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LITERATURE REVIEW

A SYSTEMATIC REVIEW AND META-ANALYSIS: RISK FACTORS OF MORTALITY COVID-19

Sistematik Review dan Meta-Analisis: Faktor Risiko Kematian COVID-19

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ABSTRACT

Background: COVID-19 is still a threat throughout the world because of its high morbidity and mortality. Comorbid diseases like hypertension, diabetes mellitus, and heart disease are some of the factors in the high severity and mortality of COVID-19 patients. **Purpose**: The study aims to analyze the effect of risk factors on COVID-19 mortality using a systematic review and meta-analysis. **Methods**: Articles were taken from online journal portals Pubmed, Garuda, and Google Cendekia, and all were published from October 2019 to December 2021 in full text and with an observational study design. The keywords used in searching the articles were "COVID-19", "sars cov 2", "2019-nCoV", "2019 novel coronavirus", "COVID-19 deaths", and "COVID-19 mortality". The articles were collected using a PRISMA diagram; then, data extraction was carried out in a systematic review. The data was synthesized by using a meta-analysis technique using the RevMan application. **Results:** This study analyzed 59 articles and found that age, hypertension OR=3.09 (2.69-3.56), sex OR= 1.29 (1.08-1.53), and diabetes mellitus OR=3.03 (2.66-3.44) are the risk factors for COVID-19 death. **Conclusion**: The death in COVID-19 patients is influenced by elderly age, gender, and comorbid disease (diabetes and hypertension). These COVID-19-death-related factors can help health workers recognize and prevent a more severe stage of the disease through more appropriate handling and treatment.

ABSTRAK

Latar Belakang: *COVID-19 masih menjadi ancaman seluruh dunia karena morbiditas dan mortalitasnya yang masih tinggi. Penyakit komorbid seperti hipertensi, diabetes mellitus, penyakit jantung, merupakan salah factor tingginya tingkat keparahan dan kematian pasien COVID-19.* ***Tujuan:*** *Menganalisis pengaruh faktor-faktor risiko terhadap kematian COVID-19*

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dengan menggunakan sistematik review dan meta analisis. ***Metode:*** *Artikel diambil dari portal jurnal online seperti Pubmed, Garuda, dan Google Cendekia yang diterbitkan dalam rentang waktu Oktober 2019 sampai Desember 2021, fulltext, dengan desain studi observasional. Kata kunci yang dipakai untuk pencerian artikel adalah "COVID-19" OR "sars cov 2" OR "2019-nCoV" OR "2019 novel coronavirus", kematian COVID-19 dan mortalitas COVID-19. Artikel dikumpulkan dengan diagram PRISMA dan selanjutnya dilakukan ekstraksi data secara systematic review. Dilakukan sintesis data dengan teknik meta-analysis menggunakan aplikasi RevMan.* ***Hasil****: Penelitian ini menganalisis sebanyak 59 artikel dan mendapati bahwa usia, hipertensi OR=3.09 (2.69-3.56) OR=, jenis kelamin OR= 1.29 (1.08-1.53) dan diabetes melitus OR=3.03 (2.66-3.44) merupakan faktor risiko kematian COVID-19.* ***Simpulan:*** *Kematian pada pasien COVID-19 dipengaruhi oleh usia lanjut, jenis kelamin, penyakit komorbit (diabetes dan hipertensi). Faktor-faktor yang berhubungan dengan kematian COVID-19 tersebut dapat membantu petugas Kesehatan untuk mengenali dan mencegah ke tahap penyakit yang lebih parah melalui penanganan dan pengobatan yang lebih tepat.*

INTRODUCTION

COVID-19 is an infectious disease caused by a new type of coronavirus. The first case was found in Wuhan, China, in December 2019. The SARS-Cov-2 virus spread rapidly worldwide (Europe, America, Western Pacific, Southeast Asia, Eastern Mediterranean, and Africa). The total number of cases reported on August 2, 2022, which showed the total number of confirmed cases of COVID-19 in the world reaching as many as 575,887,049 cases with a death toll of 6,398,412 deaths (1). The total confirmed cases in Europe on August 31, 2022, reached 247 million, with a total death of around 2 million. The number was followed by those in America and Southeast Asia, with confirmed cases of 175 million people and 59.98 million people and a death rate of around 2.8 million people and 795 thousand people (2). Based on the results of studies carried out since the beginning of this disease, the symptoms of COVID-19 vary widely. Symptoms that often appear include fever, cough, and fatigue (3); however, several patients have other symptoms, such as cough with phlegm, muscle weakness, shortness of breath, anosmia, red eye, and diarrhea (4).

Several studies regarding the relationship between comorbidities and COVID-19 mortality are still being debated. The research results (5) show that age, gender, history of hypertension, diabetes, Chronic Obstructive Pulmonary Disease (COPD), and heart disease are related to death from COVID-19. This study analyzes any of these factors: age, gender, hypertension, and diabetes. Potential risk factors related to death in COVID-19 patients can be used as data for taking action to prevent severity and reduce mortality from COVID-19.

METHODS

This study chose a systematic review and meta-analysis to find the association between age, sex, hypertension, diabetes, and COVID-19 mortality. The articles were obtained from the databases of Google Cendekia, PubMed, and Garuda. Then, the keywords used for the article search were "COVID-19", "SARS-Cov 2", "2019-nCoV", "2019 novel coronavirus", "COVID-19 deaths", and COVID-19 mortality by filtering the searched years from 2019 to 2021.

The inclusion criteria in this study are articles in Indonesian and English languages, reputable journals at least with Q2 or SINTA-2 accredited national journals. The articles studied are those published from October 2019 to December 2021. Observational research was conducted using the following research design: cross-sectional, case series, cohort, or observational study. The exclusion criteria are articles that cover only one COVID-19 patient. The measured results are an analysis of the risk factors for COVID-19 mortality and the articles that review information on comorbidities (hypertension and diabetes) and demographics (age and sex).

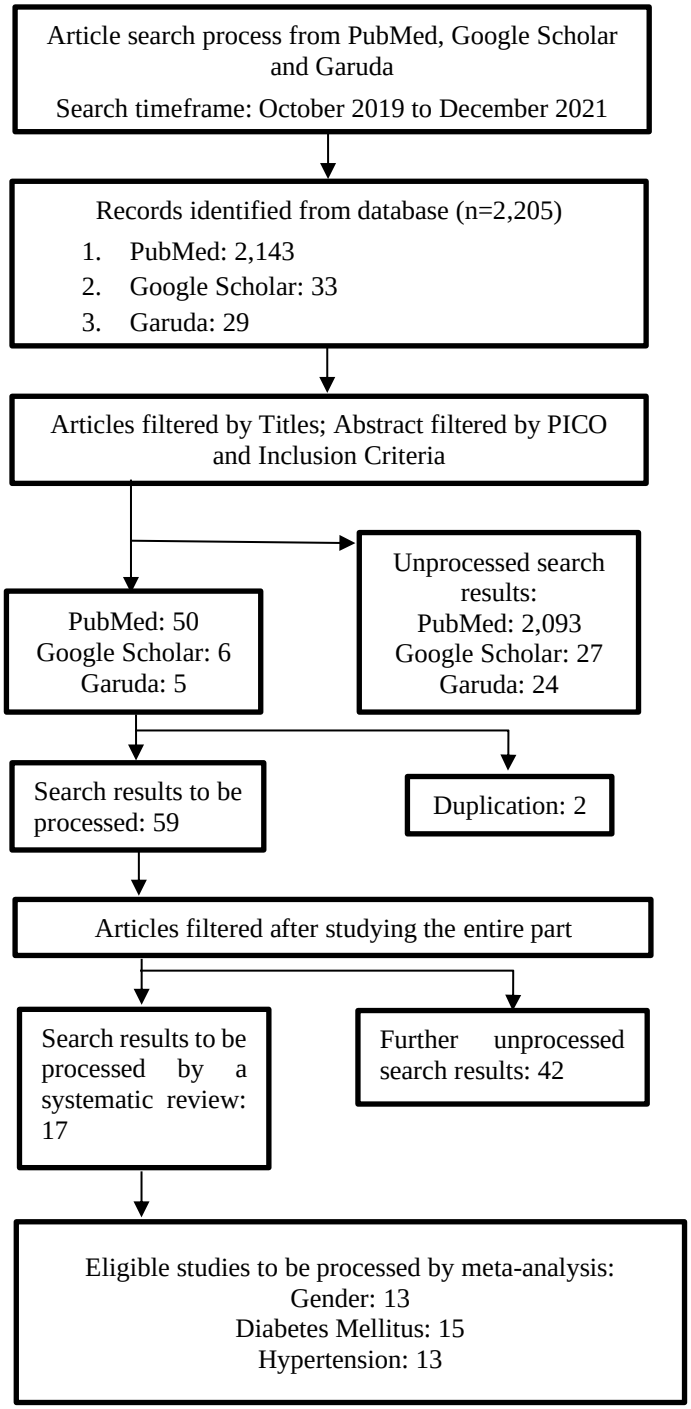

Figure 1. The Process of Selecting Articles Using PRISMA Methods

The article was selected in several stages of screening inclusion and exclusion criteria. The first screening was by looking for titles and abstracts, followed by further screening by studying all the articles. All research team members conducted the screening process. The quality assessment of the articles is based on scientific performance measurements, namely SINTA, which assesses the national articles, and ScimagoJR, which assesses the international articles.

Citations were downloaded using the Mendeley App. The process of searching and selecting the articles was completed by using the PRISMA method. The next step was data extraction, carried out in a systematic review. The data, which were by the requirements, were then synthesized using the RevMan application meta-analysis technique to calculate the difference in results among variables and provide estimates of the combined effects and variation or heterogeneity of all of the studies.

The effect size was used to calculate the pooled odds ratio (OR), and we used 95% confidence interval (CI). The heterogeneity was assessed using Cochran's Q, I2 index, and Chi-square test.

RESULTS

Based on the systematic review analysis, 15 articles on age-risk factors were processed for data extraction. All studies show a significant relationship between the youngest and oldest as risk factors and COVID-19 mortality (6,7,16–20,8–15). Table 2 shows that the age classification is categorized differently from one article to another, so no data synthesis was carried out on age risk factors in this study.

On gender-risk factors, 7 of 13 articles are significantly associated with COVID-19 mortality (Table 3) (7,10–13,17,19). Based on meta-analysis results using the random-effects model, shown in Figure 2, there is a p-value <0.01 and a pooled odds ratio of 1.29 (95% CI 1.08-1, 53). It is concluded that gender-risk factors are associated with COVID-19 mortality that men have a 1.29 times greater risk of dying compared to women (Heterogeneity I^2 = 92%).

Table 4 shows 12 articles that show that diabetes has a significant relationship with COVID-19 mortality. The remaining three articles do not have a significant relationship (7,10,21,22,12–14,16–20). In Figure 2, after synthesizing the data using the random-effects model, OR 3.03 (95% CI 2.66-3.44). Patients with a diabetes history have a 3.03 times risk of dying from COVID-19 compared to patients who do not have such diabetes history (Heterogeneity I^2 = 94%) (Figure 3).

Table 1
Demographics of the included studies

First Author	Country	Year	Reputable journals	Research design	Analized Risk Factor	Total Sampel	Male/ Female	Age Mean±SD/ Median(IQR)
Adham, Davoud	Iran	2021	Q1	retrospective cohort	Age, Sex	5587	2017/2171	52.25 ± 20.21
Albitar, Orwa	Malaysia	2020	Q1	retrospective cohort	Age, Sex, DM, HT	828	489/339	49.4 ± 20.9
Carrillo-Vega, MF	Mexico	2020	Q1	observational	Age, Sex, DM, HT	9946	5753/4193	48.15 ± 14.35
Chilimuri, Sridhar	United State	2020	Q1	retrospective cohort	Age, Sex, DM, HT	375	236/139	63.0 (52.0-72.0)
Cho, Soo Ick	Korea Selatan	2021	Q1	retrospective cohort	DM, HT	7590	2974/4389	
Du, Rong-Hui	China	2020	Q1	prospective cohort	Age, Sex	179	97/82	57.6 ± 13.7 (18-87)
Gerwen, Maaike van	United State	2021	Q2	retrospective cohort	Age, Sex, DM, HT	2015	1181/834	-
Harvey, Rachel	United State	2021	Q2	observational	Age, Sex	11304	5647/5657	63.77 (17.79)
Hernandez-Galdamez, DR	Mexico	2020	Q2	cross-sectional	DM, HT	211003	115442/95561	45.7 (±16.3)
Nogueira, Paulo Jorge	Portugal	2020	Q1	observational	Age, Sex, DM	20293	8390/11903	-
Parra-Bracamonte, GM	Mexico	2020	Q2	observational	Age, Sex, DM, HT	331298	178155/153143	44(33-56)
Rosa, FGD	Italia	2021	Q1	retrospective and prospective	Age, Sex, DM, HT	1538	892/641	74 (61-83)
Salacup, Grace	United State	2021	Q2	retrospective cohort	Age, DM, HT	242	123/119	66(58-76)
Soares, Rita DCM	Brazil	2020	Q1	cohort	Age, Sex, DM	1152	658/494	-
Wang, Dawei	China	2020	Q1	retrospective case series	Age, Sex, HT	107	57/50	51(36-65)
Yu, Caizheng	China	2020	Q1	cohort	Age, DM, HT	1464	736/728	64(51-71)
Zhou, Fei	China	2020	Q1	retrospective cohort	Age, Sex, DM, HT	191	119/72	56.0(46.0-67.0)

Table 2
Systematic Review: Association between Age and COVID-19 Mortality

First Authors	Country	Age Categories	OR (95% CI)	p-value	AOR (95% CI)	p-value
Adham, Davoud (2021)	Iran	<50				
		>=50	4.57 (3.57–5.86)	<0.001	3.11 (2.39–4.06)	<0.001
Albitar, Orwa (2020)	Malaysia	-		<0.001	1.079 (1.064–1.095)	<0.001
Carrillo-Vega, MF (2020)	Mexico	25-49 (reference)				
		50-74	1.96 (1.63-2.34)	<0.001	-	-
		>=75	3.74 (2.80-4.98)	<0.001	-	-
Chilimuri, Sridhar (2020)	United state	-	1.05 (1.03-1.73)	< 0.0001	1.04 (1.01-1.06)	0.0003
Du, Rong-Hui (2020)	China	0-49		0.9970		
		50-64	2.673 (0.859–8.318)	0.0900	-	-
		>=65	9.740 (3.113–30.476)	<0.001	0.02	0.0230
Gerwen, Maaike van (2021)	United state	18-40				
		40-60		age <0.001	5.29 (2.51-11.15)	<0.001
		>60			13.04 (6.25-27.24)	
Harvey, Rachel (2021)	United stated	-	-	<0.0001	1.05 (1.04-1.05)	<0.0001
Nogueira, Paulo Jorge (2020)	Portugal	0-55			-	-
		56-60	6.50 (2.92;14.36)	<0.001	-	-
		61-65	12.25 (6.02;25.59)	<0.001	-	-
		66-70	26.53 (13.98;53.09)	<0.001	-	-
		71-75	51.22 (28.60;98.67)	<0.001	-	-
		76-80	80.27 (45.75;152.50)	<0.001	-	-
		81-85	108.56 (63.20;203.27)	<0.001	-	-
		85-90	125.87 (73.28;235.68)	<0.001	-	-
		91-95	125.67 (71.30;239.55)	<0.001	-	-
		96-104	183.30 (94.32;374.16)	<0.001	-	-
Parra-Bracamonte, GM (2020)	Mexico	0-20				
		21-40	1.632 (1.391-1.913)		1.419 (1.134-1.775)	<0.0001
		41-60	9.664 (8.272-11.289)		3.730 (2.996-4.645)	<0.0001
		61-80	36.444 (31.194-42.579)		7.753 (6.222-9.662)	<0.0001
		>80	60.650 (51.619-71.260)		12.598 (10.000-15.871)	<0.0001

(*Continued*)

Table 2
Continued

First Authors	Country	Age Categories	OR (95% CI)	p-value	AOR (95% CI)	p-value
Rosa, FGD (2021)	Italy	≤50	1.09 (1.08–1.10)	<0.001	1.07 (1.06–1.09)	<0.001
		51–70	age per year		age per year	
		71–80				
		81–90				
		>90				
Salacup, Grace (2021)	United state	-		<0.0001	1.056 (1.023-1.090)	0.0010
Soares, Rita DCM (2020)	Brazil	< 60				
		>=60	4.42 (3.42–5.73)	<0.001	3.95 (2.95–5.33)	<0.001
Wang, Dawei (2020)	China	<45	1.102 (1.054–1.152)	<0.001	1.111 (1.042–1.184)	0.0010
		45-59				
		60-75				
		0.75				
Yu, Caizheng (2020)	China	<65		<0.0001		
		>=65	2.80 (2.05-3.82)	<0.0001	2.15 (1.35, 3.43)	0.0010
Zhou, Fei (2020)	China	-	1.14 (1.09-1.18)	<0.0001	1.10 (1.03-1.17)	0.0043

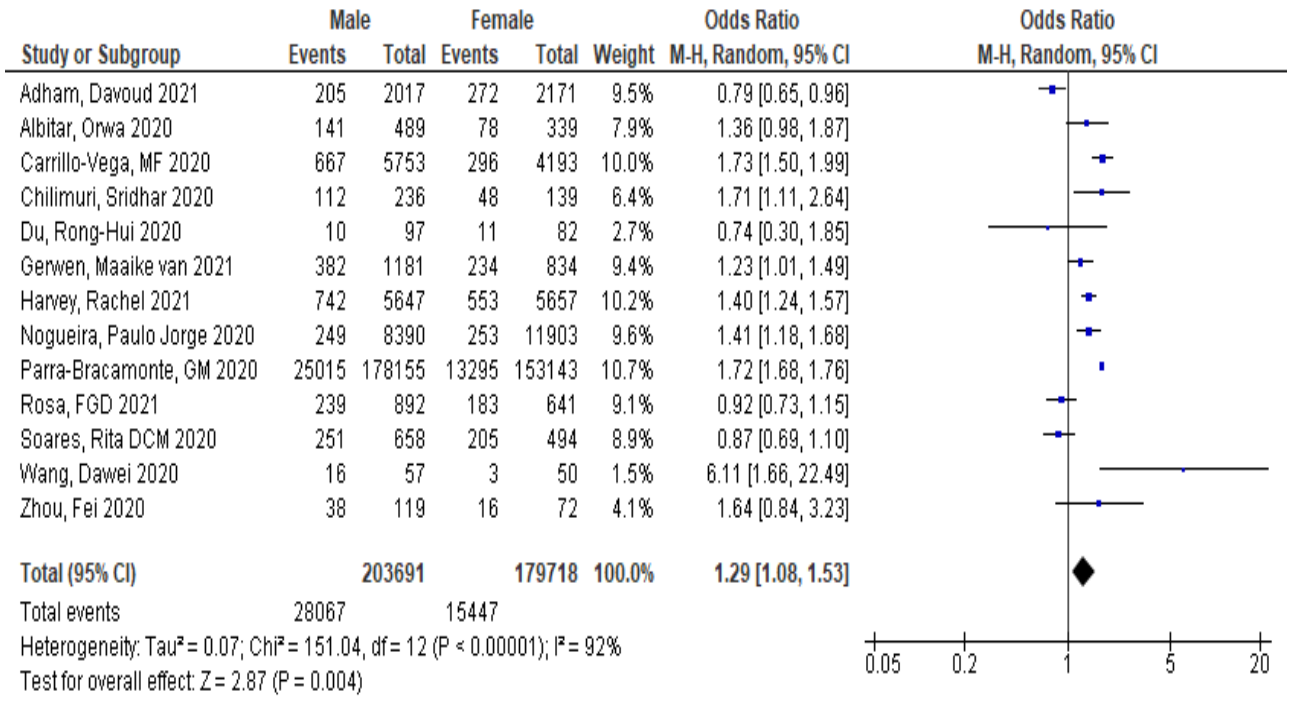

Figure 2. Forest plot shows that sex was associated with mortality COVID-19

Table 3
Systematic Review: Association between sex and mortality of COVID-19

First Authors	Country	cOR (95% CI)	p-value	AOR (95% CI)	p-value
Adham, Davoud (2021)	Iran	1.34 (1.11–1.62)	0.01	AOR 1.20 (0.98–1.47)	0.07*
Albitar, Orwa (2020)	Malaysia	-	-	AOR 1.607 (1.002–2.576)	<0.01
Carrillo-Vega, MF (2020)	Mexico	1.53 (1.30-1.81)	<0.01	-	-
Chilimuri, Sridhar (2020)	United State	1.71 (1.11-2.64)	0.01	AOR 1.37 (0.79-2.37)	0.25*
Du, Rong-Hui (2020)	China	-	0.64*	-	-
Gerwen, Maaike van (2021)	United State	-	-	AOR 1.46 (1.17-1.82)	0.03
Harvey, Rachel (2021)	United State	-	<0.01	AOR 1.43 (1.26-1.63)	<0.01
Nogueira, Paulo Jorge (2020)	Portugal	1.41 (1.17-1.69)	<0.01	-	-
Parra-Bracamonte, GM (2020)	Mexico	1.72 (1.17-1.76)	-	AOR 1.45 (1.39-1.50)	<0.01
Rosa, FGD (2021)	Italy	0.92 (0.73–1.15)	0.45*	AOR 1.13 (0.84–1.53)	0.42*
Soares, Rita DCM (2020)	Brazil	-	0.28*	-	-
Wang, Dawei (2020)	China	6.11 (1.66–22.49)	0.01	AOR 7.22 (1.29-40.19)	0.02
Zhou, Fei (2020)	China	-	0.15*	-	-

Table 4
Systematic Review: Association Between Diabetes and Mortality of COVID-19

First Authors	Country	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Albitar, Orwa (2020)	Malaysia	-	<0.01	aOR 12.23 (4.15–36.27)	<0.01
Carrillo-Vega, MF (2020)	Mexico	1.50 (1.13-1.98)	0.01	-	-
Chilimuri, Sridhar (2020)	United State	1.96 (1.29-2.98)	0.01	aOR 1.58 (0.94-2.65)	0.08*
Cho, Soo Ick (2021)	South Korea	-	<0.01	aOR 2.22 (1.63-2.95)	< 0.01
Du, Rong-Hui (2020)	China	-	0.32*	-	-
Gerwen, Maaike van (2021)	United State	-	<0.01	aOR 1.25 (1.00-1.55)	<0.01
Hernandez-Galdamez, DR (2020)	Mexico	-	0.00	aOR 1.69 (1.63-1.74)	0.00
Nogueira, Paulo Jorge (2020)	Portugal	3.49(2.72-4.43)	<0.01	aOR 1.39 (1.08-1.79)	0.01
Parra-Bracamonte, GM (2020)	Mexico	3.855 (3.77-3.95)	-	aOR 1.29 (1.24-1.34)	<0.01
Rosa, FGD (2021)	Italy	1.78 (1.37–2.31)	<0.001	aOR 1.41 (1.02–1.94)	0.04
Salacup, Grace (2021)	United State	-	0.16*	aOR 1.45 (0.67-3.13)	0.34*
Soares, Rita DCM (2020)	Brazil	1.88 (1.43–2.47)	<0.01	-	-
Wang, Dawei (2020)	China	4.88 (1.748-18.18)	0.02	-	-
Yu, Caizheng (2020)	China	3.77 (2.70-5.28)	<0.01	aOR 2.34 (1.45, 3.76)	0.01
Zhou, Fei (2020)	China	2.85 (1.35-6.05)	0.01	-	-

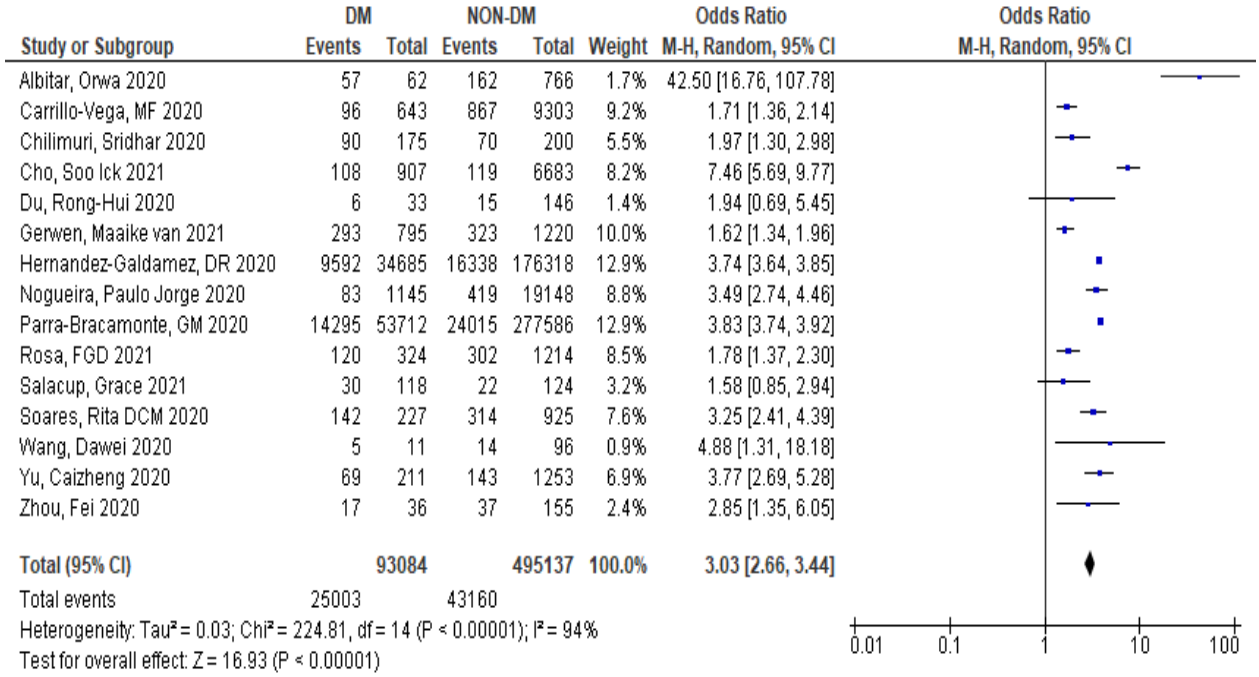

Figure 3. Forest plot shows that diabetes was associated with mortality COVID-19

Table 5
Systematic Review: Association Between Hypertension and Mortality of COVID-19

First Authors	Country	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Albitar, Orwa (2020)	Malaysia	-	<0.01	AOR 3.576 (1.694–7.548)	0.01
Carrillo-Vega, MF (2020)	Mexico	1.49 (1.15-1.92)	<0.01	-	-
Chilimuri, Sridhar (2020)	United State	2.43 (1.57-3.77)	<0.01	AOR 1.46 (0.82-2.62)	0.20*
Cho, Soo Ick (2021)	South Korea	-	<0.01	AOR 1.89 (1.38-2.60)	< 0.01
Du, Rong-Hui (2020)	China	4.08 (1.58-10.51)	<0.01	-	-
Gerwen, Maaike van (2021)	United State	-	<0.01	AOR 1.08 (0.85-1.37)	<0.01
Hernandez-Galdamez, DR (2020)	Mexico	-	0.01	AOR 1.24 (1.20-1.28)	<0.01
Parra-Bracamonte, GM (2020)	Mexico	3.69 (3.61-3.77)	-	AOR 1.24 (1.19-1.29)	<0.01
Rosa, FGD (2021)	Italy	1.74 (1.39–2.19)	<0.01	AOR 0.78 (0.58–1.05)	0.09*
Salacup, Grace (2021)	United State	-	0.23*	AOR 0.95 (0.38-2.43)	0.92*
Wang, Dawei (2020)	China	5.00 (1.75–14.30)	<0.01	AOR 1.09 (0.26–4.58)	0.89*
Yu, Caizheng (2020)	China	2.42 (1.77-3.32)	<0.01	AOR 1.08 (0.68, 1.72)	0.74*
Zhou, Fei (2020)	China	3.05 (1.57-5.92)	<0.01	-	-

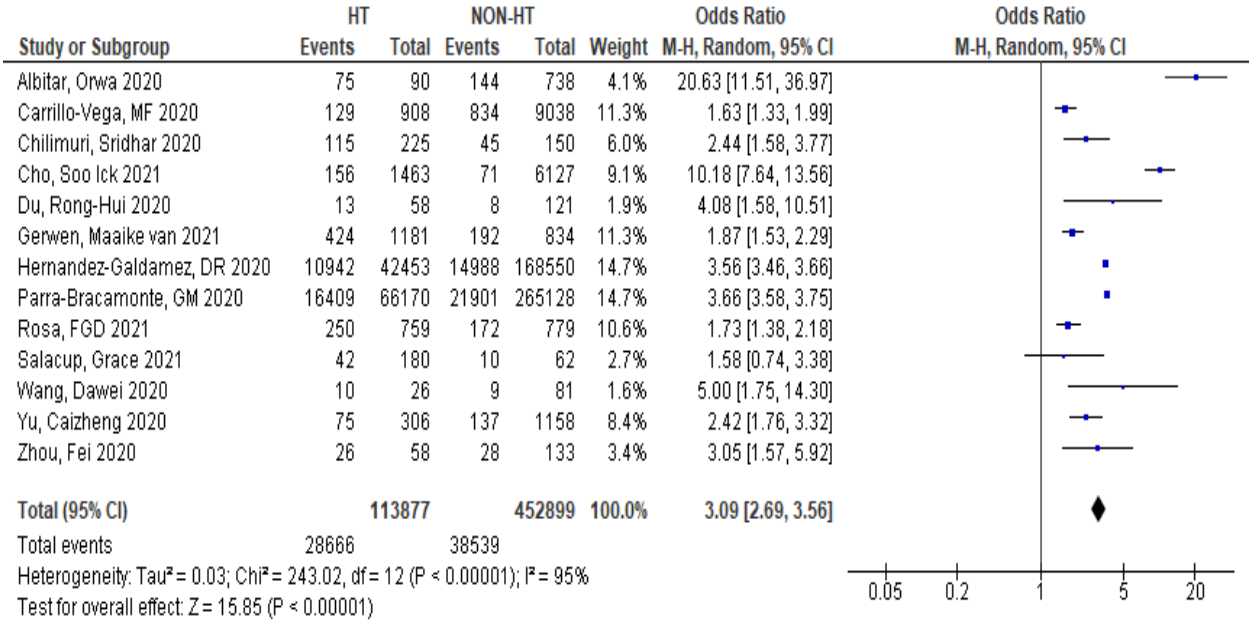

Figure 4. Forest plot shows that hypertension was associated with mortality COVID-19

In Table 5, 8 out of 13 articles on hypertension-risk factors have a significant relationship with COVID-19 mortality (7,9, 10, 13, 19–22). Based on the meta-analysis results of these articles using the random-effects model, OR 3.09 (95% CI 2.69-3.56) is shown in Figure 3. It is concluded that hypertension history has a significant relationship with COVID-19 mortality (Heterogeneity $I^2 = 95\%$) (Figure 4).

DISCUSSION

COVID-19 is a potentially fatal infectious disease and a significant concern for global health. Transmission of COVID-19 infection from person to person leads to the isolation of patients who will be given treatment (23). This study presents an association between age and mortality of COVID-19 patients. It is based on the previous systematic review conducted by Parohan et al (5), which also shows a relationship between age and COVID-19 mortality. One factor that influences mortality at the age of 65 and more is immune response impairment (24). Older patients usually have poor health conditions and often have poor medication. Another study in East Jakarta explained that age is a risk factor for COVID-19 mortality (25). The results of a study conducted in China explain that older patients have a higher risk of death than those with younger ages (26).

Males are significantly associated with the mortality increase in COVID-19 patients (27). Socio-cultural and behavioral differences can contribute to the COVID-19 death rate based on gender. In some countries, men are more likely to work, leave home, and enter crowded areas. Another study shows that men consistently have a higher risk of death from COVID-19 (19). This result is also influenced because men tend to have histories of comorbidities such as cardiovascular, diabetes, hypertension, and lung disease and have higher smoking behavior compared to women. The other study shows that women are less likely to be exposed to bacteria and viruses than men. A more robust immune response could influence this in women (28). COVID-19 death is not only influenced by one factor but also several other comorbid factors, such as hypertension, male gender, and active smokers (24). The increase in ACE2 receptor expression in people with these comorbidities is suspected to cause disease severity in COVID-19 patients (29). This meta-analysis study is in line with the study conducted by Lestari et al (30), which states that diabetes increases COVID-19 mortality by 1.65 times compared to similar deaths without diabetes.

The analysis shows that hypertension is also a risk factor for COVID-19 mortality. The research results conducted in China show the cOR = 4.081 (26). There is a relationship between male (aOR=1,607; 95% CI, 1.002–2576), elderly (aOR=1,079; 95% 1,064–1,095, hypertension (aOR, 3,576; 95% CI, 1,694–7,548), diabetes (aOR, 12,234; 95% CI, 4,126–36,272), and patients living

in USA (aOR, 7,441; 95% CI, 3,546–15,617) with COVID-19 death (19).

Research Limitations

This meta-analysis also has limitations: (a) research in different countries will have different risk influences on outcomes, considering culture greatly influences the population's health status. (b) Several studies included in this meta-analysis were cross-sectional. The weaknesses of this study need to be verified with more relevant studies, study designs that are not just observational, and articles that are selected more precisely and that use a larger sample size. This study has not analyzed the overall risk factors for COVID-19 death, such as smoking history, obstructive lung disease, and cancers. (c) Notably, the heterogeneity in the meta-analysis was very high. This may mean that the point estimates are less reliable than expected. This study includes extensive studies that answer slightly different questions with a wide range of methodological rigor and cannot represent any certainty.

CONCLUSION

The death risk of COVID-19 in older patients with comorbidities is higher. This research shows that age, gender, and comorbidities, such as a history of diabetes and hypertension, are significantly associated with COVID-19 mortality. The factors related to mortality in COVID-19 patients identified in this study can help identify COVID-19 patients who are at higher risk for prognosis. Monitoring those risk factors can be used as a reference to detect the disease early so that appropriate intervention or treatment can be conducted. To understand the disease comprehensively, conducting studies with more complex data is necessary, especially in countries with higher prevalence and mortality from COVID-19.

CONFLICT OF INTEREST

The authors have no conflict of interest associated with the material presented in this paper.

AUTHOR CONTRIBUTION

The authors confirmed their contributions to the paper: TF: Writing, conceptualization, reviewing, and editing. QF: Writing and initial draft preparation, methodology. All authors reviewed the results.

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