

## RESEARCH LETTER

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# The relationship between severe or dead COVID-19 and asthma: A meta-analysis

Dear Editor,

Coronavirus disease 2019 (COVID-19) has rapidly affected mortality in the world, leading to acute respiratory distress syndrome and occasionally into multiorgan dysfunction. Comorbidities are associated with the severity of COVID-19. The impact of underlying respiratory compromises, such as the presence of asthma on the correlated immune status of COVID-19 infection, is still uncertain. There is no clear relationship between COVID-19 and asthma. Therefore, we aimed to perform a systematic review and meta-analysis in order to investigate the association between asthma and poor outcome in patients with COVID-19 pneumonia.

We systematically searched relevant studies in Pubmed, Cochrane library, Embase, Web of Science, VIP Database of Chinese periodicals, China National Knowledge Infrastructure (CNKI), using the keywords 'asthma' or 'respiratory diseases' AND 'novel coronavirus' or 'coronavirus disease 2019' or 'SARS-CoV-2' or 'COVID-19' from their inception up to September 1st, 2020 in any language. Studies were included if they fulfilled the following entry criteria: (a) patients were diagnosed with COVID-19 infection; (b) provided data of asthma with severe or non-severe patients or between death and survivors; (c) studies sample size is more than 100 patients; study exclusion criteria: (a) studies did not provide the prevalence of asthma; (b) studies without comparisons (severe versus non-severe patients, death versus survival); (c) abstracts, letters, case reports, review articles, letters to the editor, comments were excluded. We extracted the following data: name of the first author, country where the study was conducted, size of the cohort, numbers of males and females, age and clinical outcomes. The severity of the disease was mainly determined based on symptom (eg patients required intubation and mechanical ventilation, with acute respiratory distress syndrome, hospitalization or admitted to intensive care unit). To reduce the potential confounders, adjusted odds ratios (ORs) were used for overall effect estimate if possible. Risk of bias/quality of studies was evaluated using the Newcastle-Ottawa Scale (NOS) by two investigators (YW and XQ). A total score of  $\geq 7$  indicated a high-quality study, whereas a total score of  $< 7$  were considered to a low-quality study.

The literature search, study selection and data extraction were independently conducted by two authors (YW and GA). Any disagreements were resolved by consensus or by a third author. Review Manager 5.3 (Cochrane Collaboration) and Stata 15.0 (StataCorp) were used to pool useful data and calculate odds ratios (ORs) and their 95% confidence intervals. Heterogeneity among combined study results was quantified with Cochran's Q test and the  $I^2$

statistic, with an  $I^2$  less than 25%, 25% to 50%, and greater than 50% represented low, moderate and high heterogeneity, respectively. Sensitivity analysis was also performed to evaluate the stability of the meta-analysis by excluding one single study each time.  $P < .05$  was considered statistically significant. This study is registered with PROSPERO, number CRD42020203058.

Based on the above search strategy, a total of 649 studies were yielded. After exclusion of duplicate records and studies that did not fulfil our entry criteria, 89 articles remained. After further evaluating 89 full-text for eligibility literatures, 75 literatures were excluded due to lack of sufficient data for estimation of OR and not an outcome of interest. Finally, a total of 14 articles representing data from 32 187 participants were included in this meta-analysis.<sup>1-14</sup> The sample size patients ranged from 112 to 10 926. One study included hospitalized patients  $\leq 65$  years with severe COVID-19.<sup>2</sup> Most studies included only hospitalized asthma patients with COVID-19, and three studies included both hospitalized and non-hospitalized asthma patients.<sup>1,4,9</sup> Seven studies were from America, five studies from European countries, one study from China. Only two studies were prospective in design, and the others were retrospective. Asthma is mainly defined according to the patients' medical history. All studies were published in English. The characteristics of the study are provided in Table 1. The overall quality of available literature was moderate with NOS scores ranging from 7 to 9. The quality of the included articles is evaluated and present in Table S1. The meta-analysis showed that asthma was associated with a 1.09-fold increased risk of severe COVID-19 disease (OR = 1.09, 95% CI: 0.79-1.51,  $P = .61$ ;  $I^2 = 77\%$ ) (Figure 1A). In addition, we found that asthma was not associated with increased risk of mortality in patients with COVID-19 (OR = 0.84, 95% CI: 0.58-1.23,  $P = .37$ ;  $I^2 = 54\%$ ) (Figure 1B). However, the adjusted pooled analysis of only three studies showed that asthma was associated with increased risk of mortality in patients with COVID-19 (OR = 1.86, 95% CI: 0.74-4.64,  $P = .105$ ;  $I^2 = 55.6\%$ ) (Figure 2), although these three analysis results were not statistically significant ( $P > .05$ ). The subgroup analysis based on countries indicated no significant relationship between asthma and risk of mortality in patients with COVID-19 from America (OR = 0.73, 95% CI: 0.52-1.03,  $P = .08$ ;  $I^2 = 0\%$ ). Sensitivity analyses by omitting each study at a time did not significantly change the results.

Asthma is one of the most prevalent chronic conditions. It is not yet known whether people with asthma are more susceptible to COVID-19. Our previous study revealed no significant difference between the prevalence of asthma in severe versus non-severe

TABLE 1 Characteristics of included studies

| Study                   | Country        | Age <sup>a</sup> | Sample size | Sex  |        | Study design  | Definition of asthma used                                                                                                                                                                                                                                                                                                                 | Definition of severity used                                                            | Definition of Covid-19 infection used |
|-------------------------|----------------|------------------|-------------|------|--------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------|
|                         |                |                  |             | Male | Female |               |                                                                                                                                                                                                                                                                                                                                           |                                                                                        |                                       |
| Williamson <sup>1</sup> | United Kingdom | NR               | 10 926      | NR   | NR     | Prospective   | Medical history                                                                                                                                                                                                                                                                                                                           | Death                                                                                  | SARS-CoV-2 RT-PCR (+)                 |
| Desir <sup>2</sup>      | America        | ≤65 years        | 1298        | 762  | 536    | Retrospective | Asthma was defined as having any one of the following: asthma-related ICD-10 code (J45.XX) within the preceding 5 years (collected from New York Presbyterian Clinical Data Warehouse), asthma diagnosis recorded in the problem list of the electronic health record or documented in physician notes.                                   | Intubations                                                                            | SARS-CoV-2 RT-PCR (+)                 |
| Chhiba <sup>3</sup>     | America        | NR               | 1526        | 718  | 808    | Retrospective | Assessed by International Classification of Disease, Ninth Revision or ICD-10 codes (any 493.xx or J45.xx). Manual chart review of all patients with asthma was then performed to confirm a diagnosis of asthma. The criteria used to classify asthma included either a physician diagnosis of asthma or self-reported history of asthma. | COVID-19 hospitalizations                                                              | SARS-CoV-2 RT-PCR (+)                 |
| Mahdavinia <sup>4</sup> | America        | NR               | 935         | 417  | 518    | Retrospective | Asthma diagnosis based on Global Initiative for Asthma (GINA) guidelines.                                                                                                                                                                                                                                                                 | ARDS                                                                                   | SARS-CoV-2 RT-PCR (+)                 |
| Song <sup>5</sup>       | China          | 63 (49, 70)      | 961         | 500  | 461    | Retrospective | Medical history                                                                                                                                                                                                                                                                                                                           | According to the American Thoracic Society guidelines for community-acquired pneumonia | SARS-CoV-2 RT-PCR (+)                 |
| Beurnier <sup>6</sup>   | France         | NR               | 112         | 60   | 52     | Prospective   | Medical history                                                                                                                                                                                                                                                                                                                           | ICU                                                                                    | SARS-CoV-2 RT-PCR (+)                 |

(Continues)

TABLE 1 (Continued)

| Study                    | Country | Age <sup>a</sup> | Sample size | Sex  |        | Study design  | Definition of asthma used                                                                                                     | Definition of severity used | Definition of Covid-19 infection used |
|--------------------------|---------|------------------|-------------|------|--------|---------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------|
|                          |         |                  |             | Male | Female |               |                                                                                                                               |                             |                                       |
| Barroso <sup>7</sup>     | Spain   | NR               | 189         | 109  | 80     | Retrospective | From 11 asthmatic patients, six were diagnosed by specialist (allergist or pulmonologist) and the other five in primary care. | ICU                         | SARS-CoV-2 RT-PCR (+)                 |
| Borobia <sup>8</sup>     | Spain   | 61 (46, 78)      | 2226        | 1074 | 1152   | Retrospective | Medical history                                                                                                               | ICU                         | SARS-CoV-2 RT-PCR (+)                 |
| Vega <sup>9</sup>        | Mexico  | 48.15 ± 14.35    | 9946        | 5753 | 4193   | Retrospective | Medical history                                                                                                               | COVID-19 hospitalizations   | SARS-CoV-2 RT-PCR (+)                 |
| Argenziano <sup>10</sup> | America | NR               | 850         | 511  | 339    | Retrospective | NR                                                                                                                            | ICU                         | SARS-CoV-2 RT-PCR (+)                 |
| Suleyman <sup>11</sup>   | America | NR               | 355         | 165  | 190    | Retrospective | Medical history                                                                                                               | ICU                         | SARS-CoV-2 RT-PCR (+)                 |
| Almazeedi <sup>12</sup>  | Kuwait  | 41 (25, 75)      | 1096        | 888  | 208    | Retrospective | Medical history                                                                                                               | ICU                         | SARS-CoV-2 RT-PCR (+)                 |
| Mendy <sup>13</sup>      | America | 49.5 (1.3)       | 689         | 365  | 324    | Retrospective | Assessed by International Classification of Disease (ICD-10) codes: asthma (J45)                                              | Admission to ICU or death   | SARS-CoV-2 RT-PCR (+)                 |
| Paranjpe <sup>14</sup>   | America | NR               | 1078        | 627  | 451    | Retrospective | Assessed by International Classification of Disease, ICD-9/10 codes                                                           | Death                       | SARS-CoV-2 RT-PCR (+)                 |

Abbreviations: ARDS, acute respiratory distress syndrome; ICD, international classification of diseases; ICU, intensive care units; NR, not reported; RT-PCR, Real-time reverse transcription polymerase chain reaction; SARS-CoV-2, 2019 severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>Age data presented as median (IQR) or mean (SD).

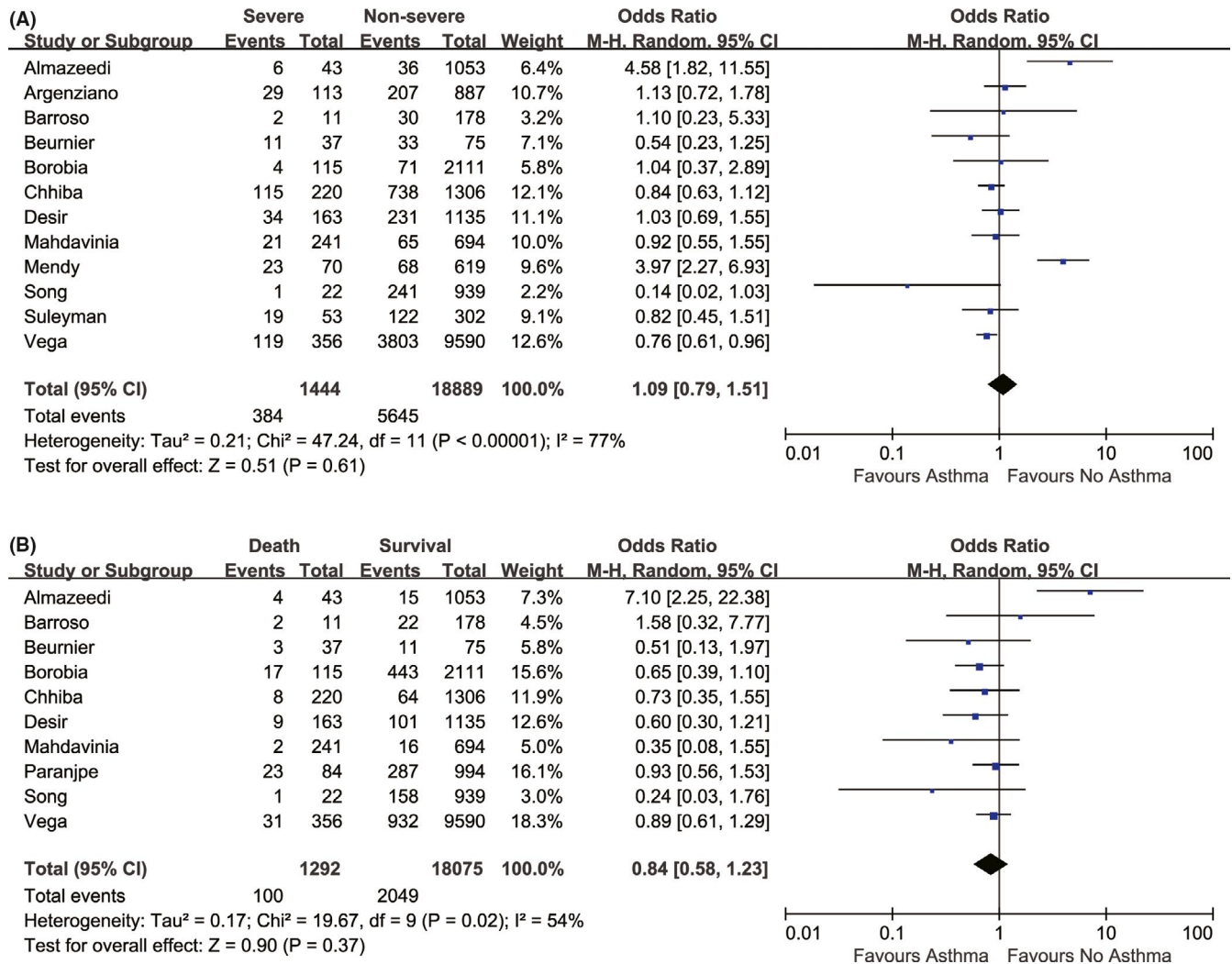


**FIGURE 1** Association between asthma and COVID-19 disease (A: Severe versus Non-severe; B: Death vs survival)

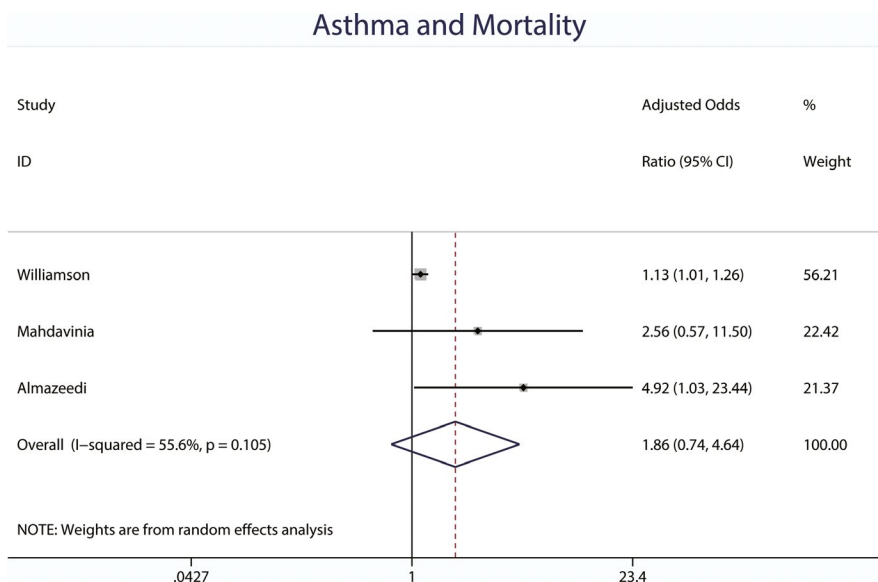


**FIGURE 2** Association between asthma and mortality

or death versus survival patients.<sup>15</sup> However, our previous study did not directly compare asthma versus non-asthma with regard to clinical outcomes due to limited data available. Recently, with more relevant articles regarding asthma versus non-asthma in severe COVID-19 and mortality published, the result of this meta-analysis, which was stable on sensitivity analysis, did not significantly show a worse prognosis of COVID-19 in patients with asthma. However, we should not ignore the importance of strict control of COVID-19 spread and a need for mitigation strategies in patients with pre-existing asthma. Several limitations in this study should be noted. The included studies of observational studies were subject to potential confounders that may weaken or strengthen the overall effect estimate. Most of the studies included were retrospective in design. Although we conducted subgroup analysis and sensitivity analysis, the heterogeneity across the studies was substantial and results based on adjusted analysis were also subjected to limited numbers of studies. The cause of heterogeneity could be related to methodological quality/risk of bias among studies, different adjusted risk factors used (such as age, gender and various underlying medical conditions), study design and severity of asthma. Data on asthma medications were lacking in the included studies, hence, cannot be analysed. In conclusion, the results of this study reveal that pre-existing asthma is not likely to worsen the prognosis of COVID-19. More studies are required to explore on the pathogenic mechanisms and therapeutic implications.

## KEYWORDS

asthma, COVID-19, meta-analysis, mortality, severe

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTION

All authors contributed equally.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed and Medrxiv.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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**Supplemental Table 1 Study quality assessment using the Newcastle-Ottawa Scale**

| First author,<br>year of publication<br>(reference) | Selection                                    |                                      |                              |                                                    | Comparability | Outcome                  |                                                      |                          | Total score |
|-----------------------------------------------------|----------------------------------------------|--------------------------------------|------------------------------|----------------------------------------------------|---------------|--------------------------|------------------------------------------------------|--------------------------|-------------|
|                                                     | Representative-<br>ness of exposed<br>cohort | Selection of<br>nonexposed<br>cohort | Ascertainment<br>of exposure | Outcome of<br>interest absent<br>at start of study |               | Assessment<br>of outcome | Follow-up<br>long enough<br>for outcomes<br>to occur | Adequacy of<br>follow-up |             |
| Williamson [1]                                      | *                                            | *                                    | *                            | *                                                  | **            | *                        | *                                                    | *                        | 9           |
| Desir [2]                                           | *                                            | *                                    | *                            | *                                                  | **            | *                        | *                                                    | *                        | 9           |
| Chhiba [3]                                          | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |
| Mahdavinia [4]                                      | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |
| Song [5]                                            | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |
| Beurnier [6]                                        | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | *                        | 8           |
| Barroso [7]                                         | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |
| Borobia [8]                                         | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |
| Vega [9]                                            | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |
| Argenziano [10]                                     | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | *                        | 8           |
| Suleyman [11]                                       | *                                            | *                                    | *                            | *                                                  | **            | *                        | ...                                                  | ...                      | 7           |

|                |   |   |   |   |    |   |     |     |   |
|----------------|---|---|---|---|----|---|-----|-----|---|
| Almazeedi [12] | * | * | * | * | ** | * | ... | ... | 7 |
| Mendy [13]     | * | * | * | * | ** | * | ... | ... | 7 |
| Paranjpe [14]  | * | * | * | * | ** | * | ... | ... | 7 |

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