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Masters Program in Public Health, Universitas Sebelas Maret

Meta-Analysis

Meta-Analysis the Effect of Asthma Comorbidity on the Mortality of COVID-19 Patients

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ABSTRACT

Background: COVID-19 is an infectious disease that spread throughout the world in December 2019. The risk factors for mortality of COVID-19 patients depend on comorbid diseases. Most of the comorbid diseases associated with COVID-19 deaths consist of hypertension, diabetes, obesity, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and asthma. This study aims to analyze the effect of comorbid asthma on mortality in COVID-19 patients.
Subjects and Method: This was a meta-analysis study using PRISMA flowchart guidelines. The article search process was carried out between 2020-2021 using databases from PubMed, Google Scholar and Scopus. Based on the database, there were 15 articles that met the inclusion criteria. The analysis was carried out using the RevMan 5.3 software.
Results: The 15 articles reviewed in the meta-analysis showed that comorbid asthma increased the mortality risk of COVID-19 patients and was statistically significant (aOR = 1.18; CI 95%= 1.02 to 1.36; p = 0.030).
Conclusion: Asthma comorbidities increase the mortality of COVID-19 patients.

Keywords: Asthma, mortality, COVID-19, SARS-CoV 2

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BACKGROUND

COVID-19 is an infectious disease that spread throughout the world in December 2019 (Huang, et al., 2020). Update on COVID-19 cases as of July 16, 2021, there are 188,655,968 confirmed cases of COVID-19 worldwide, including 4,067,517 deaths (WHO, 2020). COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Common symptoms of COVID-19 infection include fever (83%-98%), cough (50%-82%), fatigue (25%-44%), shortness of breath (19%-55%), and muscle aches (11 %-44%) (Chen et al., 2020).

Risk factors for mortality in COVID-19 patients include age, presence of comorbid diseases, secondary infection, and increased blood levels of inflammatory indicators (Ruan et al., 2020). Most of the comorbid diseases associated with COVID-19 mortality consist of hypertension (Sun et

al., 2020; Grasselli, et al., 2020), diabetes (Sticchi et al., 2021; Corcoles et al., 2020; Charoenngam et al., 2021), obesity (Kurniawati et al., 2021; Kim et al., 2021) cardiovascular disease (Shi et al., 2020), cerebrovascular disease (Fang et al., 2020), chronic obstructive pulmonary disease (Kar et al., 2021), cardiac injury disease (Song et al., 2020), and chronic kidney disease (La-Pena et al., 2020; Williamson et al., 2020).

The American Academy of Allergy, Asthma & Immunology considers asthma a risk factor for COVID-19 (CDC, 2020; Abrams et al., 2020). Several studies in China reported underlying respiratory disease as a comorbidity among hospitalized patients with COVID-19 (Zhou et al., 2020; Huang et al., 2020; Xu et al., 2020; Li et al., 2020; Zhang et al., 2020) with some specifically mentioning asthma.

Based on the large number of COVID-19 cases that afflict asthmatic patients and the need for appropriate prevention and treatment, researchers are interested in conducting a meta-analysis of the effect of asthma comorbidities on mortality of COVID-19 patients. This study aims to analyze the effect of comorbid asthma on mortality of COVID-19 patients in hospital, with a meta-analysis of previously conducted primary studies.

SUBJECTS AND METHOD

1. Study Design

This research was conducted using a meta-analysis research design with PRISMA flow chart guidelines. Article searches were performed using the following databases: PubMed, Google Scholar and Scopus. Some of the keywords used were: "asthma AND (Mortality OR Death) AND COVID-19 OR SARS-CoV-2.".

2. Inclusion Criteria

The inclusion criteria for this research article were full paper cohort study articles, articles using English, adjusted Odds Ratio (aOR) relationship size, COVID-19 patient subjects, patient mortality outcomes.

3. Exclusion Criteria

The exclusion criteria for this research article were the statistical results of bivariate analysis, and articles that did not use English.

4. Operational Definition

Articles included in this study are PICO-adjusted. The article search was carried out taking into account the eligibility criteria determined using the following PICO model: Population= COVID-19 patients, Intervention= asthma comorbidity, Comparison= no asthma comorbidity, Outcome= mortality.

Asthma is a chronic inflammatory airway disease characterized by wheezing, coughing, and tightness in the chest due to airway obstruction, and belongs to the group of chronic respiratory diseases. Asthma is categorized as asthmatic and non-asthmatic. The measurement scale is categorical.

Mortality is determined by the status of death in patients diagnosed with COVID-19. Mortality was categorized as dead and alive. The measurement scale is categorical.

5. Instrument Study

Research is guided by the PRISMA flow diagram and assessment of the quality of research articles using the Critical Appraisal Skills Program tool (CASP, 2018). The 12 questions used are as follows:

1. Did the study address a clearly focused issue?
2. Was the cohort recruited in an acceptable way?
3. Was the exposure COVID-19 accurately measured to minimize bias?
4. Was the outcome (status mortality) accurately measured to minimize bias?
5. Have the authors identified all-important confounding factors? Have the authors took account of the

confounding factors in the design and/or analysis?
6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough?
7. Was the result of this study reported in aOR?
8. How precise were the results?
9. Do you believe the results?
10. Can the results be applied to the local population?
11. Do the results of this study fit with other available evidence?
12. What are the implications of this study for practice?

6. Data Analysis

Research data were analyzed using the RevMan 5.3 application, to calculate the effect size and heterogeneity of the study. The results of data processing are presented in the form of forest plots and funnel plots.

RESULTS

The article review process using the PRISMA flowchart can be seen in Figure 1. The total articles obtained were 10 articles spread across 4 continents, namely America, Europe, Asia and Africa.

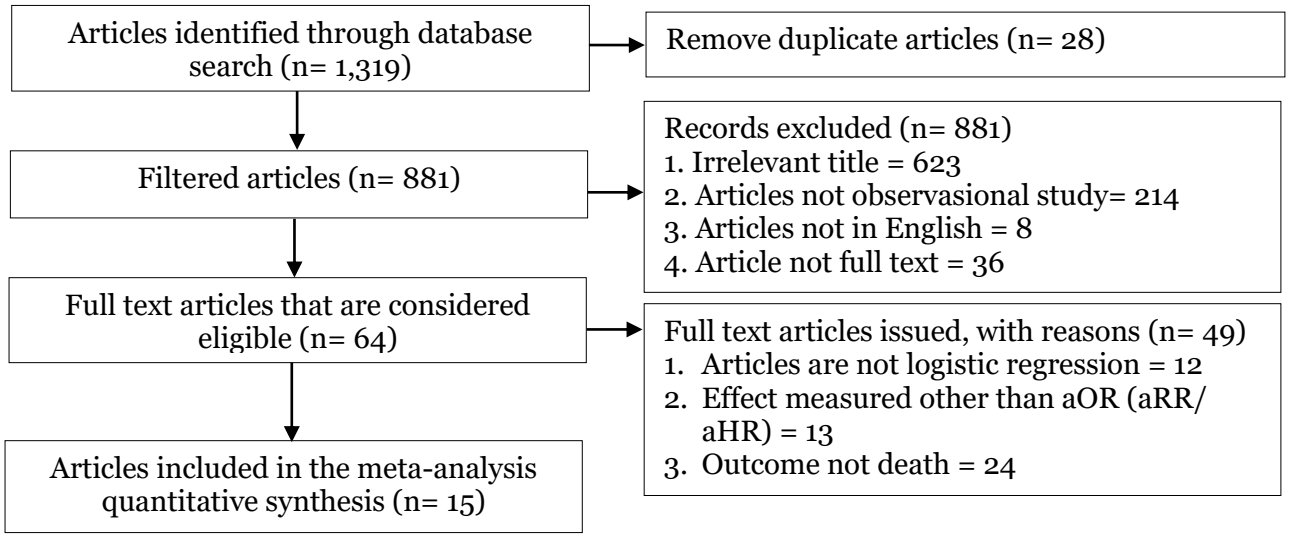

Figure 1. PRISMA flowchart

Tabel 1. The Quality Assessment of the Cohort Study on Effect of Asthma Comorbidity on Mortality of COVID-19 Patients

Primer Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Almazeedi *et al.* (2020)	2	2	2	2	2	2	2	1	2	2	2	2	23
Almirall *et al.* (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Choi *et al.* (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Cummins *et al.* (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Ken-Dror *et al.* (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Lee *et al.* (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Lohia *et al.* (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Mulhem *et al.* (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Osibogun *et al.* (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Park *et al.* (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Robles-Perez *et al.* (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Rosa *et a*l. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Shin *et al.* (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Toples *et al.* (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Trabulus *et al.* (2021)	2	2	2	2	2	2	2	1	2	2	2	2	23

Note: Answer 2= Yes; Answer 1= Can't tell; Answer 0= No

a. Forest plot

The forest plot in Figure 2 shows that COVID-19 patients with comorbid asthma have a mortality risk of 1.18 times compared to COVID-19 patients without comorbid asthma and the results are statistically significant (aOR= 1.18; CI 95%= 1.02 to 1.36; p= 0.030).

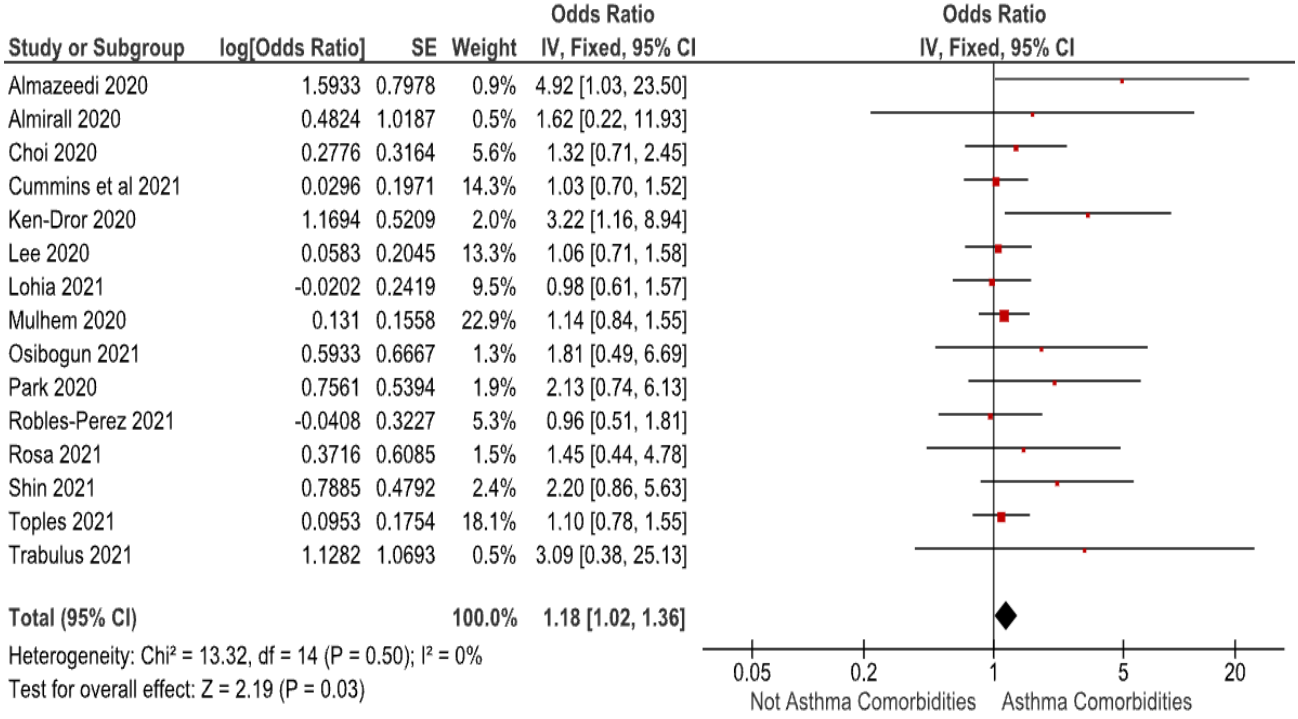

Figure 2. Forest plot Effect of Asthma Comorbidity on Mortality of COVID-19 Patients

b. Funnel plot

The funnel plot in Figure 3 shows publication bias with an overestimated effect characterized by an asymmetric distribution between the right and left plots. There are 9 plots on the right, 5 plots on the left, and 1 plot touching the vertical line. The plot on the right of the graph appears to have a standard error (SE) between 0 and 1.50. The plot on the left of the graph appears to have a standard error (SE) between 0 and 0.50.

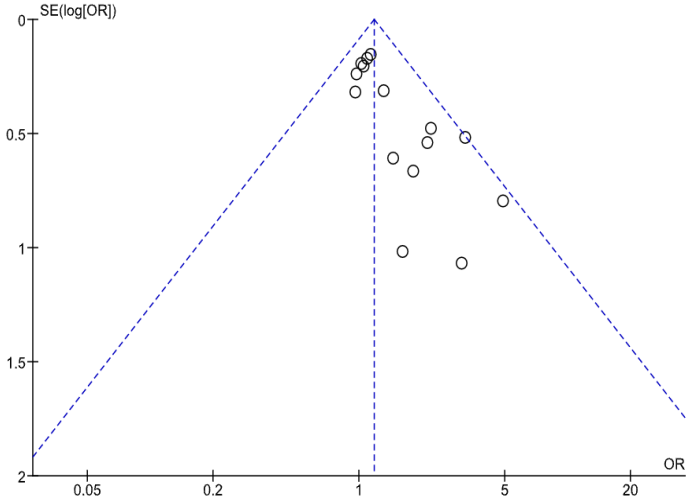

Figure 3. Funnel Plot Effect of Asthma Comorbidity on Mortality of COVID-19 Patients

Table 2. Description of the primary studies included in the meta-analysis

Author (Year)	Study Period	Country	Study Design	Sample Size		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR (CI 95%)
				Total	Asma (%)					
Almazeedi et al. (2020)	24 February to 20 April 2020	Kuwait	Retrospective cohort	1,096	43 (3.9)	Adult patients aged 25-75 years confirmed COVID-19	Obesity, Diabetes mellitus, hypertensi, chronic kidney failure, and asthma	Without comorbid asthma	Mortality	aOR= 4.92 (1.03 to 23.44)
Almirall et al. (2020)	29 February to 4 April 2020	Spanish	Retrospective cohort	486	13 (4.0)	Adult patient 56 years old confirmed COVID-19	Hypertensi, obesity, cancer, asthma, heart disease, autoimmune, COPD, and cancer	Without comorbid asthma	Mortality	aOR= 1.62 (0.22 to 7.52)
Choi et al. (2020)	January to 15 May 2020	Korea	Retrospective cohort	7,590	218 (2.9)	Inpatients aged 0-70 year with COVID-19 mild to severe symptoms	Asthma	Without comorbid asthma	Mortality	aOR= 1.32 (0.71 to 2.45)
Cummins et al. (2021)	1 February to 30 June 2020	UK	Retrospective cohort	1,781	244 (13.7)	Adult patient aged 16 years confirmed COVID-19	obesity, asthma, cancer, chronic heart disease, COPD, Diabetes mellitus, hypertension, and stroke	Without comorbid asthma	Mortality	aOR= 1.03 (0.70 to 1.50)
Ken-Dror et al. (2020)	March to April 2020	UK	Prospective cohort	429	42 (12.8)	Adult patient aged 70 years with confirmed COVID-19 hospitalized	Hypertensi and asthma	Without comorbid asthma	Mortality	aOR= 3.22 (1.16 to 8.92)
Lee et al. (2020)	20 January to 27 May 2020	UK	Retrospective cohort	7,272	686 (9.4)	Adult patients aged 20-70 confirmed year	asthma, hypertension, Diabetes mellitus, and heart failure	Without comorbid asthma	Mortality	aOR= 1.06 (0.71 to 1.59)
Lohia et al. (2021)	10 March to 30 June 2020	United States of America	Retrospective cohort	1,871	134 (7.2)	COVID-19 patient age adult 18 years old laboratory confirmed	Hypertension, Diabetes mellitus, asthma kidney failure, cancer, heart disease and stroke	Without comorbid asthma	Mortality	aOR= 0.98 (0.61 to 1.58)
Mulhem et al. (2020)	13 March to 29 April 2020	United States of America	Retrospective cohort	3219	429 (13.3)	Inpatients aged 65-85 confirmed year COVID-19	Diabetes mellitus, hypertension, asthma, COPD, chronic kidney disease, and obesity	Without comorbid asthma	Mortality	aOR= 1.14 (0.84 to 1.55)

Author (Year)	Study Period	Country	Study Design	Sample Size		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR (CI 95%)
				Total	Asma (%)					
Osibogun et al. (2021)	27 February to 6 July 2020	Nigeria	Retrospective cohort	2,184	45 (2.1)	Inpatients aged 33-55 years confirmed COVID-19	Hypertension, Diabetes mellitus, disease kidney failure, cancer, and asthma	Without comorbid asthma	Mortality	aOR= 1.81 (0.49 to 6.65)
Park et al. (2020)	15 February to 24 April 2020	Korea	Retrospective cohort	2,269	67 (3.2)	Inpatient aged 55 confirmed year COVID-19	COPD, chronic kidney disease, and asthma	Without comorbid asthma	Mortality	aOR= 2.13 (0.74 to 6.13)
Robles-Perez et al. (2021)	March to December 2020	Mexico	Retrospective cohort	75,595	2403 (3.2)	Adult patient >65 confirmed year COVID-19 being treated at hospital	Obesity, cancer, asthma, chronic kidney disease, diabetes mellitus, and cancer	Without comorbid asthma	Mortality	aOR= 0.96 (0.51 to 1.79)
Rosa et al. (2021)	27 February to 15 June 2020	Italy	Retrospective cohort	1,538	23 (1.5)	Social Security Workers confirmed COVID-19 61-83 years old	Diabetes mellitus, hypertension, cardiovascular, COPD and asthma	Without comorbid asthma	Mortality	aOR= 1.45 (0.44 to 4.78)
Shin et al. (2021)	21 January to 30 April 2020	Korea	Retrospective cohort	5,571	128 (2.3)	Adult patient age 40-85 confirmed year COVID-19 being treated in hospital	Hypertension, asthma, failure heart, asthma, kidney disease chronic and liver disease	Without comorbid asthma	Mortality	aOR= 2.20 (0.86 to 5.59)
Toples et al. (2021)	March 16 to August 24, 2020	UK	Retrospective cohort	473,139	306 (0.1)	COVID-19 confirmed patients aged 60-74 years who are hospitalized	Asthma	Without comorbid asthma	Mortality	aOR= 1.10 (0.78 to 1.54)
Trabulus et al. (2021)	15 March to 1 May 2020	Turkey	Retrospective cohort	336	20 (6.0)	COVID-19 patient age 69 year with confirmation laboratory	Diabetes mellitus, asthma, hypertension, cancer, COPD and heart disease	Without comorbid asthma	Mortality	aOR= 3.09 (0.38 to 24.96)

DISCUSSION

This systematic review and meta-analysis research raised the theme of the influence of asthma comorbidities on mortality in COVID-19 patients. The independent variable analyzed was asthma comorbidity. The dependent variable analyzed was COVID-19 mortality. This study discusses asthma comorbidities, this is considered important because it is considered a high risk group for the severity and even mortality of COVID-19 patients (CDC, 2020).

The primary studies that met the criteria were 15 articles from 3 Americas, 6 from Europe, 4 from Asia, and 1 from America. This study shows that asthma comorbidity is statistically significant in influencing mortality of COVID-19 patients. The forest plot results show the magnitude of the effect of comorbid asthma on mortality of COVID-19 patients, which is 1.18 increasing mortality of COVID-19 patients (aOR= 1.18; CI 95%= 1.02 to 1.36; p= 0.030). The heterogeneity of the research data shows I^2= 0% so that the distribution of the data is declared homogeneous (fixed effect model).

Asthma comorbidity may increase the risk of mortality in COVID-19 patients, these results are in accordance with the hypothesis. According to research Choi et al. (2020) showed that asthma is a risk factor for increased mortality in COVID-19 patients in Korea. The research of Choi et al. (2020) recommends that doctors advise asthma patients to routinely use asthma medications during the COVID-19 pandemic. This is supported by research by Lee et al. (2020) showed that asthmatic patients who had experienced an acute exacerbation prior to COVID-19 increased COVID-19 mortality. Research by Shin et al. (2021) showed that COVID-19 patients with asthma were more likely to be in critical condition requiring ventilation and have a higher risk of mortality.

The results of the study were in line with those conducted by Almazeedi et al. (2020) which stated that asthma comorbidity was a risk factor for mortality in COVID-19 patients in Kuwait (aOR= 4.92; CI 95%= 1.03 to 23.44; p= 0.046). Other similar studies were found in the UK (Fong et al., 2021), South America (Mato et al., 2020), Turkey (Trabulus et al., 2021) and Spain (Almirall et al., 2020).

The results of this study are not in line with Sunjaya et al. (2020) which showed that a 14% (CI 95%= 0.80 to 0.94) risk of contracting COVID-19 was lower in people with asthma. There are several possible explanations for the reduced risk of mortality, including the observation that people with high Th2 asthma can lower the angiotensin-converting-enzyme-2 (ACE-2) receptor, thereby reducing the risk of SARS-CoV-2 infection (Jackson et al., 2020). Other evidence from the Asthma Research Program suggests that inhaled corticosteroid therapy is associated with lower ACE-2, which makes it harder for the virus to enter the body (Peters et al., 2020; Jakson et al., 2020). Interferon levels in asthmatics are hypothesized to be protective against the cytokine storm that occurs in COVID-19 patients (Carli et al., 2020). This can provide reduced susceptibility to COVID-19 and less severe disease progression.

Another inconsistent study conducted by Lee et al. (2021) who stated that comorbid asthma reduces the risk of COVID-19 mortality in Korea. Similar results were found in the United States (Arshad et al., 2020; Izurieta et al., 2021; Kelly et al., 2021; Yehia et al., 2020; Vaughn et al., 2021), France (Beltramo et al., 2020), Brazil (Castro et al., 2021), Ireland (Bennet et al., 2021), Belgium (Calmes et al., 2021), Mexico (Parra-Bracamonte., 2020; Martos

Benítez et al., 2021) and the UK (Perez-Guzman et al., 2020; Atkins et al., 2020).

AUTHOR CONTRIBUTION

Siti Mar'atul Munawaroh is the main researcher who chooses the topic, searches for and collects research data. Hanung Prasetya and Bhisma Murti analyzed data and reviewed the research documents.

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This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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