



# The Survival Probability of Covid-19 Patients with Type 2 Diabetes Mellitus during Pandemic at Al Ihsan Hospital, West Java Province, Indonesia

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#### Abstract

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under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0) **BACKGROUND:** The high prevalence of diabetes mellitus (DM) in the population causes DM to become one of the most common comorbidities of coronavirus disease 2019 (COVID-19). Patients with diabetes have a higher risk of experiencing serious complications from COVID-19 and even death.

AIM: This study was aimed to determine the difference in survival probability of COVID-19 patients, based on their DM status and to determine the association between type 2 DM and COVID-19 mortality at AI Ihsan Hospital, West Java Province, Indonesia.

**METHODS:** The population of this retrospective cohort study were COVID-19 patients, aged ≥18 years and were treated at AI Ihsan Hospital, from March 2020 to December 31, 2021. Differences in survival probability were obtained from survival analysis with Kaplan–Meier. Cox Proportional Hazard regression was used to determine the association between type 2 DM and COVID-19 mortality.

**RESULTS:** Totally, 308 confirmed positive COVID-19 patients were recruited in this study. During the 21 days of observation, survival probability of COVID-19 patients with type 2 DM was significantly lower than those without type 2 DM (71.24% vs. 84.13% respectively, with p = 0.0056). There was a statistically significant association between type 2 DM and COVID-19 mortality after controlling for age, cough symptoms, acute respiratory distress syndrome, vaccination, chronic kidney disease, ventilator use, antiviral therapy, and the percentage of bed occupation rate COVID-19 isolation at admission. The adjusted hazard ratio showing association between type 2 DM and COVID-19 mortality in the final model of multivariate analysis was 2.68 (95% Cl 1.24–5.73).

**CONCLUSIONS:** The survival probability of COVID-19 patients with type 2 DM was significantly lower than those without type 2 DM. COVID-19 patients with DM in AI Ihsan Hospital were almost 3 times more likely to be fatal as compared COVID-19 patients without DM.

### Introduction

At present, the world is facing health, social and economic crises due to the corona virus disease 2019 (COVID-19) pandemic. On March 11, 2020, the World Health Organization declared that COVID-19 had become a pandemic due to its widespread severity [1]. As of February 27, 2022, COVID-19 has infected 433,139,235 people with a death toll of 5,939,137 or 1.37% [2]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes different clinical manifestations ranging from asymptomatic to death [3].

Patient status and comorbidities influence the clinical manifestations of COVID-19. Diabetes is one of the most common comorbidities in COVID-19 patients as a study in China stated that 8.2% of comorbidities of 1590 patients were diabetic [4]. Globally, the prevalence of diabetes in 2019 is estimated at 9.3% (463 million people) increasing to 10.2% in 2030 and 10.9% in 2045.

Thus, diabetes affects a large part of the population and is a major cause of complications [5]. The large prevalence of diabetes in this population causes diabetes to become the second most common comorbid disease after hypertension in COVID-19 patients [6]. A metaanalysis showed that mortality was higher in COVID-19 patients with diabetes [7]. A UK study of hospitalized COVID patients at the start of the 2020 pandemic reported that the risk of death was consistently higher in people with type 2 diabetes mellitus (DM) and a lower probability of survival when compared to people without type 2 DM [8].

In Indonesia, the prevalence of diabetes is still high based on the results of the Riset Kesehatan Dasar (Riskesdas) in 2018 which reported that the prevalence of diabetes based on blood glucose examinations at >15 years of age was 10.9% [9]. Al Ihsan Hospital is one of the COVID-19 referral hospitals in West Java and has excellent services, namely, a diabetic center. These services are integrated services starting with

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counseling and education, nutrition clinics, wound care, and diabetes complications management. The number of COVID-19 patients treated at the AI Ihsan Hospital from the beginning of the pandemic in March 2020– December 31, 2021, was 3,312 and the death rate was 640 or the COVID-19 case fatality rate was 19.32%. Type 2 DM is the third most common comorbid after acute pulmonary and respiratory failure in COVID-19 patients treated at AI Ihsan Hospital. This study was conducted to determine the difference in the survival probability of COVID-19 patients based on their diabetes status and to determine the relationship between type 2 DM and COVID-19 mortality at AI Ihsan Hospital, West Java Province.

### **Methods**

A retrospective cohort study design was used in this study. The population of this study was COVID-19 patients who were drawn at AI Ihsan Hospital from March 2002 to December 31, 2021. The inclusion criteria in this study were confirmed patients diagnosed by RT-PCR and aged 18 years, while the exclusion criteria were patients forced to be discharged or on their own request and the patient referred to another hospital. The exposed group was COVID-19 patients with type 2 DM who met the inclusion criteria, totaling 152 people. Meanwhile, the non-exposed group was COVID-19 patients without type 2 DM and totaled 152 people. The data used are secondary data from the register of COVID-19 inpatients obtained through medical records. Has been collected and then analyzed using the Stata software version 15.1. Survival probability was obtained through survival analysis with Kaplan-Meier. Bivariate analysis was carried out with the Cox regression test to obtain the hazard ratio, then a confounding test was performed on covariate variables consisting of demographic variables (age, sex, and occupation), vaccination status, clinical symptoms (fever, cough, shortness of breath, and acute respiratory distress syndrome [ARDS]), comorbidities. (Obesity, hypertension, cardiovascular disease, chronic kidney failure, and chronic obstructive pulmonarv disease [COPD]), treatment factors (use of ventilators and antiviral therapy), and health-care factors (place of care and percentage of BOR for COVID-19 isolation). After that, multivariate analysis was performed using the Cox Proportional Hazard Model regression test.

### Results

The main independent variable in this study was type 2 DM. The number of patients with type 2 DM

and not type 2 DM was 154 each with the characteristics of the respondents as shown in Table 1.

Table 1: Distribution of research subject characteristics based
on the status of diabetes mellitus type 2

Variable	Diabetes mell	Total (%)	
	Yes (%)		
Age group		No (%)	
<60	87 (44.62)	108 (55.38)	195 (100)
≥60	67 (59.29)	46 (40.71)	113 (100)
Gender	. ,		. ,
Female	75 (49.67)	76 (50.33)	151 (100)
Male	79 (50.32)	78 (49.68)	157 (100)
Work			
Not health workers	147 (50.00)	147 (50.00)	294 (100)
Health workers	7 (50.00)	7 (50.00)	14 (100)
Vaccination			
Vaccination booster	1 (100)	0 (0)	1 (100)
Vaccination second dose	7 (35.00)	13 (65.00)	20 (100)
Vaccination first dose	3 (37.50)	5 (62.50)	8 (100)
Not vaccinated	143 (51.25)	136 (48.75)	279 (100)
Fever	70 (20 56)	110 (60 44)	100 (100)
No Yes	72 (39.56)	110 (60.44)	182 (100)
Cought	82 (65.08)	44 (34.92)	126 (100)
No	51 (32.08)	108 (67.92)	159 (100)
Yes	103 (69.13)	46 (30.87)	149 (100)
Hard to breathe			.40 (100)
No	30 (35.71)	54 (64.29)	84 (100)
Yes	124 (55.36)	100 (44.64)	224 (100)
ARDS	(,		( /
Non ARDS	119 (45.59)	142 (54.41)	261 (100)
ARDS	30 (76.92)	9 (23.08)	39 (100)
Missing	5 (62.50)	3 (37.50)	8 (100)
Obesity			
No	106 (43.80)	136 (56.20)	242 (100)
Yes	47 (75.81)	15 (24.19)	62 (100)
Missing	1 (25.00)	3 (75.00)	4 (100)
Hypertension			
Normal	32 (36.78)	55 (63.22)	87 (100)
Elevated	32 (47.76)	35 (52.24)	67 (100)
Hypertension stage 1	49 (54.44)	41 (45.56)	90 (100)
Hypertension stage 2	41 (64.06)	23 (35.94)	64 (100)
Cardiovascular disease No	129 (47.78)	141 (52.22)	270 (100)
Yes	25 (65.79)	13 (34.21)	38 (100)
Chronic kidney failure	25 (05.75)	13 (34.21)	30 (100)
No	149 (49.83)	150 (50.17)	299 (100)
Yes	5 (55.56)	4 (44.44)	9 (100)
Chronic obstructive pulmonary disease	0 (00.00)	. ( )	0 (100)
No	154 (50.33)	152 (49.67)	306 (100)
Yes	0 (0.00)	2 (100.00)	2 (100)
Use of ventilator		(,	( /
Use ventilator	55 (84.62)	10 (15.38)	65 (100)
No ventilator	99 (40.74)	144 (59.26)	243 (100)
Antiviral therapy			
Remdesivir	72 (53.33)	63 (46.67)	135 (100)
Favipiravir	56 (45.53)	67 (54.47)	123 (100)
Oseltamivir	21 (47.73)	23 (52.27)	44 (100)
Tidak diberikan	5 (83.33)	1 (16.67)	6 (100)
Treatment room	101/10		005
COVID-19 isolation treatment room	124 (46.79)	141 (53.21)	265 (100)
Emergency room (IGD)	2 (66.67)	1 (33.33)	3 (100)
	28 (70.00)	12 (30.00)	40 (100)
BOR isolation COVID-19	20 (64 50)	11 (25 40)	24 (400)
≤45% 45 95%	20 (64.52)	11 (35.48)	31 (100)
45–85% ≥85%	68 (68.69) 66 (37.08)	31 (31.31) 112 (62.92)	99 (100) 178 (100)
-00 /0	66 (37.08)	112 (02.92)	170 (100)

Based on Table 1, it is known that the characteristics of respondents are mostly <60 years old and in that age group, most do not suffer from type 2 DM. However, in the age group, 60 years suffer from type 2 DM (59.29%). Based on gender, there were more men and in that group more suffer from type 2 DM (50.32%). Based on the type of work, most of the non-health workers work, and based on type 2 DM, both health workers and non-health workers have the same proportion. Based on the vaccination status, the most unvaccinated group were patients with type 2 DM (51.25%).

Based on the symptoms that appeared, the study subjects experienced more fever, cough, shortness of breath, and ARDS in patients with type 2

DM. Stages 1 and 2 were more common in patients with type 2 DM, while those with normal and elevated hypertension were more in the group without type 2 DM. Patients with cardiovascular disease were more in the group with DM. Likewise in patients with chronic kidney failure, more in the group with type 2 DM.

In Table 1, it can also be seen that ventilators are widely used in the group with type 2 DM. However, other antivirals, namely favipiravir, and oseltamivir, were mostly given to patients without type 2 DM. Mellitus type 2. Meanwhile, based on the percentage of COVID-19 isolation BOR at the time of admission, when the BOR was 85%, there were more patients without type 2 DM.

The results of the survival analysis of COVID-19 patients with DM can be seen in Table 2 below.

From Table 2, it is known that the mortality rate of COVID-19 patients with type 2 DM is 15.53/1000 person days, meaning that during the observation of 1000 people a day, 16 COVID-19 patients died with type 2 DM., the mortality rate is 6.67/1000 person days. This explains that in the observation of 1000 people a day, 7 COVID-19 patients died without being accompanied by type 2 DM. Kaplan–Meier's graph to explain the probability of survival of COVID-19 patients based on type 2 DM status is shown in Figure 1 below.

In Table 2 and the Kaplan–Meier chart in Figure 1, it can be seen that the probability of survival of COVID1-9 patients in the type 2 DM group was 48.98% until the end of the observation, which was 49 days. The survival probability was lower than in the group without type 2 DM with a survival probability of 84.13%. On the 21<sup>st</sup> day of observation, the probability of survival in COVID-19 patients with type 2 DM was 71.24% and on the 28<sup>th</sup> day of observation, the probability was 61.22%. In COVID-19 patients without type 2 DM, on days 21 and 28 of observation, the probability of survival was the same until the end of the observation, which was 84.13%.

The results of the log-rank test obtained the Chi-square result of 7.66 with p = 0.0056. It can be concluded that there are differences in the survival curve of COVID-19 patients in the group with Type 2 DM and the group without Type 2 DM. Based on the covariate variables, the probability of survival of COVID-19 patients is shown in Table 3.

In Table 3, information on differences in the probability of survival of COVID-19 patients based on covariate variables, namely, age, sex, occupation, vaccination status, symptoms of fever, cough, shortness of breath, ARDS, obesity, hypertension,

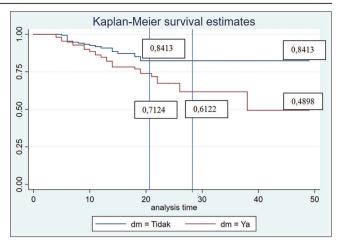


Figure 1: Graph of Kaplan–Meier probability of survival of COVID-19 patients based on type 2 DM status

cardiovascular disease, chronic kidney failure, COPD, use of ventilators, antiviral therapy, treatment rooms, and COVID-19 isolation BOR. The results of the logrank test analysis showed that there was a statistically significant difference in the probability of survival of COVID-19 patients based on the variables of age, fever, cough, shortness of breath, ARDS, hypertension, chronic kidney failure, antiviral therapy, inpatient rooms, and the BOR of COVID-19 isolation.

The multivariate analysis was preceded by making an initial model on the relationship between type 2 DM and COVID-19 mortality by involving all covariate variables. The resulting hazard ratio in the initial model is 2.506 with a 95% CI of 1.14-5.49 and p = 0.022. The results of the interaction analysis showed that there were no interacting variables in the full model. Then perform confounding analysis on covariate variables. The results of the confounding analysis showed that the confounding variables were age, cough symptoms, ARDS, chronic kidney failure, vaccination, antiviral therapy, ventilator use, and the percentage of COVID-19 isolation BOR. Hazard Ratio adjusted relationship between type 2 DM and COVID-19 mortality. The final model in multivariate analysis is shown in Table 4.

The final model from the multivariate analysis in this study showed that COVID-19 patients who were treated with co-morbidities of type 2 DM were at risk of death by 2.676 times compared to those without type 2 DM after controlling for age, cough symptoms, ARDS, kidney failure, chronic disease, vaccination, antiviral therapy, use of a ventilator, and the percentage of COVID-19 isolation BOR on admission. The magnitude of the association was statistically significant with a 95% CI of 1.24–5.73.

Table 2: Mortality rate and probability of survival of COVID-19 patients based on type 2 diabetes mellitus variable

DM type 2	Event	Sensor	Time at risk (days)	Mortality rate per 1000 persons days	Probabilities survival (CI 95%)	Median survival	Log rank (p-value) Test	
Yes	38	116	2446	15,53	48.98 (23.97-69.99)	38	0.0056	
No	18	136	2248	6,67	84.13 (72.83-91.02)	-		
COVID-19: Coronavirus disease 2019, DM: Diabetes mellitus.								

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#### Table 3: Probability of survival of COVID-19 patients based on covariate variables

No	Variable	Event		Sensor		Probabilitas survival (IK 95%)	Log Rank (p-value) Test
		n	%	n	%		
1.	Aged group						
	<60	22	11.28	173	88.72	79.35 (67.55–87.25)	0.001
	≥60	34	30.09	79	69.91	48.79 (24.02–69.70)	
	Gender						0.0597
	Female	20	13.25	131	86.75	69.76 (49.92-82.97)	
	Male	36	22.93	121	77.07	47.60 (10.91–77.98)	
	Work						0.2782
	Not health workers	55	18.71	239	81.29	61.44 (42.77–75.63)	
	Health workers	1	7.14	13	92.86	92.86 (59.08–98.96)	
	Vaccination						
	Vaccination booster	0	0	1	100.00	100	0.3135
	Vaccination second dose	1	5.00	19	95.00	50 (0.6–91.04)	
	Vaccination first dose	0	0	8	100.00	100	
	Not vaccinated	55	19.71	224	80.29	61.78 (43.1–75.91)	
	Fever						0.0462
	No	24	13.19	158	86.81	72.52 (55.78-83.79)	
	Yes	32	25.40	94	74.60	52.05 (20.10-76.66)	
	Cough						
	No	14	8.14	145	91.19	77.44 (54.13-89.90)	0.0002
	Yes	42	28.19	107	71.81	48.63 (19.67–72.64)	
	Hard to breathe						0.0447
	No	7	8.33	77	91.67	82.16 (59.01–92.94)	
	Yes	49	21.88	175	78.13	57.91 (35.83-74.76)	
	ARDS						
	Non ARDS	18	6.90	243	93.10	87.56 (79.02–92.78)	<0.001
	ARDS	37	94.87	2	5.13	2.97 (0.2–13.08)	
	Missing						
	Obesity						
	No	39	16.12	203	83.88	74.22 (61.90-83.09)	0.2488
	Yes	16	25.12	46	74.19	30.58 (1.94–71.42)	
	Missing					· · · · ·	
0.	Hipertension						
	Normal	8	9.20	74	90.80	85.69 (71.36-93.17)	0.0104
	Elevated	12	17.91	55	82.09	60.76 (26.75-82.84)	
	Hypertensi stage 1	17	18.89	73	81.11	71.95 (53.85–83.94)	
	Hypertensi stage 2	19	29.69	45	70.31	0.00	
1.	Cardiovascular disease						
	No	47	17.41	223	82.59	64.10 (42.96-79.12)	0.3323
	Yes	9	23.68	29	76.32	54.13 (10.15-83.07)	
2.	Chronic kidney failure						
	No	50	16.72	249	83.28	64.68 (44.82-7894)	< 0.001
	Yes	6	66.67	3	33.33	0.00	
3.	Chronic obstructive pulmonary di			-			
	No	56	18.30	250	81.70	62.62 (43.51-78.94)	0.5027
	Yes	0	0	2	100.00	100.00	
4.	Use of ventilator	-	-	-			
	Use ventilator	18	27.69	47	72.31	55.63 (26.63-77.11)	0.1367
	No ventilator	38	15.64	205	84.36	68.43 (51.55–80.48)	
5.	Antiviral therapy						
0.	Remdesivir	18	13.33	117	86.67	81.79 (71.42-88.69)	0.0002
	Favipiravir	29	23.58	94	76.42	32.39 (7.70–60.92)	0.0002
	Oseltamivir	5	11.36	39	88.64	87.80 (70.35–95.30)	
	Tidak diberikan	4	66.67	2	33.33	33.33 (4.61–67.56)	
6.	Treatment room	r	00.07	-	00.00	56.66 ( 61.66)	
<b>.</b>	COVID-19 isolation	33	12.45	232	87.55	74.43 (60.08-84.27)	<0.001
		55	12.40	202	01.33	77.70 (00.00-04.27)	-0.001
	treatment room	4	22.22	2	66.67	66 67 (F 41 04 F2)	
	Emergency room (IGD)	1	33.33	2	66.67	66.67 (5.41–94.52)	
-		22	55.00	18	45.00	25.85 (6.96–50.32)	
7.	BOR isolation COVID-19	,	10.00	07	07.10	75.00 (00.74.00.15)	0.0000
	≤45%	4	12.90	27	87.10	75.99 (39.74–92.15)	0.0322
	45-85%	13	13.13	86	86.87	63.56 (19.92-88.05)	
	≥85%	39	21.91	139	78.09	62.42 (48.13–73.80)	

## Discussion

The result of this study is that the survival probability of COVID-19 patients with type 2 DM is 48.98% (95% CI: 23.97-69.99%), while in COVID-19 patients without type 2 DM the survival probability is 84.13% (95% CI: 72.83-91.02%) for 49 days of observation. When viewed on 21 days of observation, this study resulted in a survival probability of COVID-19 patients with type 2 DM of 71.24%, while in COVID-19 patients without type 2 diabetes, the probability of survival was 84.13%. In COVID-19 patients with type 2 DM, the probability of survival at the Al Ihsan Hospital was higher than the results of the study at the Mogadishu Hospital, Somalia. The survival probability of COVID-19 patients with type 2 DM in Mogadishu Hospital, Somalia is 44.9% while in COVID-19 patients without type 2 DM is 54.7% [10].

Table 4: The final model of the relationship of type 2 diabetes mellitus with death in COVID-19 patients at AI Ihsan Hospital, West Java Province

Variable	Hazard ratio	CI 95%	p-value
DM type 2	2.676	1.24-5.73	0.011
Age	2.376	1.21-4.68	0.012
Cough	3.605	1.58-8.22	0.002
ARDS	2.539	1.76-3.67	0.000
Vaccination status	5.356	0.68-42.01	0.110
Chronic kidney failure	7.045	2.21-22.39	0.001
Use of ventilators	1.838	0.81-4.16	0.144
Antiviral therapy			
Remdesivir	reff		
Favipiravir	1.722	0.87-3.40	0.117
Oseltamivir	1.376	0.43-4.36	0.587
Not given antivirus	2.628	0.76-9.15	0.129
COVID-19 isolation BOR percentage			
<45%	reff		
45-85%	1.085	0.31-3.78	0.899
≥85%	3.846	1.14-12.95	0.030

In this study, the Kaplan–Meier curve shows that the survival probability of COVID-19 patients with type 2 diabetes is lower than that of COVID-19 patients without type 2 diabetes. The log-rank test results obtained a Chi-square of 7.66 with p = 0.0231. It can be concluded that there are differences in the survival curve of COVID-19 patients in the group with Type 2 DM and the group without Type 2 DM.

These results are in line with research conducted at Zhongnan Hospital and Renmin Hospital in Wuhan China which concluded that the survival probability of COVID-19 patients with type 2 DM was significantly different and lower than that of COVID-19 patients without type 2 DM. the rank of the study, p = 0.021 [11]. Research at the Tongji Hospital in Wuhan also gave the same conclusion as this study on the log-rank test with p < 0.001 [12].

Research conducted on a population in Latin America, in Ceara Brazil also provides the same conclusion that the probability of survival of COVID-19 patients with type 2 DM is lower than without type 2 DM with the results of the log-rank test on the Kaplan Meier curve p < 0.001 [13].

The results of the bivariate analysis in this study showed that type 2 DM was a risk factor associated with COVID-19 death with a crude hazard ratio of 1.89 (95% CI 1.08–3.33). This means that without considering the confounding factors, COVID-19 patients with type 2 DM have a 1.89 risk of death compared to COVID-19 patients without type 2 diabetes.

After controlling for confounders, a final model was obtained that considered confounding, namely, age, cough symptoms, ARDS, chronic kidney failure, vaccination, antiviral therapy, ventilator use, and the percentage of BOR COVID-19 isolation at admission. The multivariate analysis in this study resulted that type 2 DM was associated with COVID-19 mortality with an adjusted hazard ratio of 2.676 (95% CI: 1.24–5.73). This means that COVID-19 patients with type 2 diabetes are at risk of death by 2.23 times compared to COVID-19 patients without type 2 diabetes after controlling for confounding, namely age, cough symptoms, ARDS, chronic kidney failure, vaccination, antiviral therapy, use of ventilators, and the percentage of COVID-19 Isolation BOR upon admission.

The results of this study are in line with a retrospective cohort study in Jakarta on 20,481 patients in 2020, which stated that type 2 DM was not only associated with the development of more COVID-19 clinical symptoms but also with a high risk of COVID-19 death of 1.98 times (*adjusted* RR 1.98 with 95% CI 1.57–2.51), p < 0.001) compared to COVID-19 patients without type 2 diabetes [14].

The previous research from various countries gave the same result that type 2 DM was a risk factor for COVID-19 death. A meta-analysis of 9 studies in 8.807 in China showed that type 2 DM increased the risk by 2.96 (95% CI: 2.31-3.79; p < 0.001) [15]. In a population study in Scotland, the adjusted odds ratio for type 2 diabetes was 1.369 (1.276–1.468) [16]. In United Kingdom, national study of hospitalized COVID-19 patients from March to July 2020, type 2 DM increased the risk of death in hospitals by 1.23 (adjusted hazard ratio 1.23; 95% CI 1.14–1.32) [17]. A meta-analysis of 24 studies in 10,648 patients up to July 2021 gave results that are in line with this study. Diabetes increased the risk of in-hospital death by 2.44 (OR 2.44; 95% CI, 1.93–3.09; p < 0.0001) [18].

The relationship between type 2 DM and the severity of COVID-19 is due to increased expression of *angiotensin-converting enzyme* 2 (ACE-2) receptors, cell aging, immune system disorders, and increased pro-inflammatory responses [19] Experimental studies suggest that increased expression of ACE2 was found in the kidneys, liver, and pancreas [20]. SARS-CoV-2 enters the host cell by using a spike protein (S protein) to bind to the ACE-2 receptor on the plasma membrane of human cells, especially in lung alveoli cells, nasal mucosal goblet cells, and intestinal absorptive enterocytes [21].

People with diabetes, the immune response is impaired and contributes to disease progression in COVID-19. Natural killer cells (NK cells) are decreased in number in type 2 DM and are associated with blood sugar control. These NK cells are involved in innate immunity to eliminate pathogens and cancer cells [22]. In the context of COVID-19, after the SARS-CoV-2 virus enters, then cytokines are produced. This attracts monocytes, macrophages, and T cells to the site of infection which then causes inflammation. In healthy individuals, the initial inflammation is followed by T cell expression and the production of neutralizing antibodies, which serve to fight off the virus before it spreads and lung damage can be minimized. However, when the immune system is damaged, there is an accumulation of immune cells in the lungs which causes excessive production of pro-inflammatory cytokines which then results in lung and multi-organ damage [23].

Complications caused by DM, namely. cardiovascular disease, heart failure, and chronic kidney disease, can increase the risk of death in COVID-19 patients. Increased glucose levels directly increase SARS-CoV-2 replication. Glycolysis maintains SARS-CoV-2 replication by producing mitochondrial reactive oxygen species and activating hypoxiainducible factor  $1\alpha$ . This mechanism supports viral proliferation. In insulin-requiring patients, SARS-CoV-2 infection is associated with a rapidly increasing need for high-dose insulin (nearly approaching or exceeding 100 IU per day). Changes in insulin requirements are related to inflammatory cytokine levels. Although ketoacidosis is usually found in patients with type 1 DM, in patients with COVID-19 ketoacidosis can also occur in type 2 DM [24].

In this study, vaccination status was a confounder in the relationship between type 2 diabetes and COVID-19 mortality. The research subjects were COVID-19 patients who were treated at the AI Ihsan Hospital from 2020 to 2021. While the vaccination program only started in early 2021. From the research subjects, only 0.32% had been vaccinated with

boosters, 6.49% were vaccinated up to 2nd dose, 1st dose vaccination was 2.60% and 90.58% had not been vaccinated before being infected with COVID-19. By the purpose of vaccination, several studies have proven the benefits of vaccination. A study in the UK reported that the hazard ratio for death in the BNT162b2 booster vaccine group compared to that which had not been boosted was 0.10 (95% CI 0.07–0.14; p < 0.001) [25]. Appropriate for diabetics to prevent COVID-19.

In addition to controlling blood sugar and providing appropriate therapy for COVID-19 patients with type 2 diabetes, another important thing is to prevent infection with SARS-CoV-2. These prevention efforts include being obedient and consistent in maintaining hand hygiene, wearing masks, and maintaining distance.

# Conclusions

The results of this study can be concluded that the probability of survival COVID-19 patients with type 2 DM is lower than COVID-19 patients without type 2 DM who are treated at AI Ihsan Hospital. There is a statistically significant relationship between type 2 DM and COVID-19 mortality after controlling for confounder variables, namely age, cough symptoms, ARDS, vaccination, chronic kidney failure, ventilator use, antiviral therapy, and the percentage of BOR COVID-19 isolation at admission.

# References

 Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157-60. http://doi.org/10.23750/abm. v91i1.9397

PMid:32191675

- World Health Organization. COVID-19 Weekly Epidemiological Update. 81<sup>st</sup> ed. Geneva: World Health Organization; 2022.
- Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ. Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc Natl Acad Sci U S A. 2020;117(26):14857-63. https://doi.org/10.1073/pnas.2009637117
- 4. World Health Organization. Therapeutics and COVID-19; Living Guide Line. Geneva: World Health Organization; 2022.
- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J. 2020;55(5):2000547. http://doi.org/10.1183/13993003.00547-2020 PMid:32217650
- Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, *et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9<sup>th</sup> edition. Diabetes Res Clin Pract. 2019;157:107843. http://

doi.org/10.1016/j.diabres.2019.107843 PMid:31518657

- Bajgain KT, Badal S, Bajgain BB, Santana MJ. Prevalence of comorbidities among individuals with COVID-19: A rapid review of current literature. Am J Infect Control. 2021;49(2):238-46. http://doi.org/10.1016/j.ajic.2020.06.213
  PMid:32659414
- 8. Kemenkes RI. Laporan Nasional Riset Kesehatan Dasar. Jakarta, Indonesia: Kemenkes RI; 2018.
- 9. RSUD Al Ihsan. Laporan 10 Besar Penyakit Co Morbiditas Covid Rawat Inap Tahun 2021; 2022.
- Ali MM, Malik MR, Ahmed AY, Bashir AM, Mohamed A, Abdi A, et al. Survival analysis of all critically ill patients with COVID-19 admitted to the main hospital in Mogadishu, Somalia, 30 March-12 June 2020: Which interventions are proving effective in fragile states? Int J Infect Dis. 2022;114:202-9. https://doi. org/10.1016/j.ijid.2021.11.018 PMid:34781004
- Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: A two-center, retrospective study. Diabetes Care. 2020;43(7):1382-91. http://doi.org/10.2337/ dc20-0598

PMid:32409504

- Liu Y, Lu R, Wang J, Cheng Q, Zhang R, Zhang S, *et al.* Diabetes, even newly defined by HbA1c testing, is associated with an increased risk of in-hospital death in adults with COVID-19. BMC Endocr Disord. 2021;21(1):56. http://doi.org/10.1186/ s12902-021-00717-6 PMid:33771154
- De Souza CD, de Arruda Magalhães AJ, Lima AJ, Nunes DN, de Fátima Machado Soares É, de Castro Silva L, *et al.* Clinical manifestations and factors associated with mortality from COVID-19 in older adults: Retrospective population-based study with 9807 older Brazilian COVID-19 patients. Geriatr Gerontol Int. 2020;20(12):1177-81. http://doi.org/10.1111/ggi.14061 PMid:33111433
- Harbuwono DS, Handayani DO, 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. http://doi.org/10.1016/j.pcd.2021.11.002 PMid:34857490
- Guo L, Shi Z, Zhang Y, Wang C, Do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A metaanalysis. Diabetes Res Clin Pract. 2020;166:108346. http://doi. org/10.1016/j.diabres.2020.108346
  PMid:32710998
- McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LA, McAllister DA, etal. Risks of and risk factors for COVID-19 disease in people with diabetes: A cohort study of the total population of Scotland. Lancet Diabetes Endocrinol. 2021;9(2):82-93. http:// doi.org/10.1016/S2213-8587(20)30405-8 PMid:33357491
- Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, *et al.* Type 2 diabetes and COVID-19-related mortality in the critical care setting: A national cohort study in England, March-July 2020. Diabetes Care. 2021;44(1):50-7. http://doi.org/10.2337/dc20-1444
  PMid:33097559
- Bradley SA, Banach M, Alvarado N, Smokovski I, Bhaskar SM. Prevalence and impact of diabetes in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Diabetes. 2022;14(2):144-57. http://doi.

org/10.1111/1753-0407.13243 PMid:34939735

19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. https://doi. org/10.1016/S0140-6736(20)30183-5 PMid:31986264

- 20. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14(4):303-10. http://doi.org/10.1016/j.dsx.2020.04.004 PMid:32298981
- 21. Mason K, Hasan S, Darukhanavala A, Kutney K. COVID-19: Pathophysiology and implications for cystic fibrosis, diabetes and cystic fibrosis-related diabetes. J Clin Transl Endocrinol. 2021;26:100268. http://doi.org/10.1016/j.jcte.2021.100268 PMid:34722160
- 22. Kim JH, Park K, Lee SB, Kang S, Park JS, Ahn CW, et al. Relationship between natural killer cell activity and glucose

control in patients with Type 2 diabetes and pre-diabetes. J Diabetes Investig. 2019;10(5):1223-8. http://doi.org/10.1111/ jdi.13002

PMid:30618112

- 23. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-74. http://doi.org/10.1038/s41577-020-0311-8 PMid:32346093
- 24. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: From pathophysiology to clinical management. Nat Rev Endocrinol. 2021;17(1):11-30. http://doi.org/10.1038/ s41574-020-00435-4

PMid:33188364

25. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 vaccine booster and mortality due to Covid-19. N Engl J Med. 2021;385(26):2413-20. https://doi. org/10.1056/NEJMoa2115624

PMid:34879190