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Impact of asthma on COVID-19 mortality in the United States: Evidence based on a *meta*-analysis

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ABSTRACT

Objective: The aim of this study was to investigate the impact of asthma on the risk for mortality among coronavirus disease 2019 (COVID-19) patients in the United States by a quantitative *meta*-analysis.
Methods: A random-effects model was used to estimate the pooled odds ratio (OR) with corresponding 95% confidence interval (CI). I^2 statistic, sensitivity analysis, Begg's test, *meta*-regression and subgroup analyses were also performed.
Results: The data based on 56 studies with 426,261 COVID-19 patients showed that there was a statistically significant association between pre-existing asthma and the reduced risk for COVID-19 mortality in the United States (OR: 0.82, 95% CI: 0.74–0.91). Subgroup analyses by age, male proportion, sample size, study design and setting demonstrated that pre-existing asthma was associated with a significantly reduced risk for COVID-19 mortality among studies with age $\geq$ 60 years old (OR: 0.79, 95% CI: 0.72–0.87), male proportion $\geq$ 55% (OR: 0.79, 95% CI: 0.72–0.87), male proportion < 55% (OR: 0.81, 95% CI: 0.69–0.95), sample sizes $\geq$ 700 cases (OR: 0.80, 95% CI: 0.71–0.91), retrospective study/case series (OR: 0.82, 95% CI: 0.75–0.89), prospective study (OR: 0.83, 95% CI: 0.70–0.98) and hospitalized patients (OR: 0.82, 95% CI: 0.74–0.91). Meta-regression did reveal none of factors mentioned above were possible reasons of heterogeneity. Sensitivity analysis indicated the robustness of our findings. No publication bias was detected in Begg's test (P = 0.4538).
Conclusion: Our findings demonstrated pre-existing asthma was significantly associated with a reduced risk for COVID-19 mortality in the United States.

1. Introduction

It has been reported that the prevalence of comorbid asthma among coronavirus disease 2019 (COVID-19) patients varied greatly across countries or regions worldwide [1–3]. Previous *meta*-analyses have investigated the association between pre-existing asthma and COVID-19 mortality in the whole regions [1–3], but the conclusions were inconsistent, which might suffer limitations from substantial variation of asthma prevalence among different countries. Moreover, a previous *meta*-analysis by Sunjaya et al reported that COVID-19 patients with asthma had a significantly increased risk for mortality in Asia, but not in Europe, North America and South America [4]. Taken together, those urged us to investigate the association between pre-existing asthma and COVID-19 mortality in a specific country or region. To date, a number of individual studies have explored the association between pre-existing asthma and COVID-19 mortality in the United States with conflicting results [5–9], but no quantitative *meta*-analysis on this topic was conducted to address this issue. Therefore, we performed a quantitative *meta*-analysis to investigate the impact of asthma on the risk for COVID-19 mortality in the United States.

2. Methods

2.1. Search strategy and selection criteria

This *meta*-analysis strictly adhering to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was carried out [10]. We performed an extensive search of the literature in the online databases of PubMed, Wiley Library, Springer Link, Elsevier ScienceDirect, Web of Science, EMBASE, Scopus and Cochrane

Abbreviations: COVID-19, coronavirus disease 2019; USA, the United States.

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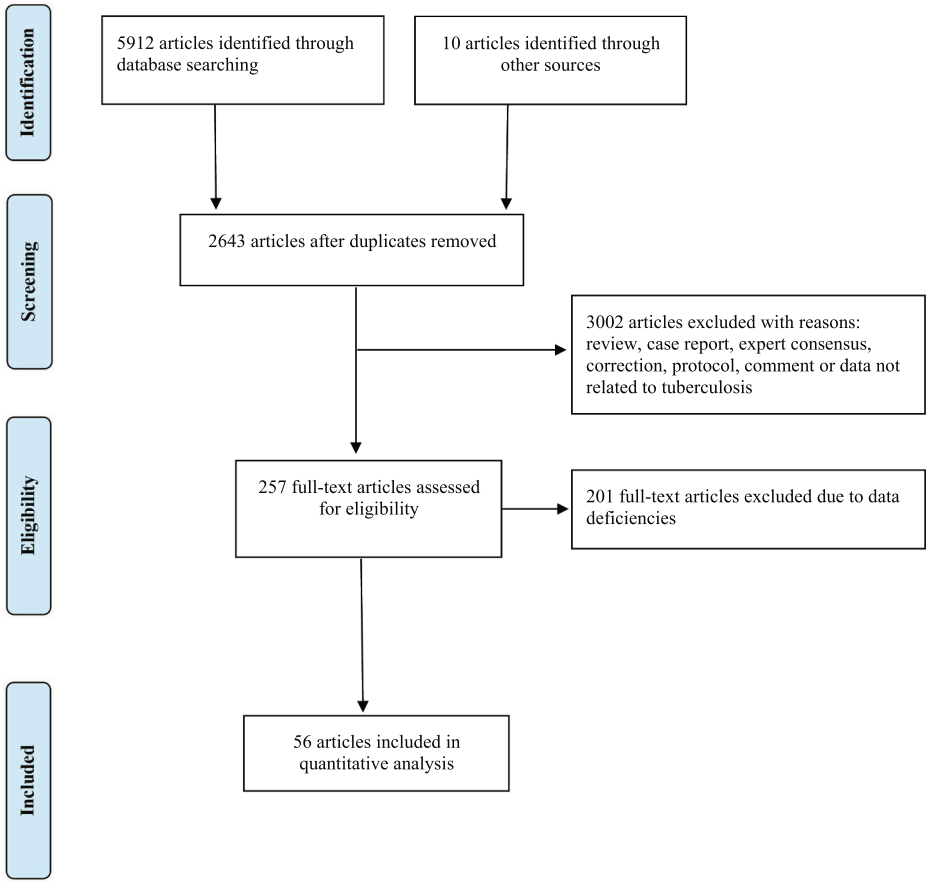

Fig. 1. Flow chart of the process of study selection of PRISMA.

Library to identify all potential articles which were published from inception to October 30, 2021, using the following keywords: "COVID-19", "coronavirus disease 2019", "2019-nCoV", "2019 novel coronavirus", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2", "asthma", "asthmatic", "mortality", "fatality", "death", "non-survivor", "deceased", "US", "USA", "America", "the United States" and "the United States of America". The references of the included studies and relevant reviews were also searched to identify additional articles. The primary outcome of interest was mortality. The participants of exposure group were COVID-19 patients with asthma and those of control group were COVID-19 patients without asthma.

All studies were included in this *meta*-analysis when they fulfilled the following inclusion criteria: (1) studies reporting adult confirmed COVID-19 patients in the United States; (2) peer-reviewed articles which were written in English language; (3) studies with the sample sizes being more than fifteen cases; (4) studies with available data on the incidence of survivors and non-survivors among COVID-19 patients with asthma and without asthma or the effect size with 95% confidence interval (CI) regarding the association between asthma and COVID-19 mortality. We excluded case reports, review papers, repeated articles, preprints, errata and studies conducted in other than the United States accordingly. Literature search, study selection and data extraction were performed by two investigators independently. Any disagreement was resolved through discussion between the investigators. The extracted information is at list: first author (PMID), study design, country, sample size, the mean (standard deviation) or median (interquartile range) age respectively, proportion of males, available data on the incidence of survivors and non-survivors among COVID-19 patients with asthma and without asthma or the effect size with 95% CI, and setting.

2.2. Statistical analysis

The pooled odds ratio (OR) with corresponding 95% CI evaluating the association between asthma and COVID-19 mortality in the United States was calculated by a random-effects *meta*-analysis model [11,12]. I^2 statistic was applied to assess the heterogeneity among studies [13]. Sensitivity analysis by deleting one single study from overall pooled analysis each time was carried out to evaluate the robustness of the findings [2]. Begg's rank correlation test was used to evaluate the potential publication bias [14]. The statistical analyses were performed with the package "meta" on R software (Version 4.1.1) [15]. Two tailed P value being less than 0.05 was considered statistically significant.

3. Results

3.1. Study selection

Yielding 5912 records from electronic databases and 10 records from hand-searching from the relevant studies or reviews in the cited lists. 2643 records were identified initially after removing duplications. After evaluating and assessing as much as 257 potential studies, 201 studies were removed due to outcome of interest being not available. In the end, what underlay this *meta*-analysis were eligible fifty-six articles with 426,261 COVID-19 patients [5–9,16–66]. The detail of selection process is shown by a chart flow in Fig. 1.

3.2. Study characteristics

A total of fifty-six eligible articles with 426,261 COVID-19 patients were included in our *meta*-analysis. The sample sizes among the included studies varied from 60 to 219,001 cases. There were forty-six

Table 1
General information of the eligible studies included in this *meta*-analysis.

Author (PMID)	Study design	Region	Cases	Male (%)	Age	Asthma		No Asthma		Setting
						Non-survivor	Survivor	Non-survivor	Survivor	
Banoei MM (PMID: 34496940)	Retrospective study	Florida	250	56	62.75 ± 17.13	2	28	29	191	Hospitalized
Chou EH (PMID: 34546880)	Retrospective study	Texas	1788	50.2	54.6 (41.9–68.2)	9	116	188	1475	All patients
Kim D (PMID: 32950749)	Retrospective study	The USA	817	54.47	57.13 ± 14.57	10	78	111	618	Hospitalized
Garibaldi BT (PMID: 32960645)	Retrospective study	Maryland, Washington	832	53	63 (49–75)	8	71	123	630	Hospitalized
Kim TS (PMID: 33128848)	Prospective study	New York	10,861	59.6	NR	Effect (95% CI): 0.81 (0.67–0.98)				Hospitalized
Rustgi V (PMID: 33409033)	Retrospective study	New Brunswick	403	56.17	62.06 ± 18.62	4	21	86	292	Hospitalized
Suzuki A (PMID: 34444232)	Cohort study	Durham	22,777	NR	NR	59	1254	1461	20,003	All patients
Pecina JL (PMID: 34452582)	Retrospective study	Minnesota	92	56.5	61 (50–74)	Effect (95% CI): 10.0 (1.8–56.0)				Hospitalized
Huang BZ (PMID: 34389242)	Retrospective study	California	61,338	46.08	43.97 ± 16.24	96	5430	901	54,911	All patients
Welder D (PMID: 34132393)	Cohort study	Texas	678	52.4	61.5 ± 16.7	6	92	50	530	All patients
Hou W (PMID: 33746590)	Retrospective study	New York	635	59.8	60 ± 11	3	38	79	515	Hospitalized
Forrest IS (PMID: 34089483)	Retrospective study	New York	688	63.52	67.22 ± 14.44	13	17	286	372	Hospitalized
Gupta YS (PMID: 33601125)	Retrospective study	New York	180	53	68 (59–80)	1	6	58	115	All patients
Jacobs JP (PMID: 34242641)	Prospective study	The USA	200	69	49.8 ± 12.1	19	14	91	76	All patients
Chhiba KD (PMID: 32554082)	Retrospective study	Chicago	1526	47	53.3	8	212	64	1242	All patients
Eggert LE (PMID: 34080210)	Retrospective study	California	605	47.8	50.68 ± 26.18	6	94	30	475	Hospitalized
Ho KS (PMID: 33647451)	Retrospective study	New York	4902	55.9	64.99 ± 16.92	54	179	1354	3315	Hospitalized
Lieberman-Cribbin W (PMID: 32522556)	Retrospective study	New York	6245	NR	57	45	227	1083	4890	Hospitalized
Lovinsky-Desir S (PMID: 32771560)	Retrospective study	New York	1298	41.3	52	9	154	101	1034	Hospitalized
Mather JF (PMID: 34143730)	Retrospective study	Hartford	1045	33.7	56.0 ± 17.58	7	81	157	800	Hospitalized
Robinson LB (PMID: 33650461)	Retrospective study	Boston	3248	72	51 ± 17	7	555	69	2617	All patients
Rosenthal JA (PMID: 33059035)	Retrospective study	Washington	727	NR	49.46 ± 17.93	10	95	51	571	All patients
Salacup G (PMID: 32617986)	Retrospective study	Pennsylvania	242	51	66 ± 14.75	0	18	52	172	Hospitalized
Shah P (PMID: 32620056)	Retrospective study	Georgia	522	41.8	63 (50–72)	11	57	81	373	Hospitalized
Miller J (PMID: 32945856)	Retrospective study	Michigan	2316	51.8	64.5 ± 16.3	31	186	402	1697	Hospitalized
Ioannou GN (PMID: 32965502)	Retrospective study	Washington	10,131	91	63.6 ± 16.2	58	687	1032	8354	All patients
Bahl A (PMID: 32970246)	Prospective study	Michigan	1461	52.7	62.0 (50.0–74.0)	30	124	297	1010	Hospitalized
Jackson BR (PMID: 32971532)	Retrospective study	Georgia	297	49.8	60 (45–69)	3	29	48	217	Hospitalized
Kim J (PMID: 33092732)	Retrospective study	New York	510	66	64 ± 14	Effect (95% CI): 0.93 (0.53–1.64)				Hospitalized
Rechtman E (PMID: 33298991)	Retrospective study	New York	8770	54.3	60 (44–72)	43	341	1071	7315	All patients
Lundon DJ (PMID: 33324596)	Cross-sectional study	New York	8928	46.2	58.0 ± 18.8	45	358	1134	7391	All patients

(*continued on next page*)

Table 1 (*continued*)

Author (PMID)	Study design	Region	Cases	Male (%)	Age	Asthma		No Asthma		Setting
						Non-survivor	Survivor	Non-survivor	Survivor	
Hobbs ALV (PMID: 33427149)	Retrospective study	Arkansas, Louisiana, Mississippi, North Carolina, and Tennessee	476	55.3	62 (49–71)	5	43	71	357	Hospitalized
Gupta R (PMID: 33461499)	Retrospective study	New York	475	NR	NR	Effect (95% CI): 2.77 (1.18–7.04)				Hospitalized
Marmarchi F (PMID: 33469873)	Retrospective study	Georgia	288	55	63 ± 16	Effect (95% CI): 0.517 (0.189–1.409)				Hospitalized
Mohamed NE (PMID: 33481113)	Case series	New York	7624	54.6	46.78	33	302	823	6466	Hospitalized
Muhammad R (PMID: 33538998)	Retrospective study	Washington	200	60.5	58.9 ± 15.1	3	17	42	138	Hospitalized
Lohia P (PMID: 33546658)	Retrospective study	Michigan	1871	51.6	64.11 ± 16	Effect (95% CI): 0.57 (0.38–0.87)				Hospitalized
Cedano J (PMID: 33552409)	Retrospective study	New Jersey	132	59	63 (53–71)	6	1	86	39	Hospitalized
Mulhem E (PMID: 33827831)	Retrospective study	Michigan	3219	49	65.2 (52.6–77.2)	67	362	449	2341	Hospitalized
Kelly JD (PMID: 34106264)	Cohort study	New York	27,640	88.6	57.2 ± 16.6	Effect (95% CI): 0.78 (0.59–1.04)				All patients
Ende VJ (PMID: 34397301)	Retrospective study	New York	294	68.7	62.61 ± 14.41	13	17	127	137	Hospitalized
Zerbo O (PMID: 34432371)	NR	California	219,001	47.3	37.21 (23.42–52.33)	287	31,057	1238	186,419	All patients
Roomi S (PMID: 33854659)	Retrospective study	Pennsylvania	1204	59.3	66	39	83	431	651	Hospitalized
Al Abbasi B (PMID: 33224386)	Retrospective study	Florida	257	52.53	63 ± 17	3	18	53	183	Hospitalized
Altonen BL (PMID: 33315929)	Retrospective study	New York	395	66.8	31.03 (27.79–34.73)	8	55	47	285	Hospitalized
Gayam V (PMID: 32672844)	Retrospective study	New York	408	56.62	67 (56–76)	16	38	116	238	Hospitalized
Morrison AR (PMID: 32646770)	Retrospective study	Michigan	81	69.1	64 (58–71)	5	6	30	40	Hospitalized
Gavin W (PMID: 32652252)	Retrospective study	Indiana	140	51.4	60 (48–72)	1	14	21	104	Hospitalized
Krishnan S (PMID: 32707517)	Retrospective study	Michigan	152	62.5	66 ± 13	16	9	76	51	Hospitalized
Li X (PMID: 33194455)	Retrospective study	New York	1022	56.46	62.13 ± 17.45	6	51	136	829	Hospitalized
Berry DA (PMID: 34329317)	Retrospective study	Texas	3123	60.36	63 (51–74)	58	218	637	2135	Hospitalized
Vu CA (PMID: 33353546)	Retrospective study	Florida	60	66.7	54 (26–87)	0	4	9	47	Hospitalized
Snider JM (PMID: 34428181)	Retrospective study	New York	90	53.3	62.3	2	5	28	55	Hospitalized
Mikami T (PMID: 32607928)	Retrospective study	New York	2820	57.1	65.33 ± 18.15	31	97	775	1917	All patients
Akama-Garren EH (PMID: 34089403)	Retrospective study	Massachusetts	835	48	64 (50–76)	15	66	134	620	All patients
Sulaiman I (PMID: 34465900)	Prospective study	New York	142	78.17	59.27 ± 18.89	1	1	33	107	Hospitalized

Note: The age (years) was presented as mean ± standard deviation or median (interquartile range, IQR); CI, confidence interval; The USA, the United States ; NR, not clearly reported.

retrospective studies, four prospective studies, three cohort studies, one cross-sectional study and one case series study. Forty studies reported the association between asthma and COVID-19 mortality among hospitalized patients. Most of studies (20/56) were conducted in New York. The summary information of included studies is presented in Table 1.

3.3. Asthma and mortality of COVID-19

Totally, this present *meta*-analysis showed that there was a statistically significant association between pre-existing asthma and the reduced risk for COVID-19 mortality in the United States (OR: 0.82, 95% CI: 0.74–0.91) (Fig. 2). Once the participants were only limited to hospitalized patients, we still observed that pre-existing asthma was associated with a significantly reduced risk for COVID-19 mortality (OR: 0.81, 95% CI: 0.74–0.88, Table 2). Subgroup analyses by age, male proportion, sample size and study design demonstrated that this significant association between asthma and the reduced risk for COVID-19 mortality did exist among studies with separated subgroup: age $\geq$ 60 years old (n = 34 studies, OR: 0.79, 95% CI: 0.72–0.87, Figure S1), male proportion $\geq$ 55% (n = 27 studies, OR: 0.79, 95% CI: 0.72–0.87, Figure S2), male proportion < 55% (n = 25 studies, OR: 0.81, 95% CI: 0.69–0.95, Figure S2), sample sizes $\geq$ 700 cases (n = 28 studies, OR:

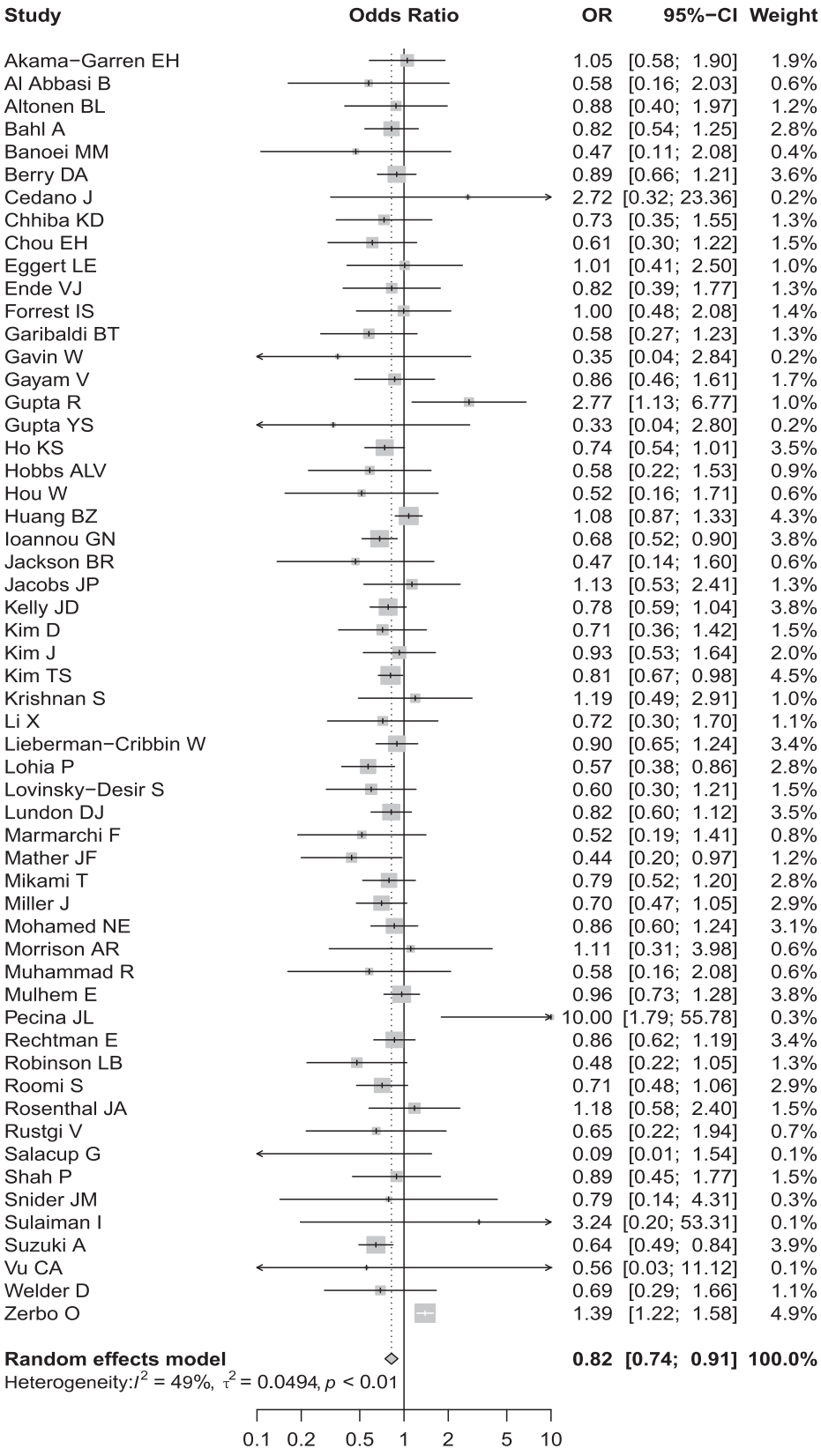

Fig. 2. Forest plot presents the relationship between COVID-19 mortality and asthma in the United States: pooled odds ratio (OR) with its 95% confidence interval (CI).

Table 2
Subgroup analysis and *meta*-regression.

Variables	No. of studies	Meta-regression			Subgroup analysis	Heterogeneity		
		Tau^2	Z-Value	*P* value	Pooled Effect (95% CI)	I^2	Tau^2	*P* value
Age (years)		0.0314	–	0.3917				
≥ 60	34	–	−1.3669	0.1717	0.79 (0.72–0.87)	0%	0	0.76
< 60	19	–	–	–	0.87 (0.73–1.03)	60%	0.0638	< 0.01
NR	3	–	−0.5549	0.5790	0.89 (0.58–1.37)	80%	0.0999	< 0.01
Male (%)		0.0400	–	0.7489				
≥ 55	27	–	−0.4003	0.6889	0.79 (0.72–0.87)	0%	0	0.80
< 55	25	–	–	–	0.81 (0.69–0.95)	60%	0.0695	< 0.01
NR	4	–	0.5062	0.6127	1.01 (0.64–1.58)	74%	0.1413	< 0.01
Sample size		0.0509	−0.6795	0.4968				
≥ 700	28	–	–	–	0.80 (0.71–0.91)	66%	0.0587	< 0.01
< 700	28	–	–	–	0.88 (0.73–1.07)	0%	0	0.46
Setting		0.0415	0.7436	0.4571				
All patients	16	–	–	–	0.85 (0.70–1.02)	74%	0.0860	< 0.01
Hospitalized	40	–	–	–	0.81 (0.74–0.88)	0%	0	0.58
Study design		0.0416	–	0.6948				
Retrospective study/Case series	47	–	−0.7816	0.4345	0.82 (0.75–0.89)	6%	0.0048	0.36
Prospective study	4	–	−0.1126	0.9104	0.83 (0.70–0.98)	0%	0	0.65
Others	5	–	–	–	0.86 (0.58–1.26)	90%	0.1583	< 0.01

Note: NR, not clearly reported; CI, confidence interval.

0.80, 95% CI: 0.71–0.91, Figure S3), retrospective study/case series (n = 47 studies, OR: 0.82, 95% CI: 0.75–0.89, Figure S4) and prospective study (n = 4 studies, OR: 0.83, 95% CI: 0.70–0.98, Figure S4), but did not exist in the subgroups with age < 60 years old (n = 19 studies, OR: 0.87, 95% CI: 0.73–1.03, Figure S1) and sample sizes < 700 cases (n = 28 studies, OR: 0.88, 95% CI: 0.73–1.07, Figure S3). Chasing up the source of heterogeneity, further *meta*-regression did reveal none of factors mentioned above were possible reasons of heterogeneity (age: P value = 0.3917; male proportion: P value = 0.7489; sample size: P value = 0.4968; study design: P value = 0.6948; setting: P value = 0.4571) (Table 2).

3.4. Sensitivity analysis and publication bias

The forest plot indicated that the pooled OR did not change significantly after deleting one single study each time (Fig. 3), which indicated the robustness of our findings.

Fig. 4 showed rank correlation test of funnel plot asymmetry in Begg's test. The statistics and asymmetry of funnel plot indicated that there was no evidence of publication bias (P = 0.4538).

4. Discussion

Our findings demonstrated that pre-existing asthma was significantly associated with a reduced risk for COVID-19 mortality in the United States based on fifty-six eligible articles with 426,261 COVID-19 patients. Taking the existence of heterogeneity into account, further *meta*-regression and subgroup analyses were conducted following by seeking the potential source of heterogeneity. None of factors in the further analyses can be used to explain the source of heterogeneity.

Asthma can be triggered exacerbation by respiratory viruses, inducing the severity of the infectious condition [67], but we found the association of asthma with the protective risk for mortality among coronavirus disease 2019 patients. At the same time, the detailed mechanisms of the association between asthma and the risk for COVID-19 mortality are unclear although several hypotheses were taken willingly to accept: (1) asthma in COVID-19 patients may take caution to build a fence to isolate themselves from the crowd and get more medical care from the paramedical practice; (2) the use of medicine to cope with asthma in convention, allergen immunotherapy, inhaled corticosteroids and biological agents, may resist the severe prognoses of COVID-19 in terms of suppressing viral replication and relieving inflammation [68]; (3) type 2 immune response modulating the expression of ACE2 and TMPRSS2 further supports an important role in inflammatory process in COVID-19 pathogenesis [69].

The prevalence of comorbid asthma among coronavirus disease 2019 patients varied greatly across countries or regions worldwide. Previous *meta*-analyses have reported the inconsistent association between asthma and COVID-19 mortality in the whole regions [1–3], which might be difficult in assessing the association on substantial variation of asthma prevalence among different countries. The strength of this study was that the included studies (56 eligible articles) with 426,261 cases were only conducted in the USA, which thought about the influences of this varied prevalence for asthma in regions among COVID-19 patients in the USA in terms of the relation between asthma and COVID-19 mortality. The *meta*-analysis only including studies conducted in the USA supported that pre-existing asthma was significantly associated with a reduced risk for COVID-19 mortality, which wards off the diversity of epidemiological characteristics and prevention and control measures in region, for the most part.

Undeniably, we indeed acknowledged that there were several limitations in this present *meta*-analysis. First, most of the included studies were retrospective, only four prospective studies were included, thus further *meta*-analyses on this topic based on prospective studies are warranted to confirm our results when more eligible data are available. Second, the pooled effect size was estimated on the crude effect sizes, which could not address the effects of certain confounders on the association between asthma and COVID-19 mortality. Therefore, further studies based on risk factors-adjusted estimates are warranted to verify our current findings. Third, this study could not address the effects of medications on the association between asthma and COVID-19 mortality, since most of the included studies did not provide the data. Forth, we noticed that the data of several studies were collected from multiple hospitals or centers, thus overlapping data might occur. In order to include more data as more as possible, we did not exclude the studies containing multiple hospitals or centers.

In conclusion, our findings demonstrated that pre-existing asthma was significantly associated with a reduced risk for COVID-19 mortality in the United States, further well-designed studies based on risk factors-adjusted estimates are warranted to confirm our findings. This study suggested that routine interventions and treatment for asthma patients with severe acute respiratory syndrome coronavirus 2 infection should be continued in the United States.

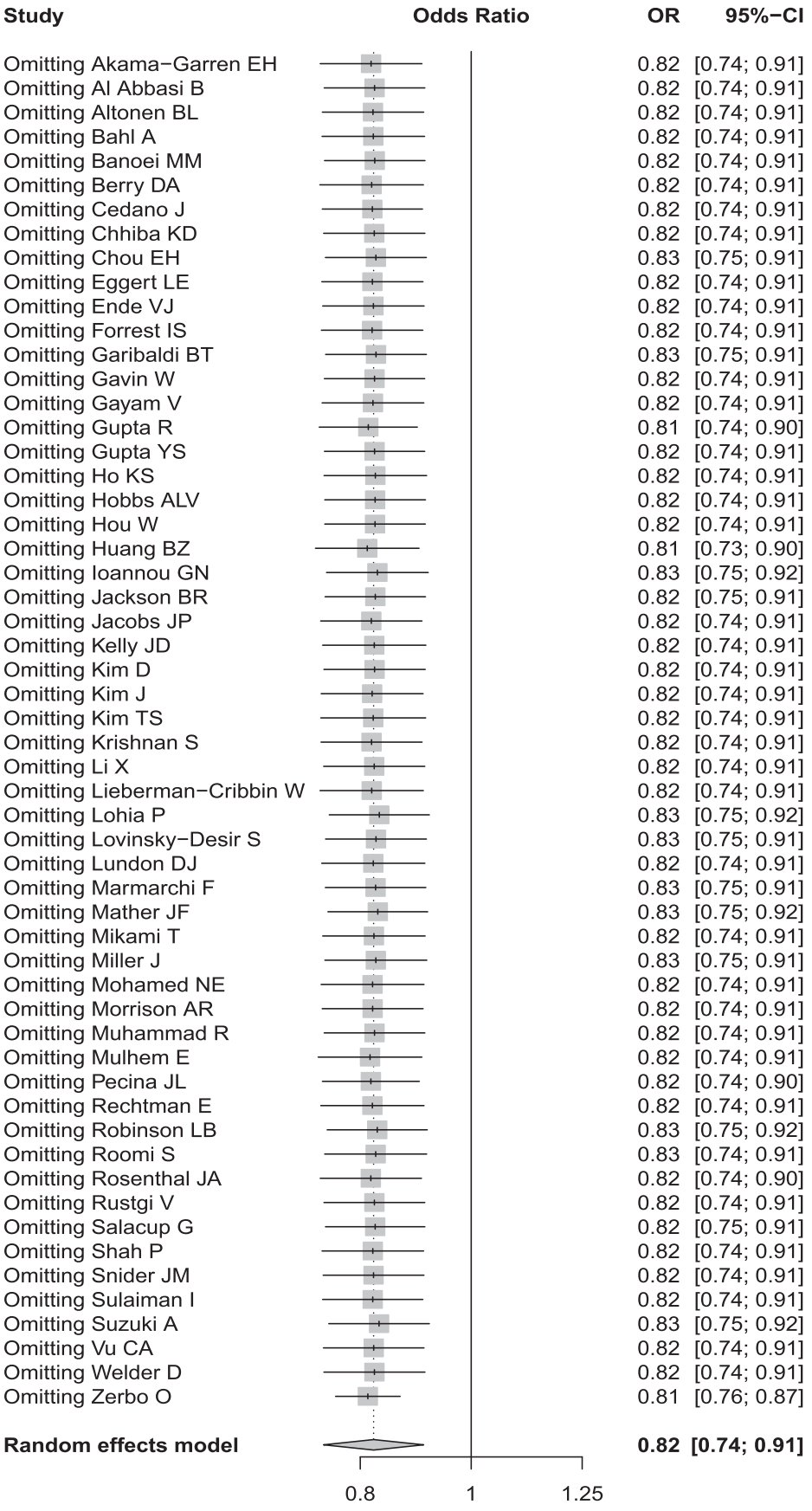

Fig. 3. Sensitivity analysis for pooled OR and 95% CI by deleting one single study from overall pooled analysis each time.

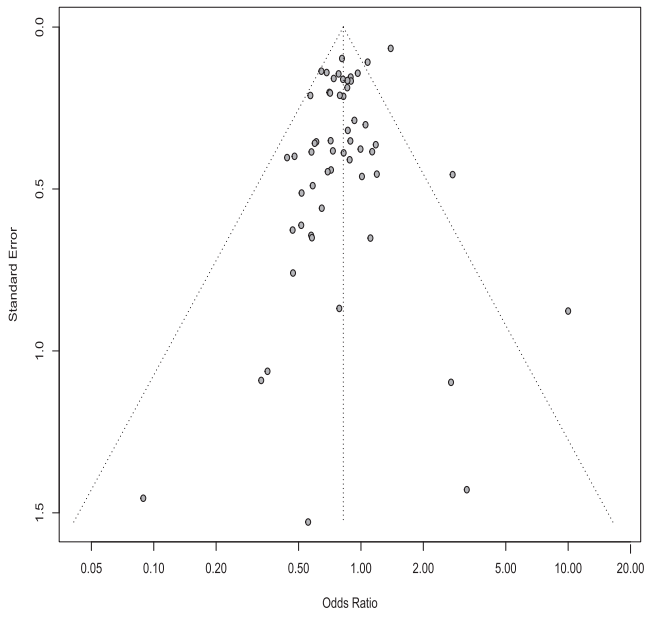

Fig. 4. Publication bias based on funnel plot.

Author contribution

Haiyan Yang and **Yadong Wang** conceptualized the study. **Xueya Han**, **Jie Xu**, **Hongjie Hou** and **Haiyan Yang** performed literature search and data extraction. **Xueya Han**, **Jie Xu** and **Hongjie Hou** analyzed the data. **Xueya Han** and **Yadong Wang** wrote the manuscript. All the authors approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement.

The data that support the findings of this study are included in this article and available from the corresponding author upon reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2021.108390.

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