by Dwi Sutiningsih

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Dwi Sutiningsih, ^{1,*} Nur Azizah Azzahra, ² Yulianto Prabowo, ³ Aris Sugiharto, ⁴ Mufti Agung Wibowo, ⁵ Endah Sri Lestari, ⁶ Estri Aurorina ⁷

Abstract

Introduction To date, the total number of COVID-19 deaths is still increasing, including in Central Java, with the third-highest total number of deaths in 19 donesia. There are still limited studies related to the cases of COVID-19. Thus, this study's objective was to provide an overview of the characteristics of 4359 COVID-19 death cases in Central Java.

Methods This research used a cross-sectional descriptive design with univariate, bivariate, and multivariate analysis involving secondary data acquired from a report by the Provincial Health Office of Central Java, recorded up to 13 December 2020.

Results The results showed that the highest frequencies of death cases were contributed from ≥60 years group (n=1897 patients; 43.52%) and the male (n=2497 patients; 57.28%) group. The case fatality rate (CFR) rose with age, and the highest CFR was recorded in the elderly (17.95%), males (7.60%), in Pati District (17.45%), while entrepreneur (14.64%) was the highest reported job. Furthermore, the eldest group (≥60 years) and males were more susceptible to die, with ORs 5.49 (95%CI: 5.15-5.86) and 1.61 (95%CI: 1.51-1.71), sequentially. The majority of death cases had comorbidities (65.79%), while the most prevalent reported comorbidities were diabetes (n=1387, 31.82%) and hypertension 114 n=817, 18.74%). Meanwhile, patients of old age were more likely to associate comorbidity, p<0.001, OR 1.664 (95%CI: 1.425-1.944).

Conclusions This study concludes that patients of older age and males may become more vulnerable than younger and females to experience death. Further study is required to measure the relationship between other characteristics of demographics, underlying medical conditions, and fatality.

Keywords CFR, gender, age, comorbidities, COVID-19.

Introduction

The pandemic of coronavirus disease-2019 (COVID-19), which is caused by SARS-CoV-2, is still a threat to public health worldwide. Thailand reported the first imported case after

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Wuhan.¹ Meanwhile, Indonesia reported its first go cases of COVID-19 on 2 March 2020.² Globally, the number of COVID-19 cases until 18 October 2020 was 40,118,333 with a case

China on 13 January 2020, originated from

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¹DVM, M.PH, Ph.D., Epidemiology and Tropical Disease Department, Public Health Faculty, Diponegoro University, Prof. Soedarto, S.H., Tembalang Street, Semarang, Central Java, Indonesia, 50275, and Master of Epidemiology, Postgraduate School, Diponegoro University, Imam Bardjo S.H., No.5 Street, Semarang, Central Java, Indonesia, 50241; ²BPH, Master of Epidemiology, Postgraduate School, Diponegoro University, Imam Bardjo S.H., No.5 Street, Semarang, Central Java, Indonesia, 50241; ³MD, M.PH, Central Java Provincial Health Office, Kapten Piere Tendean No.24 Sekayu Street, Semarang City, Central Java, Indonesia, 50132; ⁴BPH, M.PH, Ph.D., Central Java Provincial Health Office, Kapten Piere Tendean No.24 Sekayu Street, Semarang City, Central Java, Indonesia, 50132; ⁴BPH, M.PH, Ph.D., Central Java Provincial Health Office, Kapten Piere Tendean No.24 Sekayu Street, Semarang City, Central Java, Indonesia,

50132; ⁵S.Komp, M.IT, Central Java Provincial Health Office, Kapten Piere Tendean No.24 Sekayu Street, Semarang City, Central Java, Indonesia, 50132; ⁶BPH, M.PH, Central Java Provincial Health Office, Kapten Piere Tendean No.24 Sekayu Street, Semarang City, Central Java, Indonesia, 50132; ⁷BPH, M.PH, Central Java Provincial Health Office, Kapten Piere Tendean No.24 Sekayu Street, Semarang City, Central Java, Indonesia, 50132.

*Corresponding author: Dwi Sutiningsih, dwi.sutiningsih@live.undip.ac.id

Article downloaded from www.germs.ro Published June 2021 © GERMS 2021 ISSN 2248 - 2997 ISSN - L = 2248 - 2997 fatality rate (CFR) of 2.8%. Southeast Asia contributed the third-highest cumulative case death, which was 135,275 cases (12%), preceded by America and Europe with 608,727 (55%) and 256,540 (23%) respectively, the second-highest death case numbers in Southeast Asia came from Indonesia, with 12,617 cases out of 365,240 cumulative cases of COVID-19.³ According to the data up to 13 December 2020, Central Java was in the third position based on cumulative cases of deaths from COVID-19.⁴

COVID-19 is a newly emerging disease, so that 37a related to the disease are still limited, such as the distribution of COVID-19 case deat 2 based on age, gender, and patient comorbidity in Central Java Province, Indonesia. Although there was a previous study, the number of patients involved was still small, with 1,533 cumulative cases and 102 cases of 3 ath. 5 Therefore, the authors aim to give an overview of the characteristics of deaths of COVID-19 patients and reported comorbidities.

Methods

The research used a cross-sectional descriptive method using secondary data involving 70,925 total cases, including 4359 deaths and 2868 reported comorbidity histories obtained from the Provincial Health Office of Central Java until 13 December 2020. Data for case deaths consisted of age, gender, and comorbidity. Univariate analysis was used to see the cases distribution, presented in tables and figures. To calculate the p value of each variable, Chi-square and Mann-Whitney were utilized in the analysis process. All variables with p<0.25 were salesequently analyzed in logistic regression test. Univariable and multivariable logistic regression was utilized to investigate the risk factor of fatality and comorbidity. In logistic regression analysis, Hosmer-Lemeshow and Omnibus tests were used to validate model fit assumptions. Microsoft Excel, Microsoft Word, SPSS v. 24 were used to conduct univariate, bivariate, and multivariate analysis.

Results

This study involved 70,925 total cases, including 4359 deaths, 56,290 recovered cases,

and 2,868 reported comorbidity histories. Figure 1 reports that amongst 29 regencies and six cities in Central Java, there were nine regencies and two cities sharing CFR above the overall CFR in Central Java, such as Pati Regency (17.45%), Grobogan Regency (12.84%), Demak Regency (12.20%), Kudus Regency (10.78%), Brebes Regency (9.22%), Semarang City (9.16%), Rembang Regency (9.03%), Surakarta City (7.21%), Pemalang Regency (6.84%), Tegal Regency (6.23%), and Jepara Regency (6.22%), while the lowest CFRs were in Purworejo Regency (2.56%), Magelang Regency (2.44%), Cilacap Regency (2.15%), Kebumen Regency (1.59%), and Salatiga City (1.33%). The CFR of COVID-19 in Central Java was 6.15%. Meanwhile, the CFR for cases that were of unknown origin of the regency/city in Central Java was 9.45% (Figure 1). The death incidences in Central Java tended to climb from March to November, from 6 to 1123, and most of the cases were contributed in November, while the highest increase of total cases occurred in October from 30,280 to 54,092 (Figure 2).

As is presented in Table 1 A, B and C, the median age of death cases was higher than that of recovered cases with 58 years (IQR: 50-65 years) vs. 40 years (IQR: 26-53 years). It can be seen that the proportion of COVID-19 cases who died was higher in the elderly (≥60 years), with 43.52%, followed by the patients aged 45-59 years, with 43.27%. On the other hand, death cases in patients aged 6-9 had the smallest percentage (0.05%). A decrease in CFR was also seen from 0 years (1.37%) to 6-9 years (0.20%), then an upward trend to the elderly (≥60 years) with the highest CFR (17.95%). Also, most of the COVID-19 deaths occurred in male patients, with 2,497 cases (57.28%). Moreover, the CFR of male patients (7.60%) was higher than the CFR in the female group, with 4.89%. There was significant differences in categories of age (p<0.001) and gender (p<0.001) between death cases and recovered cases. The median and mean age variable in the male category of deato cases were slightly higher than in females with 10 years (IQR: 51-72 years) and 57.47 years vs. 57 years (IQR: 50-64 years) and 56.23 years, respectively. Overall, 65.79% of the dead patients had

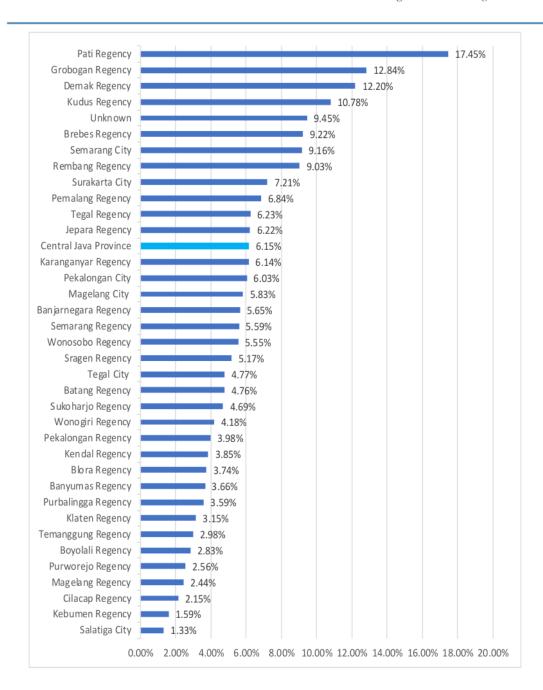


Figure 1. Case fatality rate (CFR) based on regencies and cities (%)

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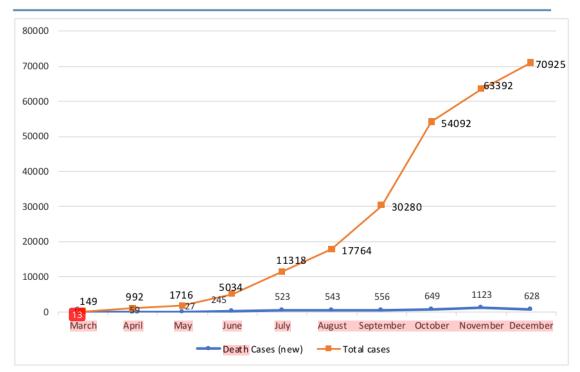


Figure 2. COVID-19 case prevalence in Central Java from March to December 2020

Table 1. Characteristics of COVID-19 cases in Central Java

Table 1 - A

Characteristics	CFR (%)	Totala	%		De	ath		P value
	Total=6.15%	F=70,925		Yes F=4359	(%)	No F=56,290	(%)	-
Age								
Median (IQR), years	-	42 (28-54)	-	58 (50-65)	-	40 (26-53)	-	<0.001*b
≥60 years (elderly)	17.95	10,568	14.90	1897	43.52	6926	12.30	
45-59 years (pre-elderly)	8.74	21,590	30.44	1886	43.27	16,275	28.91	
19-44 years (adult)	1.77	31,153	43.92	550	12.62	26,217	46.57	
10-18 years (youth)	0.24	5017	7.07	12	0.28	4566	8.11	
6-9 years (children)	0.20	1004	1.42	2	0.05	877	1.56	
1-5 years (toddlers)	0.52	1155	1.63	6	0.14	1041	1.85	
0 years (infants)	1.37	438	0.62	6	0.14	388	0.69	
Gender								
Male	7.60	32,838	46.30	2497	57.28	25,604	45.49	<0.001*b
Female	4.89	38,087	53.70	1862	42.72	30,686	54.51	

Table 1 - B

Assand		15 Male			Female	
Age and gender	Median (IQR)	Mean (95%CI)	Minimum-	Median (IQR)	Mean (95%CI)	Minimum-
gender			maximum			Maximum
Age, years	58 (51-72)	57.47	0-92	57	56.23	0-100
		(57.00-57.95)		(50-64)	(55.68-56.78)	

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Table 1 · C					30			
Comorbidity	Total	%	Male	Female	P value	≥60 years	<60 years	P value
Having comorbidity	2868/4359	65.79	1622	1246	0.394	1231	1637	<0.001*b
>1 comorbidity	784/4359	17.99	428	356		364	420	-
Diabetes mellitus	1387/4359	31.82	722	665	0.004*b	573	814	<0.001*b
Hypertension	817/4359	18.74	485	332	0.652	374	443	<0.001*b
Heart di33 se	454/4359	10.42	262	192	0.908	236	218	<0.001*b
Kidney failure	316/4359	7.25	216	100	0.002*b	115	201	0.095^{b}
Congestive heart failure	237/4359	5.44	126	111	0.184^{b}	131	106	<0.001*b
Stroke	154/4359	3.53	90	64	1.000	85	69	<0.001*b
Ischemic heart disease	97/4359	2.23	46	51	$0.053^{\rm b}$	40	57	0.055 b
Anemia	83/4359	1.90	36	47	0.012*b	40	43	0.002*b
Pulmonary TB	72/4359	1.65	46	26	0.411	29	43	0.139^{b}
Chronic obstructive	68/4359	1.56	48	20	$0.060^{\rm b}$	31	37	0.019*b
pulmonary disease								
Cancer	61/4359	1.40	23	38	0.003*b	22	39	0.506
Obesity	44/4359	1.01	24	20	0.746	7	37	0.048*b
Hepatitis	32/4359	0.73	22	10	0.313	12	20	0.567
Asthma	22/4359	0.50	11	11	0.581	7	15	1.000
Etc.	25/4359	0.57	11	14		5	20	-
No comorbidities	964/4359	22.12	561	403		300	664	-
Unknown	527/4359	12.09	314	213		365	162	

^{*}p<0.05. *Total cases including deaths, recovered, under treatment, isolation, and referred cases. *p<0.25, eligible for multivariate analysis.

underlying medical condition, while 964 out of 4359 death cases (22.12%) did not have comorbid history, and 527 patients (12.09%) had unknown histories. Besides, 17.99% of nonsurvivors were reported having more than one comorbidity. Additionally, the most reported diseases were diabetes mellitus (31.82%), followed by hypertension (18.74%). Out of all cases, age had a relationship with comorbidity (p<0.001). Specifically, categories of age had relationships with the presence of diabetes (p<0.000), heart disease (p<0.001), hypertension (p<0.001), anemia (p=0.002), congestive heart 36 ure (CHF, p<0.001), obesity (p=0.048) and chronic obstructive pulmonary disease (COPD, p=0.019). Gender had relationship with four comorbinies such as diabetes (p=0.004), kidney failure (p=0.002), anemia (p=0.012), and cancer (p=0.003).

Table 2 reveals elderly and males as the risk factors of COVID-19 fatality with OR 5.360 (95%CI: 5.022-5.720) and 1.491 (95%CI: 1.398-1.589) sequentially, and had significant difference between survivors and non-survivors with p<0.001 based on multivariable analysis. Amongst six comorbidities which were included in multivariable logistic regression, there were three comorbidities influenced by both age and gender (p<0.05) such as diabetes mellitus (OR elderly 1.577 [95%CI: 1.325-1.876], and OR female 1.307 [95%CI: 1.106-1.544]), ischemic heart disease (OR elderly 1.580 [95%CI: 1.030-2.423]), and OR female 0.568 [95%CI: 1.030-2.386]), and anemia (OR elderly 2.106 [95%CI: 1.338-3.316] and OR female 1.865 [95%CI: 1.183-2.940]). In the multivariable analysis of COPD, only the age variable had a significant result (p=0.020), whereas in univariable analysis both age and gender influenced the presence of COPD with OR elderly 1.854 [95%CI: 1.129-3.046] and OR male 1.724 [95%CI: 1.008-2.950]). Based on univariable logistic regression, the other comorbidities which were only influen 18 by age were hypertension (OR elderly 1.869 [95%CI: 1.539-2.268]), heart disease (OR elderly 2.396 [95%CI: 1.905-3.013]), CHF (OR elderly 2.735 [95%CI: 2.047-3.656], stroke (OR elderly 2.727 [95%CI: 1.930-3.852]), and obesity (OR <60 years 2.388 [95%CI: 1.053-5.418], with

p<0.001, p<0.001, p<0.001, p<0.001, and p=0.037. Meanwhile, kidney failure (OR male 1.552 [95%CI: 1.185-2.031]) and cancer ([OR female 2.300 [95%CI: 1.349-3.921]) had only significant relationship with gender with p=0.001 and p=0.002, respectively. The Omnibus test indicated that all models in multivariable logistic regression were statistically significant (p<0.05), whereas the Hosmer-Lemeshow test stated that all models were well-fitted (p>0.05).

On the other hand, there were 1156 death cases (26.52%) with unknown job, while the most general job of death cases was the entrepreneur (n=638, 14.64%), followed by unemployment (n=497, 11.40%) and minding household (n=465, 10.67) – Table 3. Furthermore, the number of medical personnel who died due to COVID-19 were 19 cases (0.43%), including midwife (n=2, 0.05%), doctor (n=7, 0.16%), and nurse (n=10, 0.23%) – Table 3.

Discussion

The CFR of COVID-19 patients in Central Java (6.15%) was double compared to the CFR globally and in Indonesia, which were 2.3% and 3.0% respectively⁴ and 3.89 times higher than the CFR in Southeast Asia (1.58%).³ The result is almost the same as the CFR in Italy based on data up to 15 March 2020, with 7.2%.⁶ Generally, the incidence of death cases climbed from March to November and decreased at the end of the month. The most probable reason is that data was collected only until 13 December 2020, so it did not represent the number of cases in December. Similarly, the represented total cases were only up to 13 December 2020.

The present finding showed that the median age of the death cases was greater compared to cured cases. In line with the previous study, the median age of non-survivors was higher than survivors with 69 vs. 52 years. Overall, there was an upward trend in CFR with age, although its trend declined from 0 years to 6-9 years and elderly patients had the highest CFR. This report is in line with research conducted in two states in India, Andhra Pradesh and Tamil Nadu, which showed decreased CFR from 0-4 years (0.16%) to 5-17 years (0.054%), and then it rose and reached

Table 2. Logistic regression analyses for risk factors of COVID-19 fatality and comorbidity

Elderly (260 years) Male Having comorbidity (Elderly) Diabetes mellitus (DM) Elderly Female Hypertension (Elderly) Heart disease (Elderly)	Univariable OR (95% CI) (95% CI) 5.492 (5.146-5.860) 1.607 (1.510-1.710) 1.664 (1.425-1.944) 1.558 (1.310-1.853)	P value <0.001*	Multivariable OR (95% CI)	P value	Ö	oodness of ar	of fit test for n	Goodness of fit test for multivariate analysis
ly (260 years) ng comorbidity (Elderly) etes mellitus (DM) Elderly Female rtension (Elderly)	(95% CI) 5.492 (5.146-5.860) 1.607 (1.510-1.710) 1.664 (1.425-1.944) 1.558 (1.310-1.853)	*0.001*				at	alysis	23
ly (260 years) g comorbidity (Elderly) etes mellitus (DM) Elderly Female rtension (Elderly)	5.492 (5.146-5.860) 1.607 (1.510-1.710) 1.664 (1.425-1.944) 1.558 (1.310-1.853)	*0.001*						
ly (260 years) g comorbidity (Elderly) etes mellitus (DM) Elderly Female rtension (Elderly)	2.492 (5.146-5.860) 1.607 (1.510-1.710) 1.664 (1.425-1.944) 1.558 (1.310-1.853)	<0.001*			Omnibus test	us test	Hosmer	Hosmer-Lemeshow test
ly (260 years) g comorbidity (Elderly) etes mellitus (DM) Elderly Female rtension (Elderly)	2.492 (5.146-5.860) 1.607 (1.510-1.710) 1.664 (1.425-1.944) 1.558 (1.310-1.853)	<0.001*			X	P value	X	P value
ly (260 years) g comorbidity (Elderly) etes mellitus (DM) Elderly Female rtension (Elderly)	2.5492 (5.146-5.860) 1.607 (1.510-1.710) 1.664 (1.425-1.944) 1.558 (1.310-1.853)	<0.001*	COVID-19 fatality					
ng comorbidity (Elderly) etes mellitus (DM) Elderly Female rtension (Elderly) t disease (Elderly)	1.607 (1.510-1.710)		5.360 (5.022-5.720)	<0.001*	2508.113	<0.001*	1.278	0.528
lderly)	1.664 (1.425-1.944)	<0.001*	1.491 (1.398-1.589)	<0.001*				
lderly)	1.664 (1.425-1.944)		Presence of comorbidity					
	558 (1.310-1.853)	<0.001*	,	,	,	,	,	,
	558 (1.310-1.853)							
		<0.001*	1.577 (1.325-1.876)	<0.001*	35.447	<0.001	0.012	0.994
	1.282 (1.086-1.513)	0.003*	1.307 (1.106-1.544)	0.002*				
	1.869 (1.539-2.268)	<0.001*	•	,	,	,	,	,
	2.396 (1.905-3.013)	<0.001*		,		,	,	•
Kidney failure								
Elderly 1	1.266 (0.970-1.653)	0.083	1.263 (0.966-1.651)	0.088	13.386	0.001	4.129	0.127
Male 1	1.552 (1.185-2.031)	0.001*	1.549 (1.183-2.029)	0.001*				
Congestive heart failure								
	2.735 (2.047-3.656)	<0.001*	2.763 (2.066-3.696)	<0.001*	49.244	<0.001*	0.001	1.000
Female 1	1.226 (0.922-1.631)	0.161	1.277 (0.954-1.710)	0.100				
Stroke (Elderly)	2.727 (1.930-3.852)	<0.001*		*		,	,	•
Ischemic heart disease								
Elderly 1	1.533 (1.014-2.380)	0.043*	1.580 (1.030-2.423)	0.036*	8.401	0.015	0.140	0.933
	1.543 (1.016-2.346)	0.042*	0.568 (1.030-2.386)	0.036*				
Anemia								
Elderly 2	2.059 (1.311-3.234)	0.002*	2.106 (1.338-3.316)	0.001*	16.882	<0.001*	0.260	0.878
Female 1	1.817 (1.156-2.858)	0.01*	1.865 (1.183-2.940)	0.007*				
Pulmonary TB (Elderly)	1.493 (0.914-2.437)	0.109		٠		,	`	*
Chronic obstructive pulmonary								
disease								
ly .	1.854 (1.129-3.046)	0.015*	1.805 (1.097-2.969)	0.020*	9.452	0.00	3.372	0.185
Male	1.724 (1.008-2.950)	0.047*	1.669 (0.974-2.862)	0.062				
Cancer (Female)	2.300 (1.349-3.921)	0.002*	•	`	,	,	·	,
Obesity (<60 years) 2	2.388 (1.053-5.418)	0.037*		,	,	,	,	,

*p<0.05 is significant.

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Table 3. Job distribution of COVID-19 death cases

Job	Frequency	%
Entrepreneur	638	14.64
Unemployed	497	11.40
Minding household	465	10.67
Private employee	443	10.16
Retired	223	5.12
Agriculture sector	235	5.39
Trading	203	4.66
Civil servant	174	3.99
Freelancer	92	2.11
Teacher	57	1.31
Driver	24	0.55
Police	19	0.44
Student	18	0.41
State/regional owned enterprises employees	13	0.30
Army	12	0.28
Fisheries	11	0.25
Nurse	10	0.23
Doctor	7	0.16
Islamic teacher	6	0.14
Regency/city/provincial people's representative council members	6	0.14
Lecturer	5	0.11
Honorary employees	4	0.09
Village apparatus	17	0.39
Breeder	4	0.09
Mechanic	3	0.07
Housemaid	3	0.07
Nun	2	0.05
Midwife	2	0.05
Pastor	2	0.05
Tailor	2	0.05
Mosque imam	1	0.02
Chef	1	0.02
Lawyer	1	0.02
Bricklayer	1	0.02
Carpenter	1	0.02
Blacksmith	1	0.02
Unknown	1156	26.52
CHRIOTH	4359	100

the peak at 16.6% occurring in ≥85 years group.⁸ This analysis is also supported by other studies in Italy, Korea, Iran, the United States, and Mexico, where the CFR increased with age.^{6,9-12}

This finding indicated that advanced age was contributing factor for fatality in cases of COVID-19. A cohort study in Wuhan involving 220 COVID-19 cases revealed that older age increased the risk of death, and the eldest age group (>70 years) had the highest CFR with 43.6%. The OR of COVID-19 cases progressed with age, and in the elderly group it had a significant rise, 50-59 years (OR 6.8), 60-69 years (OR 18.8), 70-79 years (OR 43.7), and ≥80 years (OR 86.9). Tag previous analysis indicated that advanced age was associated with an increased risk of death.

This analysis also has si¶ilarities with the previous outbreak cases of Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). The MERS patients in Korea aged ≥60 years were predicted to have a much higher CFR than the younger group (0-59 ye22), 15 where patients ≥60 years were 9.3 times more likely to die compared with younger patients. 16 A study of the SARS outbreak in China exposed a drastic climb in CFR with age, with cases aged ≥60 years having a ten times greater risk of death than cases aged <40 years (about 25% vs. 2%). 17

There are several causes of death from COVID-19 associated with old age. There was an ass 21 ation between old age and the progression of acute respiratory distress syndrome or ARDS and death, possibly due to decreased immune function.¹⁸ Increased susceptibility to infection was linked with immune system aging indicated by a low grade, and chronic systemic inflammatory condition with high markers of inflammation such as interle 38 n-6 or IL-6 and Creactive protein or CRP. 19 Patients with severe COVID-19 tended to experience frequent increases in IL-6 levels and elevated levels of IL-6 in cases who died compared to survivors, markedly throughout the clinical course and the development of disease progression.7 The results of a meta-analysis involving 16 studies consisting of 1,896 sarivors and 849 deaths showed a significant contribution of CRP in the outcome of COVID-19 infection by showing that 25 CRP levels remained high in non-survivors due to COVID-19 infection.²⁰

Based on the current research, most of the death cases were males with a higher CFR than females, and male gender elevated the risk of death. This result is consistent with a study carried out in Wuhan, China, which stated that death cases in adult inpatients with COVID-19 consisted of men (70%) and women (30%) with CFR 31.9% and 22%, sequentially.7 Other analyses conducted in Korea and Iran had similarities where men had a higher CFR than females, with 1.16% vs. 0.45% and 8.54% vs. 7.13%.10 Several studies suggest a relationship between males and death from COVID-19.8,10,21 Based on the OR calculation, men had a risk 1.85 times higher to die due to COVID-19 than women.14

The MERS case study in Saudi Arabia and South Korea was also similar to this study's result, where men's CFR was greater than women's, with 21.2% vs. 15.2% and 21.8% vs. 15.8%, respectively.²² Analysis on SARS cases in China also found that the CFR in men was greater than in females, 7.2% vs. 5.6%, sequentially. Based on the research, it was found that a higher neutrophil to lymphocyte ratio (NLR) was linked with a greater risk of death, particularly in men, with an OR of 1.10 for each unit increase in NLR.²³

Apart from old age and male gender, having comorbidity also increased the likelihood of experiencing serious COVID-19. The CFR in COVID-19 cases who had comorbidities was three times higher than that in cases without comorbidities, 23.0% vs. 7.69%, and the results of the stratified analysis showed underlying 27 dical conditions promoted risk of fatality of COVID-19 patients. 13 This research revealed that the majority of death cases had comorbidities. The comorbidities with the highest percentage were diabetes mellitus and hypertension. A study conducted in New York supported this finding where diabetes mellitus and hypertension were most common in 5700 cases with comorbidity with 1808 cases (33.8%) and 3026 cases (56.6%) sequentially.21 Also, of the 2039 hospitalized COVID-19 cases who had been deceased in two branches of Tongji hospital, Wuhan, 39.7% and 16.7% had a history of hypertension and diabetes, which were the most reported comorbidities. How the most reported having more than one medical history. Analysis of other studies showed age, comorbidities, and the total comorbidities were linked with a critical illness. Based on this finding, old age was more likely to experience comorbidity, and several of the comorbidities had an association with gender. The previous finding indicated that comorbidity was algorithms gindicated with sex and age, with p=0.002 and p<0.001, respectively. Es

Conclusions

To conclude, this study revealed that there was an increase in CFR with age. The highest CFR was in the elderly and male groups. Moreover, the COVID-19 cases in the old age and male category were at higher risk of fatality. Diabetes and hypertension 28 ere the most reported comorbidities. The limitation of this study is related to the lack of detailed data since the collection of primary data was not conducted, only limited to secondary data analysis. Further research is ne 23 d to assess an association between other demographic characteristics and comorbidities with COVID-19 mortality.

Authors' contributions statement: DS conceptualized the research and conducted data analysis, manuscript writing, and manuscript reviewing. NAZ contributed to analyzing data, writing the manuscript, and performing literature searches. YP, AS, MAW, ESL, and EA support data on COVID-19 in Central Java Province, Indonesia. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors - none to declare.

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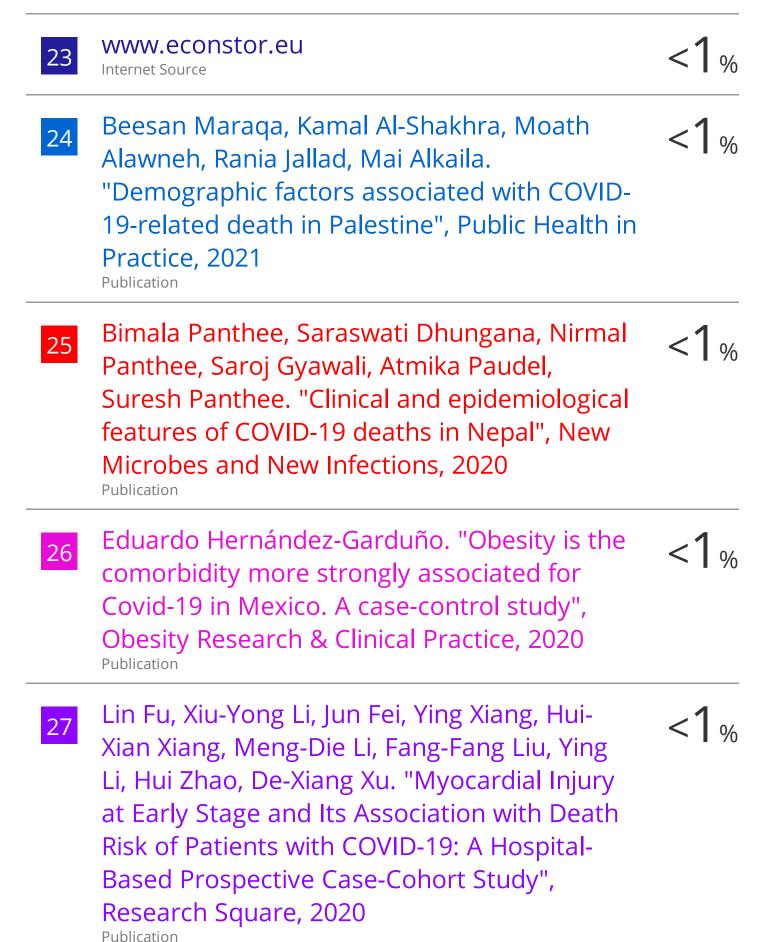
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