Wulandari, *et al. Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal)*. 2022; 17 (2): 157-164
DOI: 10.21109/kesmas.v17i2.5815

Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal)

Diabetes Mellitus and Mortality among COVID-19 Patients in Jakarta, March-August 2020

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Abstract

Diabetes mellitus (DM) comorbidity is one of the risk factors for coronavirus disease 2019 (COVID-19) mortality. This study aimed to determine the association of comorbid DM and mortality among COVID-19 confirmed cases in DKI Jakarta Province, controlled with confounding variables from March to August 2020. The study design was a retrospective cohort using cox proportional hazard regression, with a total sample of 1,480. The data consisted of 740 COVID-19 cases with and 740 without comorbid DM. The inclusion criteria were COVID-19 confirmed cases with polymerase chain reaction (PCR) laboratory testing reported to the DKI Jakarta Provincial Department of Health, and the exclusion criteria were pregnant women. The study result indicated that the Crude Hazard Ratio (CHR) of DM and mortality among COVID-19 confirmed cases was 7.4 (95% CI = 4.5-12.3, p-value<0.001), while the adjusted Hazard Ratio, controlled by covariates (comorbid hypertension and age groups) was 3.9 (95% CI = 2.2- 6.8, p-value<0.001). This concludes that the risk of death from COVID-19 cases with comorbid DM was 3.9 times compared to those without comorbid DM after controlling for confounding variables comorbid hypertension and age group (<50 years and ≥ 50 years).

Keywords: diabetes mellitus, COVID-19, DKI Jakarta, mortality

Introduction

The coronavirus disease (COVID-19) pandemic has had a devastating impact on global health and socioeconomic stability, including in Indonesia.[1–5] From January 2020 to February 21, 2021, a total of 110,763,898 COVID-19 cases with 2,455,331 deaths were reported globally, including 1,271,353 confirmed cases with 34,316 deaths reported in Indonesia and the DKI Jakarta Province reported the highest number of COVID-19 cases.[6] Several studies indicated that Diabetes Mellitus (DM) was included in the top three comorbidities in COVID-19 patients. There was an increase in the incidence and severity of COVID-19 in patients with comorbid DM.[7-10] The WHO-China joint mission report showed that the Case Fatality Rate (CFR) of COVID-19 patients with comorbid DM was 9.2%, second only to cardiovascular comorbidities (13.2%) and higher than that of patients with hypertension (8.4%). Mortality increases with age, with the most increased mortality among patients over 80 years old (estimated CFR is 14.8%).[11]

Based on the 2018 National Basic Health Research in Indonesia/*Riset Kesehatan Dasar* (Riskesdas), the prevalence of DM in Indonesia, according to a doctor's diagnosis in the age 15 population, increased from 2.5% in 2013 to 3.4% in 2018. The DKI Jakarta is the province with the highest DM prevalence in Indonesia, higher than the national DM prevalence rate in 2018 (2%).[12] According to the study by Harbuwono, *et al.,*[14] DM was observed in 705 out of 20,481 (3.44%) COVID-19 patients in Jakarta, which was included in the study. The proportion of deaths from COVID-19 patients who have comorbid DM is 21.28%, which is higher than the proportion of deaths in COVID-19 patients without comorbid DM (2.77%).[14] It is also higher than COVID-19 mortality in the overall population included in the study (3.41%).[13,14] The study by Karyono, *et al.,* indicated that the proportion of DM deaths in COVID-19 patients in Indonesia was 15.3%, the second-highest after hypertension (19.2%).[15]

In DM patients, there is an increased expression of the receptor Angiotensin-Converting Enzyme 2 (ACE-2), which increases the binding of SARS-CoV-2 and furin. This facilitates viral replication, resulting in a high viral

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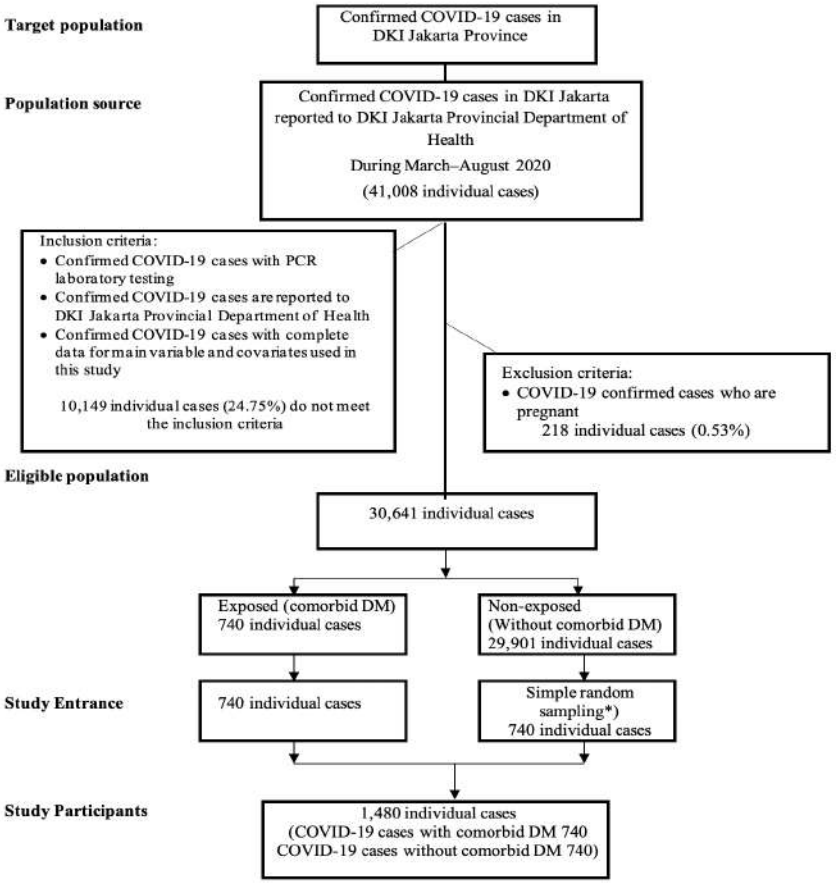
Received : March 14, 2022
Accepted : April 22, 2022
Published : May 31, 2022

load and affects severity. The DM patients infected with COVID-19 are susceptible to cytokine storms due to immune disorders that can lead to Acute Respiratory Distress Syndrome (ARDS), multi-organ failure, and death.[16] This study aimed to determine the magnitude of association between comorbid DM and death in confirmed COVID-19 cases in DKI Jakarta Province after controlling the confounding variables (Hazard Ratio Adjusted). The authors hope this study will contribute to scientific evidence based on priority interventions. These include prevention, triage, and case management to reduce the incidence and mortality of COVID-19 in patients with comorbid DM in DKI Jakarta Province.

Method

This study used a retrospective cohort design with secondary data from the COVID-19 DKI Jakarta report from March to August 2020.[17] The inclusion criteria were COVID-19 cases confirmed by a Polymerase Chain Reaction (PCR) laboratory testing, reported to the DKI Jakarta Provincial Department of Health (PDoH) with complete data of variables used in this study. The exclusion criteria were pregnant women. The conceptual framework in this study was to understand the association between comorbid DM among confirmed COVID-19 patients with COVID-19 mortality by considering potential confounders like age group, gender, comorbid hypertension, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), chronic liver failure, immunology disorder, and cancer. The operational definition of "comorbid DM" is an individual with comorbid DM in the COVID-19 report data. At the same time, "COVID-19 death" is a confirmed COVID-19 patient who is reported to have died in the COVID-19 report from the DKI Jakarta PDoH. Confirmed COVID-19 patient is based on laboratory testing results using PCR showing positive results.

Figure 1 describes the study population and sampling. Out of the total source population of 41,008 cases in the COVID-19 report from the DKI Jakarta PDoH, 30,641 cases met the inclusion and exclusion criteria. Out of 30,641 cases, 740 cases were with comorbid DM, and 29,901 cases were without. All 740 cases with comorbid DM were included in this study. Out of 29,901 cases



Notes: *) Random sampling using the random sampling function in Microsoft Excel was conducted for 740 samples out of 29,901 individual COVID-19 cases without comorbid DM.

Figure 1. Study Population and Sampling

without comorbid DM, 740 samples were selected using the random sampling function in Microsoft Excel. A total of 1,480 samples in this study consisted of all (740) cases of COVID-19 with comorbid DM and the 740 cases of COVID-19 without comorbid DM from the simple random sampling of COVID-19 cases without comorbid DM.

Data analysis was conducted using cox proportional hazard regression. Statistical analysis was performed using statistical data analysis software. The multivariate logistic regression was used to measure the association between comorbid DM with COVID-19 death.

Results

The study indicated that 164 out of 1,480 confirmed COVID-19 cases were dead (CFR 11%). Out of 1,480 total confirmed COVID-19 cases, 146 cases with comorbid DM died (CFR 9.9%), while the CFR of COVID-19 cases with comorbid DM was 20%, higher than the CFR of COVID-19 cases without comorbid DM (CFR 2%). The univariate analysis (Table 1) indicated that the proportion of death among COVID-19 cases with comorbid DM (20%), hypertension (24%), and cardiovascular diseases (29%) was higher than COVID-19 patients without comorbid DM. The proportion of death in COVID-19 cases among > 50 years old is higher (19%) than that of COVID-19 cases under 50 years old. The proportion of death among COVID-19 cases with immunity disorders, comorbid cancer, and chronic liver failure was not included in the further analysis as there were only a small number of cases.

Bivariate analysis (Table 2) indicated a significant association between comorbid DM, comorbid hypertension, comorbid cardiovascular diseases, and age group

Table 1. Frequency Distribution of Diabetes Mellitus and Covariates with COVID-19 Mortality

Variable	Category	Total	Death	
		n	n	%
Diabetes mellitus	Yes	740	146	20
	No	740	18	2
Hypertension	Yes	390	92	24
	No	1,090	72	7
Cardiovascular diseases	Yes	174	51	29
	No	1,306	113	9
Chronic liver failure	Yes	28	2	7
	No	1,452	162	11
COPD	Yes	45	7	16
	No	1,435	157	11
Immunology disorder	Yes	23	0	0
	No	1,457	164	11
Cancer	Yes	22	0	0
	No	1,458	164	11
Sex	Male	775	94	12
	Female	705	70	10
Age group	≥50 years old	750	139	19
	<50 years old	730	25	3

Note: COPD = Chronic Obstructive Pulmonary Disease

Table 2. The Association of Diabetes Mellitus and Covariates with COVID-19 Mortality

Variable	Category	Death	CHR	95 CI (%)	p-value
Diabetes mellitus	Yes	146			
	No	18	7.4	4.5-12.3	<0.001*
Hypertension	Yes	92	3.3	2.4-4.6	<0.001*
	No	72			
Cardiovascular diseases	Yes	51	3.4	2.4-4.7	<0.001*
	No	113			
COPD	Yes	7			
	No	157	1.6	0.7-3.4	0.228
Sex	Male	94			
	Female	70	1.2	0.9-1.7	0.171
Age group	≥50 years old	139			
	<50 years old	25	5	13.3-7.7	<0.001*

Notes: COPD = Chronic Obstructive Pulmonary Disease, CHR = Crude Hazard Ratio, CI = Confidence Interval, *Significant at p-value<0.01

with COVID-19 mortality (p-value<0.05). Meanwhile, there was no significant association between comorbid COPD and sex with COVID-19 death (p-value>0.005). Stratification analysis indicated that hypertension, cardiovascular diseases, and age group were potential confounders and that there was no potential interaction.

The full model of multivariate analysis is shown in Table 3. The full model included the main comorbid DM and five potential confounders; comorbid hypertension, cardiovascular diseases, COPD, age group, and sex.

The goodness of fit test indicated that the variables included in the multivariate analysis met the proportional hazard assumption. The HR value was constant over time (p-value>0.05). Log-log survival curves to evaluate PH assumption graphically. Figure 2 indicates Log-Log Survival Curve of DM Comorbid with COVID-19 Mortality after Controlling for Comorbid hypertension and Age Group meet PH assumption.

A Schoenfeld scale graph indicated that comorbid DM, hypertension, cardiovascular diseases, COPD, sex, and age group were in a relatively horizontal line, thus indicating that the proportional hazard assumption was fulfilled, where the risk of death in confirmed COVID-19 cases with comorbid DM compared to confirmed COVID-19 cases without comorbid DM tended to be constant during the observation time. Log-log survival curves indicated that the proportional hazard assumption was fulfilled. Therefore, the multivariate analysis used Cox proportional hazard regression.

Interaction analysis was performed for all independent variables included in the full model (initial model) by comparing -2 LL (log-likelihood) in the complete model with interaction and full model without interaction. No interaction was found based on the analysis conducted (p-value>0.05). Confounding assessment found covariates hypertension and age group variable as confounding variables (changes of HR>10%). Therefore, these were included in the final multivariate model. Changes in HR>10% were indicated as confounding variables.[18] The final model of multivariate analysis is shown in Table 4. The final model indicated that the adjusted HR was 3.9 (95% CI = 2.2–6.8; p-value<0.001). This meant the

Table 3. Full Model of Multivariate Analysis

Variable	SE	p-value	HR	95% CI
Diabetes mellitus	0.28	<0.001*	3.6	2.1-6.3
Hypertension	0.17	0.045**	1.4	1-1.99
Cardiovascular diseases	0.18	0.001*	1.8	1.2-2.6
COPD	0.4	0.703	0.9	0.4-1.9
Age group	0.23	<0.001*	2.7	1.74-4.3
Sex	0.16	0.224	1.2	0.9-1.7

Notes: COPD = Chronic Obstructive Pulmonary Disease, SE = Standard Error, HR = Hazard Ratio, CI = Confidence Interval, *Significant at p-value<0.01, **Significant at p-value<0.05.

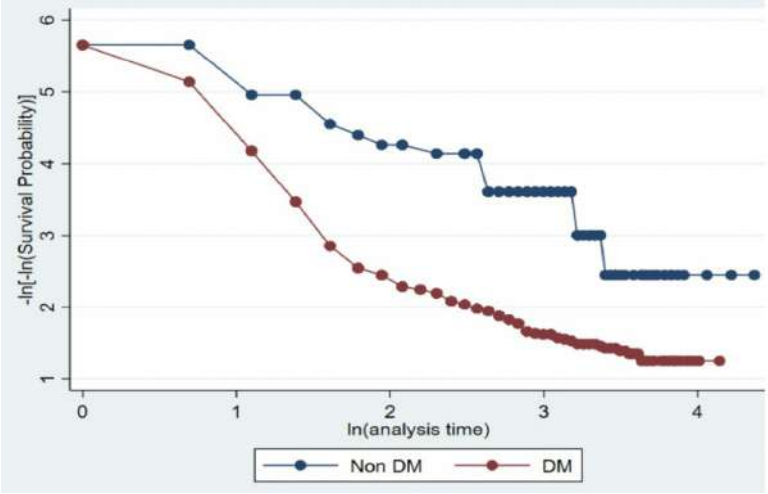


Figure 2. Graph of Log-Log Survival Curve of DM Comorbid with COVID-19 Mortality after Controlling for Comorbid Hypertension and Age Group

Table 4. The Final Model of Multivariate Analysis

Variable	SE	p-value	HR	95% CI
Diabetes mellitus	0.28	<0.001*	3.9	2.2–6.8
Hypertension	0.17	0.005*	1.6	1.2–2.2
Age group	0.23	<0.001*	2.7	1.7–4.3

Notes: SE = Standard Error; HR = Hazard Ratio; CI = Confidence Interval, *Significant at p-value<0.01.

incidence of death among confirmed COVID-19 cases with comorbid DM was 3.9 times higher than confirmed COVID-19 cases without comorbid DM after controlling for confounding variables comorbid hypertension and age group.

Discussion

This study indicated that deaths from COVID-19 cases with comorbid DM were 20% higher than deaths from COVID-19 cases without comorbid DM (2%). After controlling for comorbid hypertension and age group, the incidence of death among confirmed COVID-19 cases with comorbid DM was 3.9 times higher risk than confirmed COVID-19 cases without comorbid DM. This study was in line with Zhang's on 258 COVID-19 patients in China, showing that comorbid DM increased mortality (HR = 3.6; 95% CI = 1–12),[19] and Harbuwono, *et al.*,'s study that indicated higher mortality in patients with DM in DKI Jakarta.[14] Study on the factors of COVID-19 death in DKI Jakarta Province on 4,265 COVID-19 patients during March–July 2020 showed that DM is one of the risk factors for COVID-19 death (Crude Odd Ratio = 3.8; 95% CI = 2.5–4.1).[20] Several other studies have shown that comorbid DM increases the risk of death in COVID-19 cases from 1.5 to 4.3 times.[10,11,19,21-25] A study in Korea of 12,646 patients showed that comorbid DM increases the death risk from COVID-19 (HR 1.5 with 95% CI = 1.1–1.9).26 A meta-analysis study conducted by Kun'ain, *et al.*,[27] showed that comorbid DM increased the risk of death from COVID-19 (OR = 2.17; 95% CI = 1–4.5). Another meta-analysis conducted by Huang, *et al.*,[10] which included 30 studies with 6,542 patients, showed that comorbid DM increased the death risk from COVID-19 (RR = 2.12; 95% CI = 1.44–3.11). Satria, *et al.*,'s study on 253 COVID-19 patients in Surabaya showed that comorbid DM increased the risk of COVID-19 death 4.3 times (OR = 4.3, p-value 0.016).[24] The study by Graselli, *et al.*,[28] showed an association of comorbid DM with an increased risk of dying from COVID-19 in the ICU (HR = 1.7; 95% CI = 1.47–1.88). Kshanti, *et al.*,'s study showed high mortality in COVID-19 patients with comorbid type 2 DM, who were hospitalized with hyperglycemia.[29] Complications of DM increase the risk of death, and respiratory failure and septic shock are more commonly found in hospitalized patients with hyperglycemia.[29]

There is an increase in ACE-2 receptors in response to hyperglycemia and an increase in furin in people with comorbid DM, which facilitates viral replication, thus influencing the susceptibility to SARS-CoV-2 infection and an increase in viral load in the body, which can increase the severity of illness and death.[30] In DM patients infected with COVID-19, dysregulation of the immune response can occur, which increases the pro-inflammatory cytokine response, leading to a cytokine storm that results in multi-organ failure. This condition increases the risk of death. Inflammatory conditions due to dyslipidemia and insulin resistance in comorbid DM patients exacerbates the inflammatory response to SARS-CoV-2 and result in pulmonary dysfunction, leading to ARDS.[31] In DM patients, the virus can also attack the pancreas, damaging pancreatic cells that produce insulin, thereby exacerbating hyperglycemic conditions.[16,31]

ACE-2 receptor expression is increased in patients with comorbid DM. SARS-CoV-2 binds to target cells via the ACE-2 receptor on epithelial cells of the lung, throat, intestine, kidney, and blood vessels.[23,33] The increased expression of ACE-2 predisposes DM patients to SARS-CoV-2 infection and affects the viral load, increasing the severity of the disease and can lead to death. In COVID-19 patients with DM, there is dysregulation of the immune response. These include dysfunction of neutrophils, decreased T-cell-mediated response, increased pro-inflammatory cytokine response, increased interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF)-alpha, which causes severity in COVID-19 patients due to a cytokine storm that increases the risk of death.[16,30]

COVID-19 infection that occurs in patients with comorbid DM triggers a stress response, increases the secretion of hyperglycemic hormones such as glucocorticoids and catecholamines, and results in increased blood sugar levels and complications of DM.[30,32] Inflammatory conditions in DM patients due to dyslipidemia and insulin resistance exacerbates the inflammatory response to SARS-CoV-2.[32] In patients with DM, more ACE2 protein is also present in the pulmonary alveolar, which can cause more severe disease manifestations.[32,34,35] In DM patients, there are thicker alveolar, epithelial, and basal pulmonary capillaries. Hyperglycemia in DM patients can cause alveolar capillary microangiopathy, causing reduced lung elasticity and resulting in impaired lung function. High glucose causes oxidative stress and triggers inflammatory reactions.[36] The studies of Graselli, *et al.*, and Roncon, *et al.*, showed that comorbid DM is associated with an increased risk of death for COVID-19 patients in the ICU.[28,37]

In this study, the association between comorbid DM

and death in confirmed COVID-19 cases was controlled by confounding variables comorbid hypertension and age group (less than 50 years and more than 50 years), where covariates of comorbid hypertension and age group influenced the association between comorbid DM and death in confirmed COVID-19 cases. These results were in line with meta-analysis studies showing that comorbid hypertension affected the risk of death from COVID-19.[38,39] Several studies have shown that age more than 50 years increases the risk of dying from COVID-19. The study by Kandi, *et al.*, showed that the proportion of deaths in patients aged 50 years and over (50–80 years 12.9% and > 80% 14.8%) was higher than the proportion of deaths in patients aged less than 50 years (1%).[40] Kang's study confirmed that deaths at age more than 50 years are higher than the proportion of deaths at age less than 50 years (1%).[41] This is in line with Freund's study, which mentions an increase in pro-inflammatory mediators such as IL 6 and TNF alpha which is quite significant (2–4 times) in patients older than 50 years compared to the group younger than 50 years.[42] This study found that the adjusted Hazard Ratio (HR = 3.9) was lower than the Crude Hazard Ratio (CHR = 7.4) because comorbid hypertension and age group covariates (confounders) also increased the risk of death from COVID-19. People with comorbid hypertension and aged more than 50 years have a higher risk for COVID-19 death, thus influencing the association between comorbid DM and COVID-19 mortality. Therefore, after controlling for these covariates, the adjusted Hazard Ratio became HR = 3.9 (95% CI = 2.2–6.8; p-value<0.001).

This study used data from DKI Jakarta Provincial Department of Health to determine the association between DM and COVID-19 mortality after controlling the confounding variables of hypertension and age group using the retrospective cox proportional hazard cohort method. This cohort study is the best research design to determine exposure and outcome with causality and temporal relationships that are better than other study methods carried out using the logistic regression method. The limitations of this study included the use of secondary data, whereas the researcher cannot control the data quality, incomplete data, and limited data used for variables included in this study. Due to the limitation of data, this study does not have data on other potential confounders such as obesity, COVID-19 treatment, other supporting laboratory tests such as complete blood count, blood levels, blood sugar, vaccination, occupation, education, socioeconomic status, and others, as well as information on the treatment of comorbid diseases.

Secondary data on the COVID-19 report from the DKI Jakarta PDoH was obtained from the results of epidemiological investigations. The comorbid data reported was based on anamnesis, interviews of health workers with patients, and not from laboratory examinations. The comorbid DM cases included in this study were comorbid cases that a doctor had previously diagnosed. Selection bias could occur because this study uses COVID-19 data from the DKI Jakarta PDoH. The cases in this study were detected by the DKI Jakarta PDOH surveillance system. However, other cases may not be detected, especially asymptomatic cases or have mild symptoms. Information bias could also occur if health workers incorrectly input data on COVID-19 case reports in DKI Jakarta Province. This limitation has been minimized by training health workers in data entry, reporting, and verifying data by surveillance officers in DKI Jakarta municipalities and province offices. DKI Jakarta PDoH conducted training on case detection and reporting for health workers according to COVID-19 guidelines, using standard reporting form, and increasing detection by increasing laboratory testing and contact tracing.

Conclusion

The risk of death from COVID-19 cases with comorbid DM was found to be 3.9 times compared to COVID-19 cases without comorbid DM after controlling for confounding variables; comorbid hypertension and age group (less than 50 years and more than 50 years). This study emphasizes that special attention and priority should be given to people with comorbid DM to prevent, early detection, and manage COVID-19 to reduce COVID-19 mortality among COVID-19 cases with DM. People with comorbid DM should be a priority for COVID-19 prevention efforts, including COVID-19 vaccination, targeted Education Information Communication (EIC) materials for people with DM for COVID-19 prevention, and ensuring continued essential health services for DM patients, like the access to physician consultation and DM drugs via telemedicine to avoid the severity that can increase risk of death. Further studies can be conducted to understand the association between death in COVID-19 patients with comorbid DM, considering COVID-19 vaccination status, DM drug administration, and blood sugar level.

Abbreviations

DM: Diabetes Mellitus; COVID-19: coronavirus disease 2019; PCR: Polymerase Chain Reaction; CHR: Crude Hazard Ratio; CI: Confidence Interval; Riskesdas: Riset Kesehatan Dasar; ACE-2: Angiotensin-Converting Enzyme 2; ARDS: Acute Respiratory Distress Syndrome; SARS-CoV-2: Severe Acute Respiratory Infection Corona Virus 2; PdoH: DKI Jakarta Provincial Department of Health; COPD: chronic obstructive pulmonary disease; CFR: Case Fatality Rate; SE = Standard Error; HR: Hazard Ratio; IL: Interleukin; OR: Odd Ratio; TNF: Tumor Necrosis Factor; EIC: Education Information Communication.

Ethics Approval and Consent to Participate

This study has received approval from the Ethics Committee of the Faculty of Public Health, Universitas Indonesia, with a certificate of ethical approval: No. 37/UN2. F10.D11/PPM.00.02/2021.

Competing Interest

The author declares that there is no significant competing financial, professional, or personal interest that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

The data is obtained from COVID-19 Surveillants DKI Jakarta Provincial Department of Health.

Authors' Contribution

EW conceptualized, designed, prepared the initial draft, and conducted data analysis. SR delivered technical inputs for the design, data analysis, and interpretation of data. NS provided input for data analysis and interpretation.

Acknowledgment

The authors would like to acknowledge the DKI Jakarta Provincial Department of Health for allowing the authors to use and analyze the COVID-19 surveillance data for this study.

References

1. Gates B. Responding to COVID-19 — A once-in-a-century pandemic? N Engl J Med. 2020; 382: 1677-9.
2. Mckibbin W, Fernando R. The global macroeconomic impacts of COVID-19: seven scenarios. Asian Economic Papers. 2021; 20 (2): 1-30.
3. Kandel N, Chungong S, Omaar A, Xing J. Review of health security capacities in light of 2019-nCoV outbreak – opportunities for strengthening IHR (2005) implementation. SSRN eLibrary; 2020.
4. Global Preparedness Monitoring Board. A world at risk; 2019.
5. Djalante R, Lassa J, Setiamarga D, Sudjatma A, Indrawan M, Haryanto B, et al. Review and analysis of current responses to COVID-19 in Indonesia: period of January to March 2020. Prog Disaster Sci. 2020; 6: 1-9.
6. World Health Organization. COVID-19 weekly epidemiological - update 23 February 2021. 2021.
7. Hu Y, Sun J, Dai Z, Deng H, Lin X, Huang Q, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Virol. 2020; 127: 104371.
8. Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, et al. Association of blood glucose control and outcomes in patients with covid-19 and pre-existing type 2 diabetes. Cell Metab. 2020; 31 (6): 1068-77.
9. Singh AK, Gupta R, Misra A. Comorbidities in COVID-19: outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. Diabetes Metab Syndr Clin Res Rev. 2020; 14 (4): 283-7.
10. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr Clin Res Rev. 2020; 14 (4): 395-403.
11. World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). 2020.
12. Kementerian Kesehatan Republik Indonesia. Hasil utama riset kesehatan dasar tahun 2018. Kementrian Kesehat Republik Indones; 2018.
13. Gugus Penanganan COVID-19. Peta sebaran COVID-19. Gugus Tugas Percepatan Penanganan COVID 19; 2020.
14. Harbuwono DS, Handayani DOTL, Wahyuningsih ES, Supraptowati N, Ananda, Kurniawan F, et al. Impact of diabetes mellitus on COVID-19 clinical symptoms and mortality: Jakarta's COVID-19 epidemiological registry. Prim Care Diabetes. 2022; 16 (1): 65-8.
15. Karyono DR, Wicaksana AL. Current prevalence, characteristics, and comorbidities of patients with COVID-19 in Indonesia. J Community Empower Heal. 2020; 3 (2): 77-84.
16. Muniyappa R, Gubbi S. COVID-19 Pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020; 318: 736-41.
17. DKI Jakarta Provincial Health Officer. COVID-19 data reporting, March-August 2021; 2021.
18. Rothman KJ. Epidemiology: an Introduction. 2nd ed. New York: Oxford University Press; 2012.
19. Zhang Y, Cui Y, Shen M, Zhang J, Liu B, Dai M, et al. Association of diabetes mellitus with disease severity and prognosis in COVID-19: a retrospective cohort study. Diabetes Res Clin Pract. 2020; 165: 108227.
20. Surendra H, Elyazar IRF, Djaafara BA, Ekawati LL, Saraswati K, Adrian V, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: a hospital-based retrospective cohort study. The Lancet Regional Health - Western Pacific. 2021; 9: 1-9.
21. Abu-Farha M, Al-Mulla F, Thanaraj TA, Kavalakatt S, Ali H, Ghani MA, et al. Impact of diabetes in patients diagnosed with COVID-19. Front Immunol. 2020; 11.
22. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care. 2007; 30 (9): 2251-7.
23. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS Coronavirus. J Virol. 2020; 94 (7).
24. Satria RMA, Tutupoho RV, Chalidyanto D. Analisis faktor risiko kematian dengan penyakit komorbid Covid-19. J Keperawatan Silampari. 2020; 4 (1): 48-55.
25. Shang J, Wang Q, Zhang H, Wang X, Wan J, Yan Y, et al. The relationship between diabetes mellitus and covid-19 prognosis: a retrospective cohort study in Wuhan, China. Am J Med. 2021; 134 (1): e6-e14.
26. Byeon KH, Kim DW, Kim J, Choi BY, Choi B, Cho KD. Factors affecting the survival of early COVID-19 patients in South Korea: an observational study based on the Korean National Health Insurance big data. Int J Infect Dis. 2021; 105: 588-94.
27. Kun'ain UIA, Rahardjo SS, Tamtomo DG. Meta-analysis: the effect of diabetes mellitus comorbidity on the risk of death in Covid-19 patients. Indones J Med. 2020; 5 (4): 368-77.
28. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020; 180(10): 1345-55.

29. Kshanti IA, Aji G, Eprilliawati M, Mokoagow Md-I, Nasarudin J, Magfira N, et al. Clinical presentation and outcome of covid-19 infection in type 2 diabetes mellitus: a preliminary data from a tertiary hospital in Jakarta during the early days of the pandemic. Bali Med J. 2020; 9 (3): 663-9.
30. Ganesan SK, Venkatratnam P, Mahendra J, Devarajan N. Increased mortality of COVID-19 infected diabetes patients: role of furin proteases. Int J Obes. 2020; 44: 2486–8.
31. Huang J, Zhu L, Bai X, Jia X, Lu Y, Deng A, et al. Multidimensional analysis of risk factors for the severity and mortality of patients with COVID-19 and diabetes. Infect Dis Ther. 2020; 9 (4): 981-1002.
32. Rajpal A, Rahimi L, Ismail-Beigi F. Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. J Diabetes. 2020; 12 (12): 895-908.
33. Giovannelli J, Trouiller P, Hulo S, Cherot-Kornobis N, Ciuchete A, Edme J-L, et al. Low-grade systemic inflammation: a partial mediator of the relationship between diabetes and lung function. Ann Epidemiol. 2018; 28 (1): 26-32.
34. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 2020; 16: 297-8.
35. Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. Mol Cell Endocrinol. 2009; 302 (2): 193-202.
36. Morigi M, Angioletti S, Imberti B, et al. Leukocyte-endothelial interaction is augmented by high glucose concentrations and hyperglycemia in an NF-kB-dependent fashion. J Clin Invest; 1998.
37. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol. 2020; 127: 104354.
38. Guan WJ, Liang WH, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: a nationwide analysis. MedRxiv; 2020.
39. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male. 2020; 23(5): 1416-24.
40. Kandi V, Thungaturthi S, Vadakedath S, Gundu R, Mohapatra RK. Mortality rates of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Cureus. 2021; 13 (3): e14081.
41. Kang SJ, Jung SI. Age-related morbidity and mortality among patients with COVID-19. Infect Chemother. 2020; 52 (2): 154-64.
42. Freund A, Orjalo AV, Desprez PY, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med. 2010; 16 (5): 238-46.