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# Comorbid Asthma Increased the Risk for COVID-19 Mortality in Asia: A Meta-Analysis

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**Abstract:** We aimed to explore the influence of comorbid asthma on the risk for mortality among patients with coronavirus disease 2019 (COVID-19) in Asia by using a meta-analysis. Electronic databases were systematically searched for eligible studies. The pooled odds ratio (OR) with 95% confidence interval (CI) was estimated by using a random-effect model. An inconsistency index ($I^2$) was utilized to assess the statistical heterogeneity. A total of 103 eligible studies with 198,078 COVID-19 patients were enrolled in the meta-analysis; our results demonstrated that comorbid asthma was significantly related to an increased risk for COVID-19 mortality in Asia (pooled OR = 1.42, 95% CI: 1.20–1.68; $I^2$ = 70%, $p < 0.01$). Subgroup analyses by the proportion of males, setting, and sample sizes generated consistent findings. Meta-regression indicated that male proportion might be the possible sources of heterogeneity. A sensitivity analysis exhibited the reliability and stability of the overall results. Both Begg's analysis ($p = 0.835$) and Egger's analysis ($p = 0.847$) revealed that publication bias might not exist. In conclusion, COVID-19 patients with comorbid asthma might bear a higher risk for mortality in Asia, at least among non-elderly individuals.

**Keywords:** asthma; coronavirus disease 2019; mortality; meta-analysis; Asia

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## 1. Introduction

Coronavirus disease 2019 (COVID-19), which is brought on by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has ravaged the world. As of 26 October 2022, 624 million patients have been confirmed with the COVID-19 diagnosis globally of which 6.5 million patients have died [1]. Vaccines have shown to be very effective against severe COVID-19 disease and mortality [2–7]; it is also important to understand risk factors (e.g., to decide whom to prioritize for vaccination). Until now, several variables (age, sex, and certain past medical history) have been identified as risk factors for COVID-19 mortality [8–13]. Although there have been several meta-analyses exploring the relationship of comorbid asthma with the risk for COVID-19 mortality in the full regions [14–18], the findings from previous meta-analyses were still inconclusive, which might suffer limitations from considerable variability in the prevalence of asthma across different regions [14,19,20]. Therefore, it is an urgent requirement to investigate the relationship of comorbid asthma with the risk for COVID-19 mortality based on specific regions.

To the best of our knowledge, three meta-analyses have explored this relationship in Asia [15,18,21]. However, the number of included studies (all are less than twelve) and the sample sizes are limited. Moreover, the conclusions drawn from these articles are inconsistent or even contradictory. Additionally, a substantial number of articles on this topic in Asia have emerged since then. Taken together, we conducted this updated meta-analysis to ascertain the relationship between comorbid asthma and COVID-19 mortality in Asia on the basis of the latest data.

## 2. Methods

### 2.1. Search Strategy and Literature Management

This quantitative meta-analysis was performed according to the statement of PRISMA (preferred reporting items for systematic reviews and meta-analyses). A systematic literature search was undertaken among electronic databases containing PubMed, Scopus, EMBASE, Springer, Web of Science, and Wiley to recognize eligible studies from inception to 22 October 2022. Searching strategies were as follows: ("COVID-19" OR "coronavirus disease 2019" OR "SARS-CoV-2" OR "2019-nCoV" OR "novel coronavirus") and ("asthma" OR "bronchial asthma") and ("mortality" OR "non-survivor" OR "fatality" OR "deceased" OR "death"). Additionally, to achieve extensive searches, relevant references of included studies and reviews were also taken into consideration.

### 2.2. Selection Criteria

Studies were selected if they were amenable to the following criteria: (1) Adult COVID-19 patients should be diagnosed in line with the World Health Organization (WHO) guidance. (2) Studies were conducted in Asia and explicitly reported the number of COVID-19 patients with comorbid asthma and outcome of interest (alive or dead) or the effect size with 95% confidence interval (CI) concerning the relationship of asthma with COVID-19 mortality. (3) Articles should be written in English. Studies based on criteria as follows must be cast off accordingly: (1) preprints, comments, errata, reviews, and repeated articles. (2) articles without available data concerning the incidence of asthma and death among patients with COVID-19 in Asia.

### 2.3. Data Extraction

Two researchers respectively inspected all the literature depending on the criteria of inclusion and exclusion and then extracted the relevant information, including author, male proportion, country, cases, study design, setting, mean age with standard deviation or median age with interquartile range, incidence of non-survivors and survivors among patients with COVID-19 and comorbid asthma and those without, or the effect size with corresponding 95% CI. If two or more publications are sourced with the same author or the same institute, we then reviewed the time period of participant enrollment among the studies. If the time period of participant enrollment was the same or the study start and end times were crossed among the studies, we regarded these studies as having the same participants or overlapping participants; otherwise, we regarded these studies as different. For these studies based on the same data source, we included only the articles with the most complete data. If there was any disagreement, it was settled through a third investigator or by discussion to reach a consensus.

### 2.4. Statistical Analysis

All the statistical analyses were implemented on STATA (Version 16) and R software (Version 4.2.1) with attached "meta" package (Version 5.5-0). Pooled OR and 95% CI were computed by a random-effect model to describe the relationship of asthma with COVID-19 mortality in Asia. Two tailed $p$-value less than 0.05 was considered as statistical significance. An inconsistency index ($I^2$) was applied to evaluate the statistical heterogeneity among studies [22]. Meta-regression and subgroup analyses were undertaken to find possible sources of heterogeneity. To test the stability of our study, a sensitivity analysis by omitting one single study at a time was carried out. Both Begg's analysis and Egger's analysis were implemented to test the potential publication bias [23,24].

## 3. Results

### 3.1. Study Selection

Online literature searches yielded 22,361 citations from electronic databases, and an additional 50 records were found from the references of cited lists. After removing 19,168 duplicates, 3243 articles were initially identified. Next, 2943 articles were excluded

after reading the abstracts. After that, 300 articles were evaluated for full-text eligibility, and 197 articles with available data but not Asian were excluded. Ultimately, 103 studies conducted in Asia were enrolled in this meta-analysis [25–127]. The flow chart of the literature search and selection process is illustrated in Figure 1.

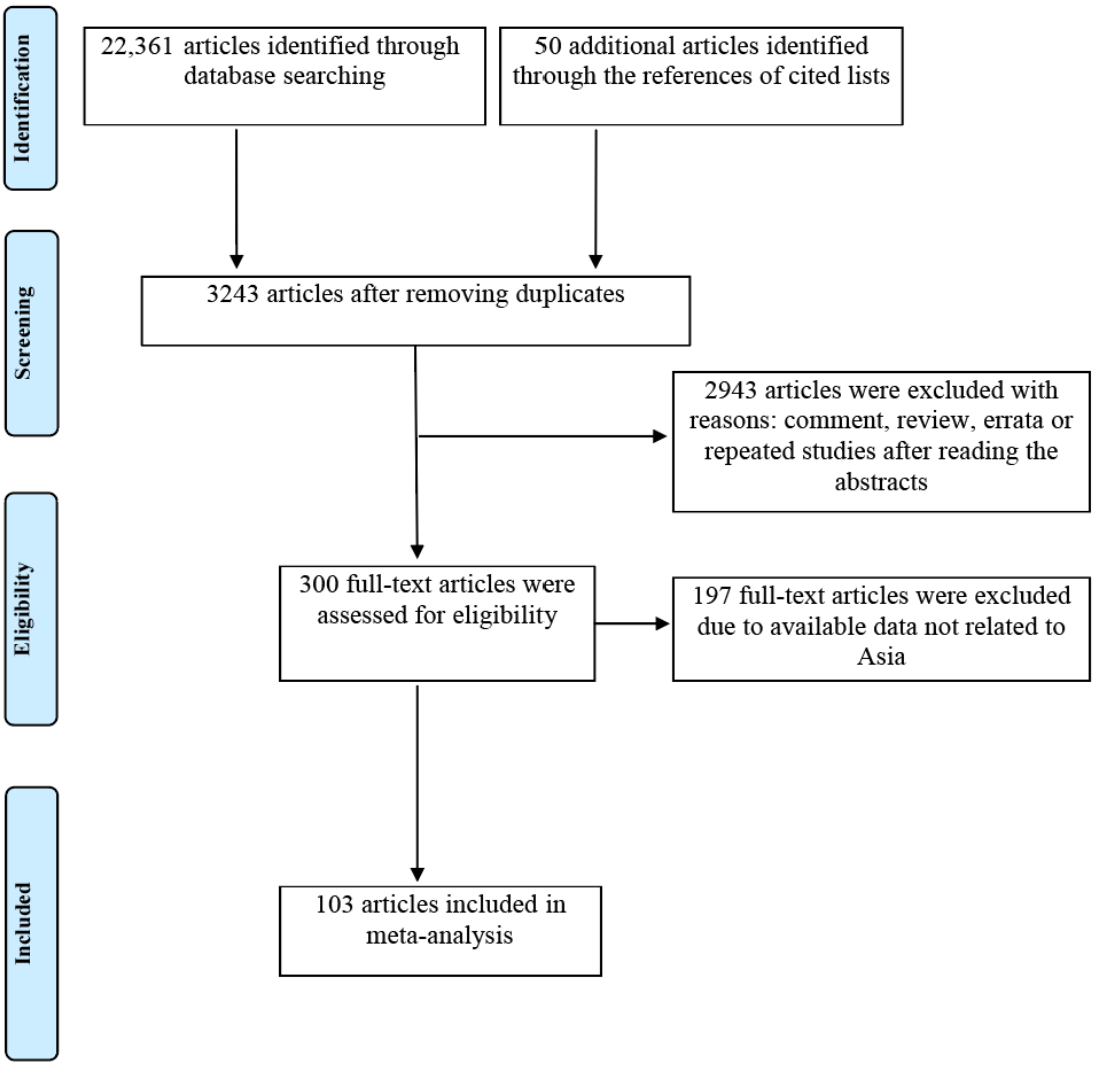



**Figure 1.** Flow chart of study search and selection process.

### *3.2. Descriptive Characteristics*

Summary characteristics of the enrolled studies are tabulated in Table 1. This meta-analysis was based on a total of 103 eligible studies with 198,078 COVID-19 patients. In terms of study design, there were eighty-five retrospective studies, ten prospective studies, six cross-sectional studies, one case series study, and one clinical trial study. From the point of view of geographical settings, we characterized the country's levels of social and economic development based on the 4-tier Human Development Index (HDI) from the United Nation's 2022 Human Development Report. Additionally, countries were categorized as very high HDI country (Korea, Singapore, Israel, Japan, Turkey, Kuwait, Saudi Arabia, and United Arab Emirates), high HDI country (China, Iran, and Indonesia), medium HDI country (India, Philippines, and Bangladesh), and low HDI country (Pakistan). Among these studies, ninety-eight studies reported the exact numbers of non-survivors and survivors of COVID-19 patients with asthma, while five studies reported OR with 95% CI to reflect the effect of comorbid asthma on Asian COVID-19 mortality.

**Table 1.** Main characteristics of the included studies.

| Author | Country | Study Design | Setting | Cases | Male (%) | Mean/Median Age | Asthma | | Non-Asthma | | Comorbidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dead | Alive | Dead | Alive | Hypertension | Diabetes |
| Lee SC [90] | Korea | Retrospective | All patients | 7272 | 40.3 | 45.3 | 44 | 642 | 183 | 6403 | 19.3 | 14.3 |
| Choi YJ [60] | Korea | Retrospective | All patients | 7590 | 40.8 | 46.6 (27.1–61) | 17 | 201 | 210 | 7162 | NA | NA |
| Trabulus S [123] | Turkey | Retrospective | Hospitalized | 336 | 57.1 | 55.0 ± 16.0 | 1 | 19 | 42 | 274 | 35.7 | 18.8 |
| Aksel G [30] | Turkey | Prospective | Hospitalized | 168 | 53.6 | 59.5 (48.3–76) | 2 | 12 | 30 | 124 | 48.2 | 25.6 |
| Serin I [117] | Turkey | Retrospective | All patients | 2217 | 53.0 | 47.66 ± 17.23 | 0 | 103 | 68 | 2046 | 20.6 | 16.2 |
| Ayaz A [46] | Pakistan | Retrospective | Hospitalized | 66 | 61.0 | 50.6 ± 19.1 | 0 | 2 | 9 | 55 | 45.5 | 37.9 |
| Ayed M [48] | Kuwait | Retrospective | ICU patients | 103 | 85.5 | 53 (44–63) | 8 | 4 | 39 | 52 | 35.0 | 39.2 |
| Lee SG [91] | Korea | Retrospective | All patients | 7339 | 40.1 | 47.1 ± 19.0 | 21 | 376 | 206 | 6736 | 18.6 | 11.6 |
| Choi HG [59] | Korea | Retrospective | Hospitalized | 4057 | 42.5 | 54.1 | 8 | 88 | 118 | 3843 | 20.4 | 12.1 |
| Zhou S [127] | China | Retrospective | Hospitalized | 134 | 63.4 | 59.04 ± 17.74 | 14 | 6 | 58 | 56 | 28.4 | 13.4 |
| Omar SM [96] | Saudi Arabia | Retrospective | Hospitalized | 88 | 81.8 | 62 (55–70) | 4 | 3 | 29 | 52 | 25.0 | 20.5 |
| Caliskan T [56] | Turkey | Retrospective | Hospitalized | 565 | NA | 48 ± 19.66 | 4 | 17 | 71 | 473 | 22.7 | 12.7 |
| Kim SW [83] | Korea | Retrospective | Hospitalized | 2254 | 35.8 | 58 (42–70) | 9 | 57 | 170 | 2018 | 28.7 | 16.6 |
| Park BE [100] | Korea | Retrospective | Hospitalized | 2269 | 35.9 | 55.5 ± 20.2 | 9 | 58 | 155 | 2047 | 28.8 | 17.0 |
| Alwafi H [42] | Saudi Arabia | Retrospective | Hospitalized | 706 | 68.5 | 48.0 ± 15.6 | OR (95% CI): 0.80 (0.07–8.82) | | | | 30.2 | 36.0 |
| Kridin K [87] | Israel | Retrospective | Hospitalized | 3618 | 39.7 | 38.6 ± 17.7 | 8 | 504 | 32 | 3074 | NA | NA |
| Kim SH [82] | Korea | Retrospective | All patients | 7590 | 40.8 | 45.87 ± 19.77 | 48 | 716 | 179 | 6647 | NA | 13.9 |
| Bae S [50] | Korea | Retrospective | Hospitalized | 1760 | 63.6 | 60.9 ± 18.6 | 9 | 52 | 159 | 1540 | 33.1 | 19.3 |
| Moon HJ [94] | Korea | Retrospective | Hospitalized | 4426 | 42.1 | 51 (30.2–63.7) | 8 | 92 | 118 | 4208 | 21.4 | 12.3 |
| Kong KA [85] | Korea | Retrospective | Hospitalized | 5307 | 40.8 | 52.1 (33.7–64.5) | 13 | 113 | 228 | 4953 | 22.6 | 12.9 |
| Akhtar H [29] | Pakistan | Retrospective | Hospitalized | 659 | 68.6 | 53.8 | 53 | 11 | 416 | 179 | 57.2 | 50.2 |
| Al Mutair A [31] | Saudi Arabia | Retrospective | ICU patients | 1470 | 74.0 | 55.9 ± 15.1 | 45 | 83 | 569 | 773 | 46.0 | 52.4 |
| Sehgal T [115] | India | Prospective | Hospitalized | 68 | 63.2 | 48 (20–85) | 0 | 2 | 9 | 57 | 22.1 | 20.6 |
| Rai D [107] | India | Retrospective | Hospitalized | 984 | 77.4 | 50.73 ± 16.50 | 16 | 21 | 238 | 709 | 31.1 | 33.5 |
| Jung Y [77] | Korea | Retrospective | Hospitalized | 4066 | 37.5 | 53.38 | 24 | 338 | 108 | 3596 | 29.2 | NA |
| Kolivand P [84] | Iran | Prospective | Hospitalized | 960 | 100.0 | 56.99 ± 6.71 | 7 | 16 | 117 | 820 | NA | NA |
| Rehman S [108] | Pakistan | Retrospective | Hospitalized | 2048 | 59.4 | 56 (18–88) | 77 | 58 | 513 | 1400 | 47.6 | 29.7 |
| Tanaka C [122] | Japan | Retrospective | Hospitalized | 1529 | 79.1 | 66.69 ± 12.38 | 19 | 63 | 382 | 1065 | 48.7 | 35.8 |

**Table 1.** *Cont.*

| Author | Country | Study Design | Setting | Cases | Male (%) | Mean/Median Age | Asthma | | Non-Asthma | | Comorbidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dead | Alive | Dead | Alive | Hypertension | Diabetes |
| Cakir Guney B [55] | Turkey | Retrospective | ICU patients | 134 | 60.4 | 68.90 ± 15.67 | 2 | 2 | 80 | 50 | 56.0 | 33.6 |
| Ong AN [97] | Philippines | Retrospective | Hospitalized | 355 | 55.8 | 62.69 ± 12.21 | 5 | 22 | 85 | 243 | 74.6 | NA |
| Kwok WC [89] | China | Retrospective | Hospitalized | 4498 | 48.8 | 47 | 10 | 155 | 60 | 4273 | 21.0 | 11.4 |
| Abrishami A [26] | Iran | Retrospective | Hospitalized | 80 | 65.0 | 54.29 ± 15.21 | 1 | 6 | 12 | 61 | 25.0 | 15.0 |
| Cilingir BM [61] | Turkey | Prospective | Hospitalized | 162 | 62.3 | 56.98 ± 17.79 | OR (95% CI): 0.214 (0.001–77.242) | | | | NA | NA |
| AbuRuz S [27] | United Arab Emirates | Retrospective | Hospitalized | 3296 | 76.3 | 44.3 ± 13.4 | 6 | 159 | 84 | 3047 | 28.6 | 27.4 |
| Aydin Guclu O [47] | Turkey | Retrospective | Hospitalized | 202 | 50.5 | 50.17 ± 19.68 | OR (95% CI): 2.793 (0.750–10.402) | | | | 30.2 | 16.3 |
| Cortez KJC [62] | Philippines | Retrospective | Hospitalized | 280 | 36.1 | 48.4 ± 18.5 | 1 | 16 | 12 | 251 | 44.3 | 17.0 |
| Kouhpeikar H [86] | Iran | Retrospective | Hospitalized | 583 | 52.3 | 61.4 ± 0.9 | 12 | 4 | 61 | 506 | 26.6 | 13.9 |
| He C [70] | China | Retrospective | Hospitalized | 702 | 52.3 | 66.0 (58–73) | 3 | 34 | 19 | 646 | NA | 25.2 |
| Pramudita A [104] | Indonesia | Retrospective | Hospitalized | 243 | 53.1 | 48.04 ± 14.43 | 0 | 6 | 32 | 205 | 32.5 | 20.6 |
| Hesni E [71] | Iran | Retrospective | Hospitalized | 27,256 | 53.7 | 53.34 ± 22.74 | 26 | 284 | 2620 | 24,326 | 12.7 | 7.4 |
| Chang Y [58] | Korea | Retrospective | All patients | 3122 | 30.7 | NA | OR (95% CI): 1.14 (0.68–1.90) | | | | 32.8 | 14.8 |
| Alam MT [33] | Pakistan | Retrospective | All patients | 209 | 71.3 | 56 (50–65) | 2 | 8 | 58 | 141 | 50.2 | 40.2 |
| Araban M [44] | Iran | Retrospective | All patients | 3181 | 47.2 | 52.6 ± 20.8 | 10 | 84 | 300 | 2787 | 14.8 | 16.2 |
| Patgiri P [102] | India | Cross-sectional | Hospitalized | 165 | 75.8 | 68.4 ± 6.9 | 1 | 2 | 38 | 124 | 37.6 | 24.2 |
| Alimohamadi Y [37] | Iran | Retrospective | Hospitalized | 3759 | 57.1 | 57.48 ± 17.27 | 8 | 111 | 305 | 3335 | 29.5 | 24.7 |
| Shin E [120] | Korea | Retrospective | Hospitalized | 5625 | 41.2 | NA | 11 | 108 | 230 | 5276 | 21.4 | 12.3 |
| Basaran NC [52] | Turkey | Prospective | Hospitalized | 368 | 46.5 | 57 | 2 | 29 | 37 | 300 | 38.0 | 24.2 |
| Kibar Akilli I [81] | Turkey | Retrospective | Hospitalized | 1511 | 58.2 | 60.1 ± 14.7 | 12 | 123 | 121 | 1255 | 48.0 | 33.3 |
| Malundo AFG [93] | Philippines | Retrospective | Hospitalized | 1215 | 52.5 | 55 (42–66) | 9 | 78 | 212 | 916 | 48.0 | 25.6 |
| Alhowaish T [36] | Saudi Arabia | Retrospective | Hospitalized | 122 | 18.9 | 48.3 ± 16 | 1 | 6 | 13 | 102 | 32.0 | 27.9 |
| Rohani-Rasaf M [110] | Iran | Cross-sectional | Hospitalized | 1228 | 49.8 | 58.8 ± 16.2 | 8 | 80 | 80 | 1060 | NA | 23.7 |
| Dana N [63] | Iran | Cross-sectional | Hospitalized | 831 | 54.3 | 63.9 ± 16.2 | OR (95% CI): 0.67 (0.08–5.41) | | | | 39.1 | 32.6 |
| Jalili M [73] | Iran | Retrospective | Hospitalized | 28,981 | 56.0 | 57.33 ± 17.67 | 141 | 432 | 5552 | 22,856 | NA | 11.3 |
| Nakamura S [95] | Japan | Retrospective | Hospitalized | 32 | 69.0 | 74.5 (24–90) | 1 | 1 | 10 | 20 | 40.6 | 21.9 |
| Saha A [112] | Bangladesh | Retrospective | ICU patients | 168 | 79.8 | 56.26 (45.68–75.33) | 3 | 12 | 92 | 61 | 41.1 | 52.4 |
| Almazeedi S [40] | Kuwait | Retrospective | All patients | 1096 | 81.0 | 41 (25–75) | 4 | 39 | 15 | 1038 | 16.1 | 14.1 |

**Table 1.** *Cont.*

| Author | Country | Study Design | Setting | Cases | Male (%) | Mean/Median Age | Asthma | | Non-Asthma | | Comorbidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dead | Alive | Dead | Alive | Hypertension | Diabetes |
| Alshukry A [41] | Kuwait | Retrospective | Hospitalized | 417 | 63.0 | 45.39 ± 17.06 | 12 | 29 | 48 | 328 | 29.5 | 23.3 |
| Jin M [75] | China | Retrospective | Hospitalized | 121 | 33.9 | 57.52 ± 14.71 | 1 | 20 | 2 | 98 | 26.5 | 13.2 |
| Rahimzadeh P [106] | Iran | Case series | ICU patients | 70 | 66.0 | 66.22 ± 14.36 | 5 | 0 | 51 | 14 | 50.0 | 42.0 |
| Zhang JJ [126] | China | Retrospective | Hospitalized | 289 | 53.4 | 56 ± 11.56 | 1 | 0 | 48 | 240 | 28.0 | 9.3 |
| Aljouie AF [39] | Saudi Arabia | Retrospective | Hospitalized | 1513 | 56.8 | 54.83 ± 17.00 | 8 | 135 | 128 | 1242 | 40.0 | 40.2 |
| Agrupis KA [28] | Philippines | Retrospective | Hospitalized | 367 | 57.0 | 51 ± 18 | 0 | 15 | 60 | 292 | 38.1 | 20.2 |
| Islam MA [72] | Bangladesh | Clinical trial | Hospitalized | 199 | 79.0 | 64.0 (53.0–70.0) | 2 | 0 | 75 | 122 | 77.9 | 9.5 |
| Khalid A [79] | Pakistan | Retrospective | Hospitalized | 317 | 62.5 | NA | 2 | 11 | 55 | 249 | 39.1 | 35.3 |
| Safari M [111] | Iran | Retrospective | Hospitalized | 66 | 60.6 | 61.6 ± 13.5 | 16 | 20 | 9 | 21 | 24.4 | 21.2 |
| Pakdel F [99] | Iran | Cross-sectional | Hospitalized | 15 | 66.0 | 47.25 ± 16.39 | 1 | 1 | 6 | 7 | 46.0 | 86.0 |
| Satici C [113] | Turkey | Retrospective | Hospitalized | 681 | 51.0 | 56.9 ± 15.7 | 1 | 42 | 54 | 584 | 34.4 | 28.0 |
| Doganay F [66] | Turkey | Retrospective | Hospitalized | 481 | 53.0 | 67 (52–79) | 4 | 20 | 116 | 341 | 32.0 | 25.2 |
| Ucan ES [124] | Turkey | Retrospective | Hospitalized | 298 | 49.7 | 61.85 ± 20.01 | 2 | 16 | 42 | 238 | 45.6 | 16.8 |
| Statsenko Y [121] | United Arab Emirates | Retrospective | ICU patients | 72 | 80.6 | 58.66 ± 13.02 | 6 | 1 | 9 | 56 | 31.9 | 37.5 |
| Burhamah W [54] | Kuwait | Retrospective | ICU patients | 133 | 68.0 | 59 (49–68) | 10 | 3 | 68 | 52 | 55.0 | 57.0 |
| Khani M [80] | Iran | Prospective | Hospitalized | 207 | 57.5 | 54.5 ± 14.8 | 0 | 10 | 22 | 175 | 38.2 | 25.1 |
| Doganay F [67] | Turkey | Retrospective | Hospitalized | 489 | 51.7 | 59.33 ± 19.42 | 7 | 24 | 147 | 311 | 36.6 | 26.0 |
| Degerli E [65] | Turkey | Retrospective | Hospitalized | 45 | 51.0 | 60.3 ± 15.65 | 2 | 1 | 28 | 14 | 24.0 | 20.0 |
| Ayten O [49] | Turkey | Retrospective | Hospitalized | 73 | 64.4 | 56.9 ± 13.3 | 1 | 0 | 26 | 46 | 45.2 | 20.5 |
| Puah SH [105] | Singapore | Prospective | Hospitalized | 102 | 73.5 | 62 (54–68) | 1 | 3 | 14 | 84 | 62.7 | 37.3 |
| Celik I [57] | Turkey | Retrospective | Hospitalized | 160 | 65.6 | 53 (24–65) | 2 | 14 | 37 | 107 | 33.1 | 23.8 |
| Jandaghian S [74] | Iran | Cross-sectional | Hospitalized | 4152 | 56.2 | 61.10 ± 16.97 | 10 | 98 | 467 | 3577 | 33.9 | 28.9 |
| Ozger HS [98] | Turkey | Prospective | Hospitalized | 37 | 64.9 | 61 (50–72) | 2 | 3 | 6 | 26 | 54.1 | 27.0 |
| Kaya T [78] | Turkey | Retrospective | Hospitalized | 148 | 45.3 | 63.2 ± 16.9 | 3 | 7 | 39 | 99 | 45.3 | 29.7 |
| Ma X [92] | China | Retrospective | Hospitalized | 459 | 55.3 | 44 (32–54) | 0 | 3 | 15 | 441 | 15.9 | 9.1 |
| AlBahrani S [34] | Saudi Arabia | Retrospective | Hospitalized | 169 | 60.9 | 53.1 ± 16.7 | 0 | 6 | 3 | 160 | 43.2 | 12.4 |
| Ro S [109] | Japan | Retrospective | Hospitalized | 17 | 64.7 | 73.71 ± 21.30 | 1 | 1 | 6 | 9 | 47.1 | 35.3 |

**Table 1.** *Cont.*

| Author | Country | Study Design | Setting | Cases | Male (%) | Mean/Median Age | Asthma | | Non-Asthma | | Comorbidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dead | Alive | Dead | Alive | Hypertension | Diabetes |
| Deeb A [64] | United Arab Emirates | Retrospective | Hospitalized | 1075 | 90.4 | 46.0 ± 12.3 | 2 | 28 | 99 | 946 | 23.7 | 31.1 |
| Shah M [118] | Pakistan | Prospective | Hospitalized | 250 | 66.0 | 54.22 ± 12.56 | 1 | 6 | 56 | 187 | 34.0 | 32.8 |
| Satici MO [114] | Turkey | Retrospective | Hospitalized | 272 | 58.1 | 64.7 ± 14.7 | 8 | 23 | 78 | 163 | 52.7 | 34.6 |
| Bokhary DH [53] | Saudi Arabia | Retrospective | Hospitalized | 656 | 63.3 | 50 ± 19.4 | 2 | 21 | 130 | 503 | NA | 35.9 |
| Argun Barıs S [45] | Turkey | Retrospective | Hospitalized | 213 | 50.2 | 50.75 ± 13.61 | 0 | 11 | 6 | 196 | 21.6 | 15.0 |
| Alhamar G [35] | Kuwait | Retrospective | Hospitalized | 417 | 62.8 | 45.38 ± 17.07 | 12 | 29 | 48 | 328 | 29.5 | 23.3 |
| Alizadehsani R [38] | Iran | Retrospective | Hospitalized | 660 | 56.6 | 68 ± 14 | 2 | 19 | 100 | 539 | 40.2 | 32.3 |
| Emami A [69] | Iran | Retrospective | Hospitalized | 2625 | 55.5 | 56.85 ± 18.84 | 35 | 210 | 840 | 1540 | 37.7 | 34.0 |
| Abedtash A [25] | Iran | Retrospective | Hospitalized | 180 | 36.7 | 67.76 ± 18.72 | 1 | 4 | 70 | 105 | 40.0 | 35.6 |
| Parvin S [101] | Bangladesh | Cross-sectional | Hospitalized | 972 | 64.1 | 54.47 ± 12.73 | 15 | 80 | 146 | 731 | 43.6 | 42.2 |
| Bakhshwin D [51] | Saudi Arabia | Retrospective | Hospitalized | 145 | 55.2 | 69.22 ± 8.12 | 1 | 5 | 15 | 124 | 41.4 | 57.9 |
| Zarei J [125] | Iran | Retrospective | Hospitalized | 10,657 | 52.7 | 55.88 ± 18.46 | 28 | 198 | 1683 | 8748 | 5.5 | 18.3 |
| Elhazmi A [68] | Saudi Arabia | Prospective | ICU patients | 1468 | 74.0 | 55.9 ± 15.1 | 37 | 91 | 503 | 837 | 48.6 | 54.8 |
| Kuwahara M [88] | Japan | Retrospective | ICU patients | 70 | 71.4 | 67 (38–84) | 4 | 2 | 25 | 39 | 41.4 | 59.4 |
| Shesha N [119] | Saudi Arabia | Retrospective | Hospitalized | 1583 | 61.8 | 50.8 ± 15.8 | 6 | 30 | 172 | 1375 | 12.2 | 19.1 |
| Sener MU [116] | Turkey | Retrospective | Hospitalized | 58 | 70.7 | 66.5 (57–71) | 3 | 0 | 32 | 23 | 62.1 | 32.8 |
| Alzahrani MA [43] | Saudi Arabia | Retrospective | Hospitalized | 536 | 53.4 | 54.3 ± 16.6 | 5 | 40 | 27 | 464 | 44.9 | 44.9 |
| ALGhamdi MA [32] | Saudi Arabia | Retrospective | Hospitalized | 248 | 75.8 | 49.38 ± 15.46 | 3 | 3 | 42 | 200 | 29.8 | 34.7 |
| Jo S [76] | Korea | Retrospective | Hospitalized | 5153 | 41.5 | 49.3 (33.2–65.7) | 13 | 109 | 212 | 4819 | 22.2 | 13.0 |
| Paul G [103] | India | Retrospective | Hospitalized | 690 | 65.4 | 60.5 (46.7–80.2) | 4 | 2 | 342 | 342 | 38.7 | 52.2 |

Abbreviations: ICU, intensive care unit; NA, not available; OR, odds ratio; CI, confidence interval.

### 3.3. Asthma and COVID-19 Mortality in Asia

Overall, combining the data from 103 studies, our meta-analysis indicated there was a significant association between comorbid asthma and increased risk for mortality of COVID-19 patients (pooled OR = 1.42, 95% CI: 1.20–1.68; $I^2$ = 70%, $p < 0.01$, Figure 2). Consistent results were observed in the subgroup analyses stratified by sample sizes (pooled OR = 1.41, 95% CI: 1.10–1.82 for <1000 cases and 1.43, 95% CI: 1.14–1.79 for ≥1000 cases), setting (pooled OR = 1.37, 95% CI: 1.14–1.64 for hospitalized patients and 1.91, 95% CI: 1.36–2.68 for all patients) and male proportion (pooled OR = 2.08, 95% CI: 1.78–2.44 for <50% and 1.24, 95% CI: 1.00–1.55 for ≥50%). When the subgroup analysis was performed by age, the significant relationship existed in the subgroup of mean/median age <60 years old (pooled OR = 1.44, 95% CI: 1.18–1.76) but did not exist in the subgroup of mean/median age ≥60 years old (pooled OR = 1.36, 95% CI: 0.95–1.94). The significant association existed among studies with the prevalence of obesity ≥20% (pooled OR = 2.27, 95% CI: 1.65–3.12) but did not exist among studies with the prevalence of obesity <20% (pooled OR = 1.21, 95% CI: 0.60–2.46). The subgroup analysis according to ICU and non-ICU patients suggested COVID-19 patients with asthma had a significantly increased risk of mortality among studies with non-ICU patients (pooled OR = 1.45, 95% CI: 1.22–1.72) but not among studies with ICU patients (pooled OR = 1.40, 95% CI: 0.58–3.38). A further subgroup analysis by country characterized by homogenous socioeconomic features revealed COVID-19 patients with asthma had a significantly increased risk for mortality compared with patients without asthma among very high HDI countries (pooled OR = 1.55, 95% CI: 1.29–1.87) but not among high HDI countries (pooled OR = 1.38, 95% CI: 0.91–2.11), medium HDI countries (pooled OR = 0.88, 95% CI: 0.50–1.56), and low HDI countries (pooled OR = 1.60, 95% CI: 0.77–3.33) (as shown in Figure 2). The meta-regression displayed male proportion ($p = 0.034$) might be the potential sources of heterogeneity, while country ($p = 0.301$), sample sizes ($p = 0.966$), setting ($p = 0.254$), age ($p = 0.961$), and obesity ($p = 0.103$) might not.

Considering comorbidities could lead to additional "noise" and measurement error, we subsequently calculated the pooled OR on the basis of adjusted effect estimates. The results indicated asthma was significantly associated with the increased risk of mortality among Asian COVID-19 patients on the basis of 19 studies (adjusted OR = 1.22, 95% CI: 1.05–1.42), which supported the findings based on crude effects.

### 3.4. Sensitivity Analysis and Publication Bias

The sensitivity analysis showed the effect estimate was not unduly impacted by any single study, indicating the stability and robustness of our results. Begg's analysis ($p = 0.835$, Figure 3A) and Egger's analysis ($p = 0.847$, Figure 3B) demonstrated publication bias might not exist in this study.

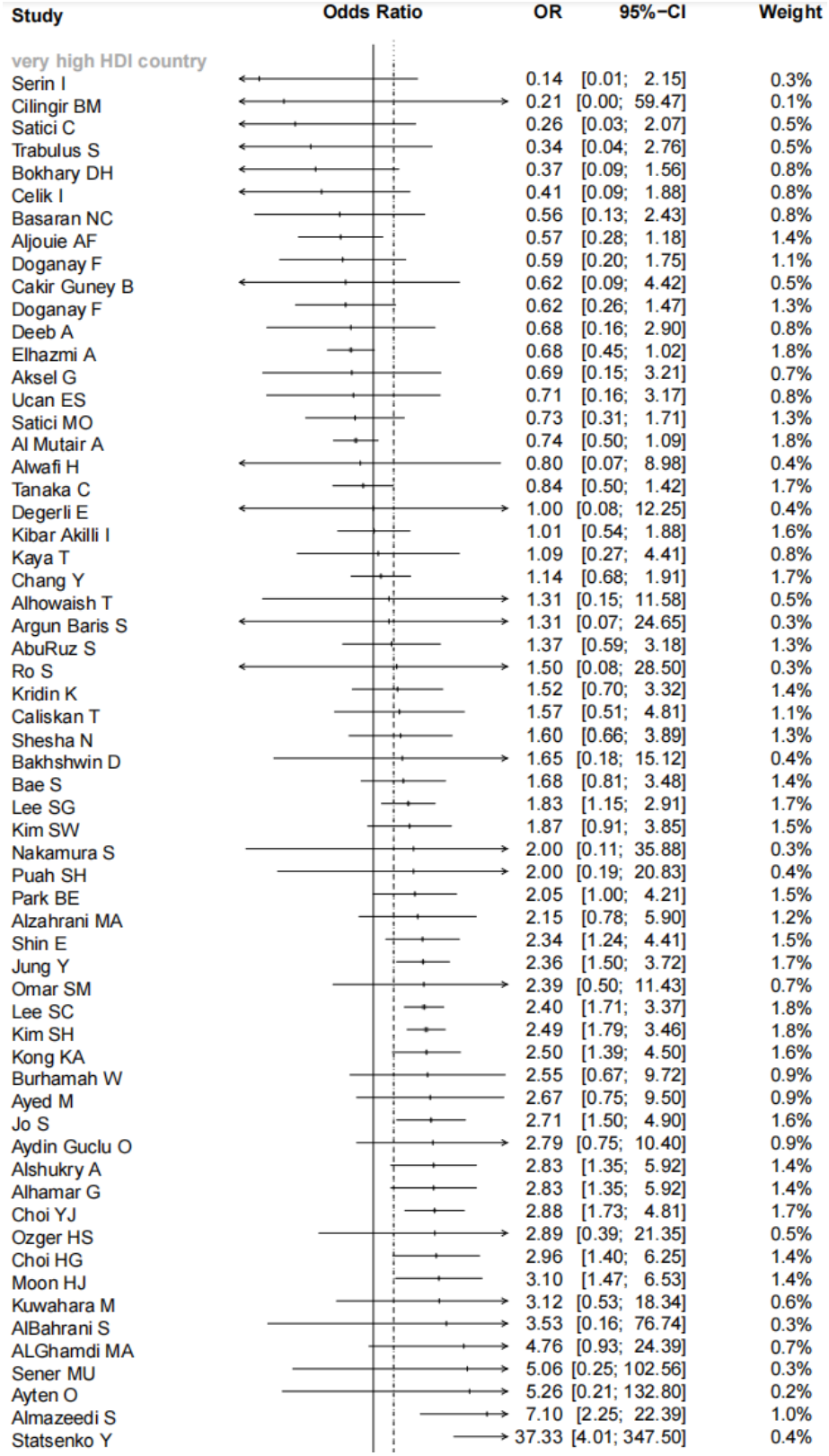



**Figure 2.** *Cont*.

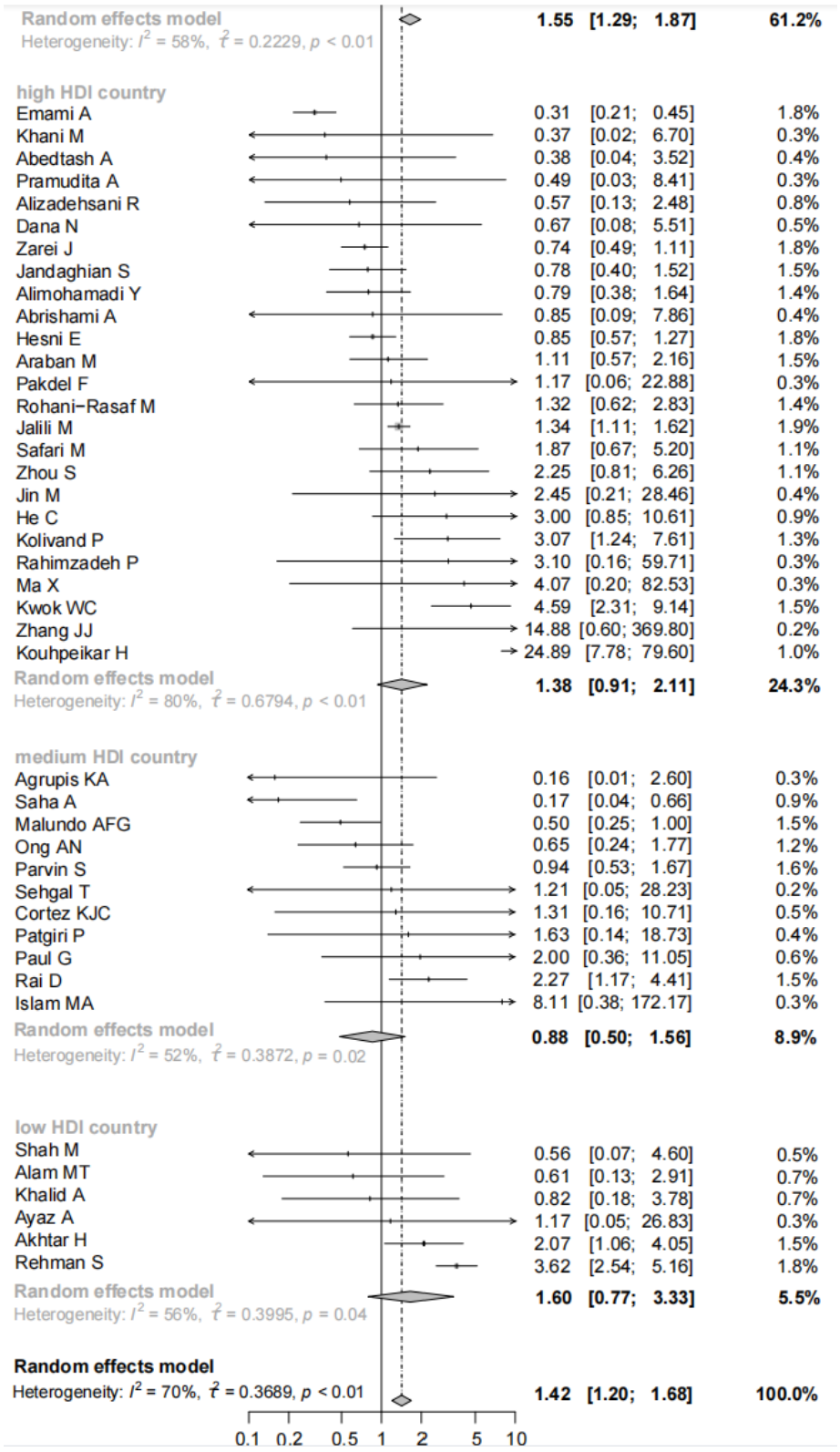



**Figure 2.** Forest plot indicated there was a significant association between comorbid asthma and the increased risk for mortality of COVID-19 patients in Asia.

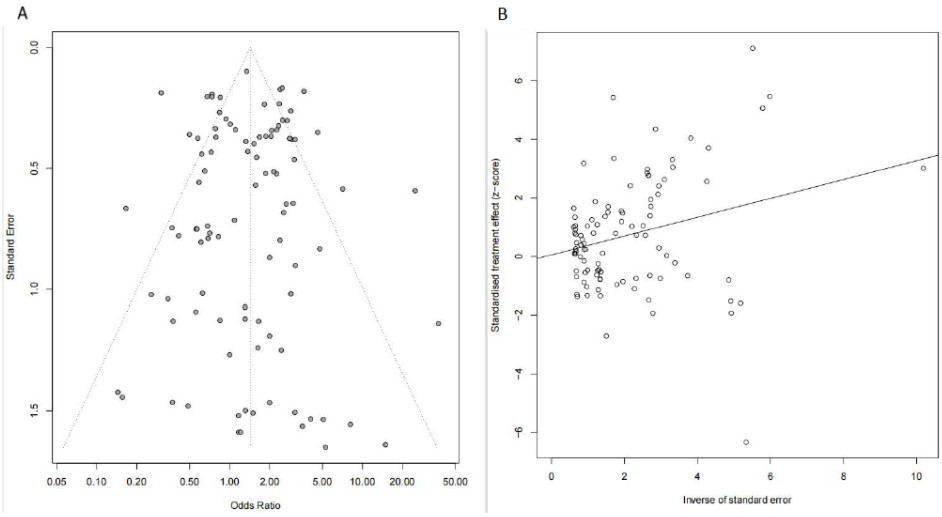



**Figure 3.** Publication bias was evaluated by Begg's analysis (**A**) and Egger's analysis (**B**).

## 4. Discussion

Our findings based on 103 eligible studies indicated comorbid asthma was significantly associated with an increased risk for mortality in COVID-19 patients compared with those without in Asia. The subgroup analyses by male proportion, sample sizes, and setting yielded consistent results, but the subgroup analysis by age indicated comorbid asthma was significantly associated with higher risk for COVID-19 mortality in Asia among studies with mean/median age <60 years old and not among studies with mean/median age ≥60 years old. Previous studies have shown advanced age and asthmatic patients are prone to other comorbidities, such as hypertension and diabetes mellitus, which are closely related to the severity and mortality of COVID-19 patients [128]. We also investigated the proportion of hypertension and diabetes mellitus in enrolled studies among age <60 years old and ≥60 years old and found the proportions of hypertension and diabetes mellitus were relatively higher in groups ≥60 (44.39% and 30.64%, respectively) than in groups <60 years old (32.03% and 25.8%, respectively). Thus, we speculated the existence of other comorbidities (such as hypertension and diabetes mellitus) might mask the relationship between asthma and COVID-19 mortality.

Asthma is a heterogeneous disease, and some phenotypes are related to obesity, which has continued to attract respiratory experts' attention since the pandemic of COVID-19 [129]. Furthermore, high body mass index has been identified as a risk factor for COVID-19 mortality. In our subgroup analyses stratified according to the proportion of males, the odds ratio increased to 2.08 in the group with males being less than 50% and was reduced to 1.24 in the subgroup where males dominated, while Wenzel et al. showed females usually dominate in obesity-related asthma [129]. This suggested part of the conflicting results on asthma and COVID-19 mortality could be due to the differences in handling of obesity in different studies. Our further analysis stratified by obesity prevalence supported this opinion. The subgroup results regarding ICU versus non-ICU deaths may be explained by the facts that ICU patients may rely either on a better economic status (theirs or for their countries) than non-ICU patients (whose access to intensive care may be impaired by economic status).

At present, research has explored the potential mechanism of the association between COVID-19 and asthma from the standpoints of pathophysiology. Viral infections, including SARS-CoV-2 and Middle East respiratory syndrome coronavirus (MERS) could directly result in the exacerbation of asthma and thus lead to serious airway inflammation, which might be linked to critical unfavorable outcomes [130,131]. Additionally, several researchers proposed host antiviral immunity was decreased due to asthma associated type II inflammatory response [132,133]. In addition, interferon responses as a crucial step of

antiviral immune reaction were shown to be lacking in asthmatic patients attributed to decreased production [134,135]. Additionally, asthma resulted in mucus plugging in the lower respiratory tract, limiting the airflow and worsening the hypoxemia from diffuse alveolar damage by SARS-CoV-2 infection [136]. However, these theoretical relationships remain to be observed. Further studies focusing on the molecular mechanisms underlying the association between comorbid asthma and the increased risk for COVID-19 mortality are warranted to verify our results.

The strengths of this study were the number of eligible studies included (103 eligible studies), and the sample sizes (198,078 cases) were large, and subgroup analyses were conducted. However, several limitations need to be acknowledged in this study. First, although the investigators tried to avoid duplicates in the process of article selection, several studies collected clinical records of COVID-19 patients retrospectively from large national public databases. This inevitably led to repeated populations and selective bias. Second, most of the included articles were observational retrospective studies, which resulted in lack of proof for casual links between asthma and mortality risk of COVID-19. Third, the medical history of enrolled patients could not be clearly analyzed, especially for the use of theophylline, inhaled corticosteroids, leukotriene receptor antagonists, and other drugs. Length of in-hospital treatment, the severity of asthma, types of asthma, and other comorbidities could not be extracted either, which should be a focus in the future study. Fourth, the existence or history of other comorbidities, such as coronary artery disease, chronic obstructive pulmonary disease, and so on was not addressed presently, which still restricted the generalization of our findings.

## 5. Conclusions

Our findings demonstrated comorbid asthma significantly increased the risk for mortality among patients with COVID-19 in Asia, at least among non-elderly individuals.

**Author Contributions:** F.L. and H.Y. conceptualized the study. L.S., J.R. and H.F. performed the literature search. L.S., J.R. and Y.W. performed data extraction. L.S. and J.R. analyzed the data. L.S. and J.R. wrote and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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