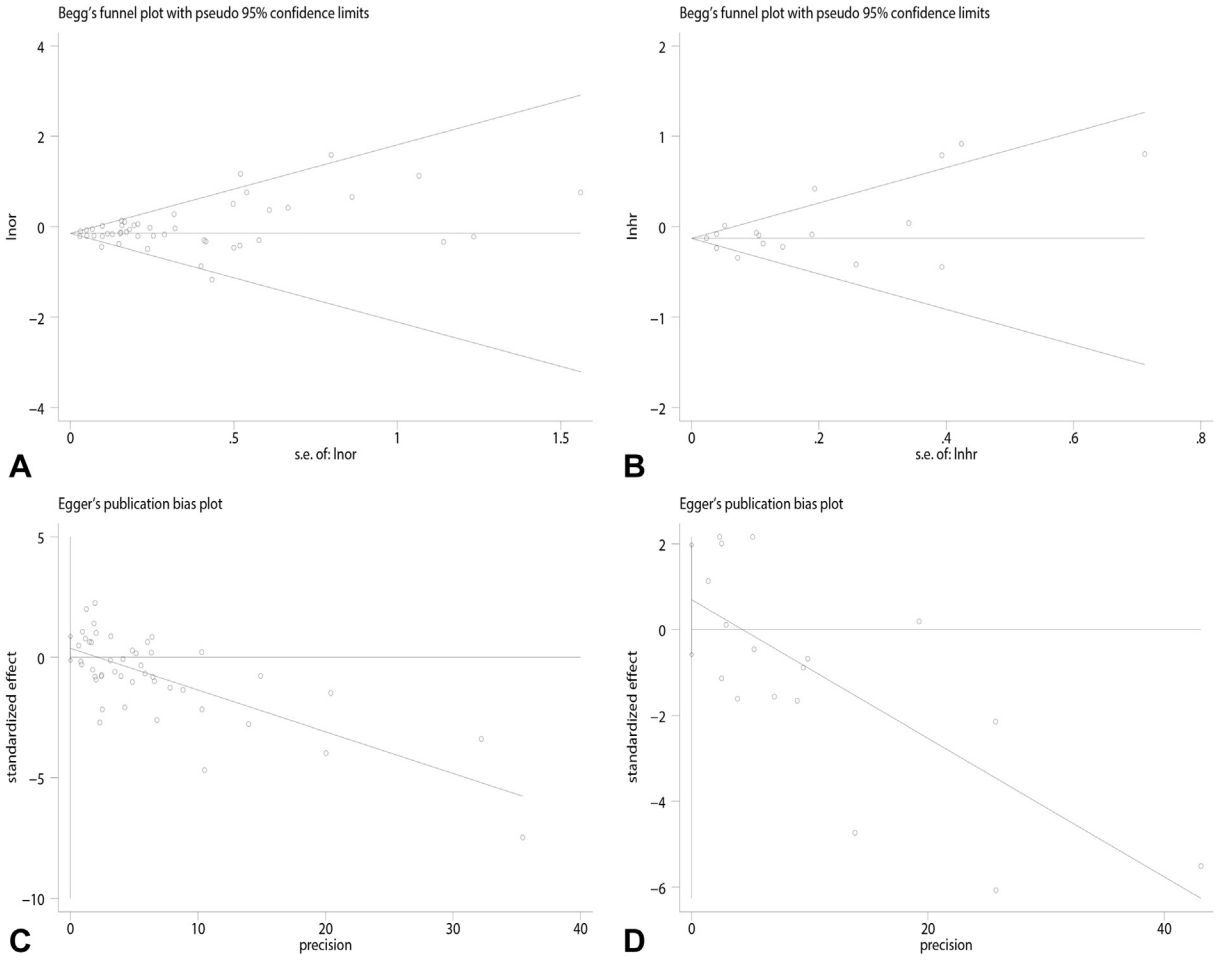

FIGURE 7. Publication bias was evaluated by Begg's test: (**A**) pooled odds ratio (OR); (**B**) pooled hazard ratio (HR) and Egger's test; (**C**) pooled OR; (**D**) pooled HR.

patients. However, several limitations should be acknowledged. First, most included studies were from North America, and one should be cautious when extrapolating the findings to other regions. Second, most of the eligible studies were designed retrospectively. Thus, further well-designed prospective studies with large sample sizes are warranted to verify the findings. Third, the pooled effects were estimated based on risk factor-adjusted effects, but the adjusted risk factors were not fully consistent across the included studies. We performed subgroup analysis according to the types of adjusted factors, which yielded inconsistent results. These results may have been because the number of studies adjusting only for demographic variables was significantly smaller than the number of studies adjusting for demographic, clinical, and epidemiologic variables, which warrants further studies based on more primary studies and larger sample sizes. Fourth, we did not investigate the effects of medication on the association between asthma and COVID-19 mortality, which should be addressed in the future when sufficient data are available. Fifth, there was heterogeneity across studies, which was why we performed meta-regression and further subgroup analyses but did not identify potential sources of heterogeneity. In addition, excluding articles that were not written in English might be a source of publication bias. However, publication bias was not detected by Begg's test or Egger's test. Our data indicate that asthma is related to a significantly reduced risk for COVID-19 mortality. Thus, routine interventions and treatment for asthma patients infected with severe acute respiratory syndrome coronavirus 2 should be continued. We hope the updated data will contribute to more accurate elaboration and substantiation of findings from the study of Liu et al.[1]

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ONLINE REPOSITORY

TABLE E1. Search strategies

Database	Search strategies
PubMed	("coronavirus disease 2019" OR "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "novel coronavirus") AND ("mortality" OR "fatality" OR "death" OR "non-survivor" OR "deceased") AND ("asthma")
EMBASE	('coronavirus disease 2019' OR 'covid-19' OR 'sars-cov-2' OR '2019-ncov' OR 'novel coronavirus') AND ('asthma') AND ('mortality' OR 'fatality' OR 'death' OR 'non-survivor' OR 'deceased')
Web of Science	TS = (("coronavirus disease 2019" OR "covid-19" OR "sars-cov-2" OR "2019-ncov" OR "novel coronavirus") AND ("asthma") AND ("mortality" OR "fatality" OR "death" OR "non-survivor" OR "deceased"))

TABLE E2. Assessment of risk for bias in each study with National Institutes of Health Study Quality Assessment tools in prognosis meta-analysis

First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Cohort and cross-sectional studies															
Arshad S[E1]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Mato AR[E2]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Poblador-Plou B[E3]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
van Gerwen M[E4]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Hernandez-Galdamez DR[E5]	Yes	Yes	No	Yes	No	Yes	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Hernandez-Vasquez A[E6]	Yes	Yes	NR	Yes	No	Yes	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Almazeedi S[E7]	Yes	Yes	Yes	Yes	No	Yes	NA	No	Yes	NR	Yes	NR	Yes	Yes	i
Perez-Guzman PN[E8]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Tartof SY[E9]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Parra-Bracamonte GM[E10]	Yes	Yes	NR	Yes	No	NR	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Fox T[E11]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	NR	Yes	NR	Yes	Yes	i
Yehia BR[E12]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Emami A[E13]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Trabulus S [E14]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Santos MM[E15]	Yes	Yes	NR	Yes	No	NR	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Ioannou GN[E16]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Gutierrez JP[E17]	Yes	Yes	NR	Yes	No	Yes	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Clift AK[E18]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Kim TS[E19]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Tang O[E20]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Ken-Dror G[E21]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Choi HG[E22]	Yes	Yes	NR	Yes	No	Yes	NR	No	Yes	NR	Yes	NR	NR	Yes	i
Nyabera A[E23]	Yes	Yes	NR	Yes	No	Yes	NR	No	NR	NR	NR	NR	Yes	Yes	i
Lee SC[E24]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	ii
Murillo-Zamora E[E25]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Ling SF[E26]	Yes	Yes	NR	Yes	No	Yes	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Izurieta HS[E27]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Lundon DJ[E28]	Yes	Yes	Yes	Yes	No	NR	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Schwartz KL[E29]	Yes	Yes	NR	Yes	No	NR	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Martos-Benítez FD[E30]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Oh TK[E31]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Park BE[E32]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	NR	Yes	i
Lopez Zuniga MA[E33]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Mollalo A[E34]	Yes	Yes	Yes	Yes	No	NR	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Lohia P[E35]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Cedano J[E36]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Cao L[E37]	Yes	Yes	NR	Yes	No	Yes	NR	No	Yes	NR	Yes	NR	NR	Yes	i
Ho KS[E38]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Guan WJ[E39]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Bloom CI[E40]	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	ii
Osibogun A[E41]	Yes	Yes	NR	Yes	No	Yes	Yes	No	No	NR	Yes	NR	Yes	Yes	i
de Souza FSH[E42]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Mulhem E[E43]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Topless RK[E44]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Bennett KE[E45]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Lieberman-Cribbin W[E46]	Yes	Yes	NR	Yes	Yes	NR	NA	No	No	NR	Yes	NR	NA	Yes	i
Calmes D[E47]	Yes	Yes	NR	Yes	No	NR	NR	No	Yes	No	Yes	NR	Yes	Yes	i
Choi YJ[E48]	Yes	Yes	NR	Yes	No	Yes	NR	Yes	Yes	NR	Yes	NR	Yes	Yes	i
Kim S[E49]	Yes	Yes	Yes	Yes	No	Yes	NA	No	Yes	NR	Yes	NR	NA	Yes	i
Alwafi H[E50]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Vera-Zertuche JM[E51]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	i
Elhadi M[E52]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Cummins L[E53]	Yes	Yes	Yes	Yes	No	Yes	NR	No	Yes	NR	Yes	NR	Yes	Yes	i

(continued)

TABLE E2. *(Continued)*

First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Castro MC[E54]	Yes	Yes	Yes	NR	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Beltramo G[E55]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Robles-Pérez E[E56]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	NR	NR	Yes	Yes	i
De Rosa FG[E57]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Marciniak SJ[E58]	Yes	Yes	NR	Yes	No	Yes	NR	No	Yes	NR	Yes	NR	NR	Yes	i
Kelly JD[E59]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Yes	i
Case-control studies															
Shah P[E60]	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	NR	Yes	i		
Ahlstrom B[E61]	Yes	Yes	NR	Yes	Yes	Yes	NR	NR	Yes	Yes	NR	Yes	i		
Case series studies															
Girardin JL[E62]	Yes	Yes	NR	NR	Yes	NR	NR	Yes	Yes	i					

NA, not applicable; *NR*, not reported.

For cohort and cross-sectional studies, quality was rated as 0 for poor (0-4 of 14 questions), i for fair (5-10 of 14 questions), or ii for good (11-14 of 14 questions): (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Was the participation rate of eligible persons at least 50%? (4) Were all of the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (5) Was a sample size justification, power description, or variance and effect estimates provided? (6) For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured? (7) Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)? (9) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (10) Was the exposure(s) assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was loss to follow-up after baseline 20% or less? (14) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? For case-control studies, quality was rated as 0 for poor (0-3 of 12 questions), i for fair (4-8 of 12 questions), or ii for good (9-12 of 12 questions): (1) Was the research question or objective in this paper clearly stated and appropriate? (2) Was the study population clearly specified and defined? (3) Did the authors include a sample size justification? (4) Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same time frame)? (5) Were the definitions, inclusion and exclusion criteria, algorithms, or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? (6) Were the cases clearly defined and differentiated from controls? (7) If less than 100% of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? (8) Was there use of concurrent controls? (9). Were the investigators able to confirm that the exposure or risk occurred before the development of the condition or event that defined a participant as a case? (10) Were the measures of exposure or risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? (11) Were the assessors of exposure or risk blinded to the case or control status of participants? (12) Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? For case series studies, quality was rated as 0 for poor (0-2 of nine questions), i for fair (3-6 of nine questions), or ii for good (7-9 of nine questions): (1) Was the study question or objective clearly stated? (2) Was the study population clearly and fully described, including a case definition? (3) Were the cases consecutive? (4) Were the subjects comparable? (5) Was the intervention clearly described? (6). Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Was the length of follow-up adequate? (8) Were the statistical methods well-described? (9) Were the results well-described?

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