Original Article

Is Vaccination Related to The Cure Rate of COVID-19 Patients with Comorbidities?

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Abstract

Background: Prior vaccination can prevent a COVID-19 patient from falling into moderate, severe, and critical conditions. The effect of vaccination on COVID-19 patients' recovery has been widely studied. However, its correlation in critically severe COVID-19 patients with comorbidity has not been fully understood yet. This study aims to determine the correlation of vaccination in critically severe COVID-19 patients with comorbidity of hypertension and/or Diabetes Mellitus (DM).

Methods: A retrospective cohort study was conducted in critically severe COVID-19 patients with hypertension and/or DM treated in Dr. Moewardi Hospital, Surakarta, Indonesia from March 2021 to September 2021. The data were taken from patients' medical records. We analyzed all data statistically with Chi-Square and Fisher's exact test, and $P<0.05$ was considered significant.

Results: There were 489 patients included in our study, 247 patients with hypertension and DM, and 242 patients without comorbidities. Vaccination status was significantly associated with the cure rate of critically severe COVID-19 patients with hypertension ($P=0.018$), but not with DM ($P=0.606$). There was no significant association between age to the cure rate of critically severe COVID-19 patients with hypertension and DM ($P=0.953$). Vaccination status was related among patients with comorbidities and without comorbidities ($P<0.001$).

Conclusion: Vaccination was significantly correlated with the cure rate of moderate to critically severe COVID-19 patients with hypertension and without comorbidities.

Keywords: COVID-19, cure rate, diabetes, hypertension, vaccination

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INTRODUCTION

The World Health Organization (WHO) has declared COVID-19 as a pandemic since March 11, 2020.[1] Its clinical manifestations are diverse ranging from asymptomatic to fatal complications, such as acute respiratory distress syndrome (ARDS) and respiratory failure.[1,2]

The common comorbidities are hypertension (15.6%), diabetes mellitus (7.7%), and cardiovascular disease (4.7%). Approximately 44.5% of diabetes patients and 41,7% of hypertension patients are included in critical cases. Research in Indonesia stated that hypertension, diabetes mellitus (DM), and cardiovascular disease are the most common comorbidities, which are then related to the severity of symptoms. However, its role in mortality and treatment duration has not been widely known yet.[3–5] Various attempts have been made to develop SARS-CoV-2 vaccines in recent decades.[3]

The SARS-CoV-2 antigen vaccine can prevent COVID-19 infection and/or minimize its morbidity.[6] This study aimed to determine the relationship between COVID-19 vaccination and the recovery of moderate, severe, and critical COVID-19 patients with comorbid factors.

METHODS

The study was a retrospective cohort, taking medical records of moderate, severe, and critical COVID-19 patients undergoing intensive care in the isolation room from 1st March to 30th September 2021 at Dr. Moewardi Hospital, Surakarta. The sample size was measured using total purposive sampling.

The inclusion criteria were adult patients more than 18 years old, patients with hypertension and/or DM, patients without comorbidities, patients with a history of vaccination, patients undergoing treatment in isolation rooms with confirmed moderate, severe, and critical COVID-19 cases, and a patient who

underwent laboratory examination (GDP, G2PP, HbA1C, D dimer). The exclusion criteria were patients with absent or incomplete medical records and non-confirmed COVID-19. It was approved by the Ethics Feasibility Committee of the Dr. Moewardi Hospital, Faculty of Medicine, Sebelas Maret University, Surakarta in January 2022 with the ethical approval number 26/I/HREC/2022.

The data was statistically analyzed using SPSS version 25.0. Kolmogorov-Smirnov Test was used to determine the normality. The hypothesis test was Chi-square/Fischer's exact test. The confidence interval was 95%. The value of *P*<0.05 was declared as a statistically significant relationship.

RESULTS

This study analyzed 489 moderate, severe, and critical COVID-19 patients undergoing treatment in Melati 1 isolation room at Dr. Moewardi Hospital Surakarta from 1st March to 30th September 2021. Among them, 247 patients have hypertension and/or DM and 242 patients have no comorbidities.

The median value of patients' age was 47 (18–87) years old. The patients were mostly female accounting for 320 patients (65.4%). In this study, most participants (50.7%) had not been vaccinated against COVID-19 with the most comorbidities being DM (20.2%) and the living outcomes were 55.5% (Table 1).

Table 1. Characteristics of Subjects (N=489)

Characteristics	Result
Age (years) [median (min-max)]	47 (18–87)
Gender	
Male	169 (34.6%)
Female	320 (65.4%)
Vaccine Status	
No Vaccine	248 (50.7%)
1st Vaccine	34 (7.0%)
2nd Vaccine	207 (42.3%)
Comorbid	
Hypertension	89 (18.2%)
Diabetes	99 (20.2%)
Hypertension and Diabetes	59 (12.1%)
Without comorbidities	242 (49.5%)
Outcome	
Non-survivor	220 (45.0%)
Survivor	269 (55.0%)

Based on age, patients who were non-survivor tended to be older than those who survived. The median age of patients with both comorbidities was 61 (19–87) years old in non-survivor and 58 (19–79) years old in surviving patients. There was no significant difference (*P*=0.953) in the age of non-survivor and survivor patients. In patients with both comorbidities and no history of vaccines, 85.6% were non-survivor and 14.4% were survivors.

Table 2. The correlation between the vaccination status of moderate, severe, and critical COVID-19 patients and the outcome (N=489)

Vaccination status	N	Non-survivor	Survivor	*P*
1st Vaccine with HT and DM	21	18 (85.7%)	3 (14.3%)	<0.001*
1st Vaccine without comorbidities	13	3 (23.1%)	10 (76.9%)	
2nd Vaccine with HT and DM	31	21 (67.7%)	10 (32.3%)	
2nd Vaccine without comorbidities	176	3 (1.7%)	173 (98.3%)	
No Vaccine with HT and DM	195	167 (85.6%)	28 (14.4%)	
No Vaccine without comorbidities	53	8 (15.1%)	45 (84.9%)	

Note: **Chi-square* - significant if *P*<0.05; HT=hypertension; DM=diabetes mellitus

While in patients with 1st vaccine and 2nd dose vaccines, non-Survivor occurred in 85.7% and 67.7% were patients, respectively. There was a significant relationship (*P*=0.043) between vaccination status in moderate, severe, and critical COVID-19 patients with comorbid on their recovery. Around 88.9% of patients with comorbid hypertension complicated with DM who have not been vaccinated were dying. Non-Survivor occurred in patients with the 1st dose and 2nd dose was 80.0% and 55.6%, respectively. It means that the vaccination status of COVID-19 patients with moderate or higher severity levels combined with both comorbidities was not significantly correlated to its recovery. It was known that COVID-19 survivors were mostly patients with 2nd vaccine without comorbidities counted as 98.3%. It also had a higher cure rate up to 32.3%. There was a significant relationship (*P*≤0.001) between the vaccination status of moderate, severe, and critical COVID-19 patients with comorbid factors and no comorbidity to its outcome (Table 2).

It was also known that COVID-19 survivors were mostly patients without comorbidities (94.2%),

while non-survivor subjects were mostly patients with comorbid hypertension and DM (83.4%). There was a significant relationship (*P*≤0.001) between comorbid factors with the recovery outcome (Table 3).

Table 3. The correlation between comorbidities of moderate, severe, and critical COVID-19 patients and the outcome

Comorbidities	N	Non-survivor	Survivor	*P*
With comorbidities HTand/or DM	247	206 (83.4%)	41 (16.6%)	<0.001*
Without comorbidities	242	14 (5.8%)	228 (94.2%)	

Note: *Chi-square/Fisher exact test - significant at *P*<0.05; HT= hypertension; DM= diabetes mellitus

The survival rate of patients with both comorbidities who had not been vaccinated was only 14.4%. The survival rate of patients who were vaccinated with the 1st dose and 2nd dose was 14.3% and 32.3%, respectively. Vaccination status was significantly related to the recovery of moderate, severe, and critical COVID-19 patients with comorbid hypertension and/or DM (*P*=0.043). On the other hand, the survival rate of patients with hypertension who have not been vaccinated was 13.2%. In patients with the 1st dose and 2nd dose vaccine, the survival rate was 0% and 41.7%, respectively. The vaccination status was significantly related to the recovery status of moderate, severe, and critical COVID-19 patients with hypertension (*P*=0.018) (Table 4).

Table 4. The correlation between vaccination status of moderate, severe, and critical COVID-19 patients with comorbidities and the outcome

Characteristics	Non-survivor	Survivor	*P*
Vaccination (All Comorbidities)			
No Vaccine	167 (85.6%)	28 (14.4%)	
1st Vaccine	18 (85.7%)	3 (14.3%)	0.043*
2nd Vaccine	21 (67.7%)	10 (32.3%)	
Age (Hypertension)			
No Vaccine	59 (86.8%)	9 (13.2%)	
1st Vaccine	9 (100.0%)	0 (0.0%)	0.018*
2nd Vaccine	7 (58.3%)	5 (41.7%)	
Age (DM)			
No Vaccine	68 (82.9%)	14 (17.1%)	
1st Vaccine	5 (71.4%)	2 (28.6%)	0.606
2nd Vaccine	9 (90.0%)	1 (10.0%)	
Age (DM+Hypertension)			
No Vaccine	40 (88.9%)	5 (11.1%)	
1st Vaccine	4 (80.0%)	1 (20.0%)	0.051
2nd Vaccine	5 (55.6%)	4 (44.4%)	

Note: *Chi-square - significant at *P*<0.05

Table 5 showed that non-survivor subjects tended to be older, with the median age of subjects with comorbid hypertension and DM being 61 (19–87) years, while the median age of subjects living was 58 (19–79) years (*P*=0.953). The average age of COVID-19 subjects with comorbid hypertension whom non-survivor was 60.28±13.13 years, while the survivor was 60.93±10.25 years (*P*=0.862). Based on their vaccination status, there was no significant difference in patients who had not been vaccinated (*P*=0.640), received 1st dose, and 2nd dose (*P*=0.687).

Table 5. The correlation between age and vaccination status of moderate, severe, and critical COVID-19 patients with comorbidities and the outcome

Characteristics	Non-survivor (year)	Survivor (year)	*P*
Age (All Comorbidities)[a]	61 (19–87)	58 (19–79)	0.327
Age (Hypertension)[a]	60.28±13.13	60.93±10.25	0.862
No Vaccine[a]	59.59±13.18	57.44±9.28	0.640
1st Vaccine[b]	61.89±12.08	-	-
2nd Vaccine[a]	64.00±15.11	67.20±9.63	0.687
Age (DM)[a]	60.68±9.72	55.82±12.96	0.080
No Vaccine[a]	60.09±10.01	55.07±13.15	0.110
1st Vaccine[b]	63 (52–63)	52 (46–68)	0.228
2nd Vaccine[b]	65 (54–78)	74 (74–74)	0.384
Age (DM+Hypertension)[a]	61.47±8.77	67.40±7.97	0.982
No Vaccine[a]	61.40±9.09	58.40±8.96	0.490
1st Vaccine[b]	62 (56–72)	67 (67–67)	0.480
2nd Vaccine[a]	60.80±8.93	63.75±7.14	0.609

Note: [a]Uji Mann-Whitney; [b]Uji independent t-test

The average age of non-survivor subjects with DM comorbidities was 60.68±9.72 which was older than those who survive (*P*=0.080). Based on their vaccination status, there was no significant difference in patients who had not been vaccinated (*P*=0.110), received 1st dose (*P*=0.228), and 2nd dose (*P*=0.384). The average age of COVID-19 patients with comorbid hypertension complicated with DM who were non-survivor was 61.47±8.77 years, while for those who were survivors was 67.40±7.97 years (*P*=0.982). Based on their vaccination status, there was no significant difference in patients who had not been vaccinated (*P*=0.490), received 1st dose (*P*=0.480), and 2nd dose (*P*=0.609). There was no significant relationship between age and vaccination status in moderate, severe, and critical COVID-19 patients with or without comorbidities on its recovery.

DISCUSSION

Caifang et al, and Gili et al, showed that S can prevent the severity of COVID-19.[7,8] Sowmya et al, stated patients without comorbidities and who had been vaccinated showed better recovery.[9] Christian et al, concluded that vaccination in hypertension patients required more research to determine its effectiveness. This study found that there was a significant relationship between vaccination and recovery in moderate to critical COVID-19 patients with comorbid factors (hypertension and diabetes mellitus) and without comorbidities (*P*≤0.001). It was known that COVID-19 survivor were mostly patients with 2nd vaccine without comorbidities counted 98.3%, while non-survivor was mostly those with comorbidities who had not been vaccinated yet (85.6%) or only received the 1st vaccine (85.7%).

Hypertension is strongly correlated with lower antibodies. There is a similar mechanism of immune dysfunction in hypertension and vaccination's inappropriate response. Hypertension was previously found to be correlated with worse outcomes, suggesting higher morbidity as well as mortality in COVID-19 infection, and thus may be involved in the development of an immunologic response to vaccination.[10,11]

The prevalence of DM in COVID-19 patients ranges from 8.2% to 10.3%. In several studies, the presence of DM in COVID-19 was stated as an independent factor associated with severity and increased mortality. A meta-analysis of 33 studies concluded that DM in COVID-19 was associated with a twofold increased risk of non-survivor and disease severity, compared to patients without DM.[12]

The success of vaccination can be seen in COVID-19 patients without comorbidities as its cure rate was better than patients with comorbidities. It was also shown that 94.2% of patients without comorbidities stayed survivors, while 83.4% of patients with comorbid hypertension and DM were non-survivor (*P*≤0.001). In 2021, Irawaty et al showed that patients with comorbid hypertension and DM had a lower cure rate than those without comorbidities which were aligned with our study.

SARS-CoV-2 vaccination mostly targets glycoprotein or protein S as the main inducer of antibodies. The S protein-based vaccines induce antibodies that block both the viral receptor binding and the uncoating viral genome. The C-terminal domain of the S1 subunit of the coronavirus delta represents a dominant immune region. This region exhibits the strongest neutralization.[11–13]

Protein S has been known to have a big role in promoting protective immunity during SARS-CoV2 infection by inducting antibodies and T-cells. Glycoprotein S is believed to be the most promising candidate for CoV vaccine composition. Other structural proteins affect the immunogenicity of protein S or ACE2 receptor-binding which is an important initial step for viruses to access host cells. Both RBD-containing recombinant protein and RBD-encoding recombinant vector have superior abilities to induce neutralizing antibodies which can be used to develop an effective SARS-CoV vaccine.[11–13]

This research found vaccination status was significantly related to the recovery of moderate, severe, and critical COVID-19 patients with comorbid hypertension and/or DM (*P*=0.043) and with hypertension only (*P*=0.018). Patients with 2nd dose of the vaccine had a higher cure rate than patients with 1st dose and who had not been vaccinated yet. The vaccination triggers a memory immune response that eliminates the SARS-CoV- 2 virus and improves its clinical outcomes in hypertensive patients. The ACE2 converts angiotensin II to angiotensin I-VII to neutralize the inflammatory effects of angiotensin II, reduce the level of pro-inflammatory cytokine interleukin 6, increase the anti-inflammatory and antioxidant role of angiotensin I-VII, increase the concentration of alveolar surfactant protein D, and induce vasodilation.[14,15]

On the other hand, the vaccination was not significantly correlated in DM patients (*P*=0.606) or patients with complications of hypertension with DM (*P*=0.051). The results of this study are not in line with previous studies that showed an impaired antibody response to influenza and hepatitis B vaccines in DM patients. Recent studies showed people with DM can enhance an appropriate immune

response post-vaccination. Several case-control studies showed that the effectiveness and safety of the pneumococcal vaccine ranged from 56% to 81%. The effectiveness of the 23-valent Pneumococcal Polysaccharide Vaccine (PPV23) was 84% in people with DM. The PPV23 effectively prevents pneumococcal disease and reduces the utilization of medical services in patients aged 75 years old or older with DM. Young and elderly adults with DM have been shown to promote optimal B cell responses to the seasonal influenza vaccine.[16–19]

Based on the existing theory, DM causes glucotoxicity and endothelial damage due to inflammation, and oxidative stress. Thereby, thromboembolic complication increases putting organ vitals at a high risk of malfunction. Microangiopathy in DM may also reduce lung compliance which in turn will interfere with air exchange in the lungs. There are also some changes in the respiratory in DM patients that affect lung volume and lung diffusion capacity. DM and hypertension are chronic inflammations that further exacerbate the dysfunction of T cells, dendritic cells and other inflammatory factors.[19,20]

Blood sugar control also affects the mortality of COVID-19 patients with DM, as in a study of 10,926 on COVID-19 which concluded that there was an increased risk of non-survivor in patients with poor HbA1c. A multicenter retrospective research in China also found that one of the independent factors of mortality in COVID-19 patients was the high fasting glucose levels at admission (≥7.0 mmol/L OR 126 mg/dL). DM was associated with the risk of COVID-19 with severe symptoms including the risk of ARDS, use of the ICU room, and the need for a ventilator.[16,18]

All age groups are at risk of being infected with COVID-19. Based on the research, it was known that non-survivor patients tended to be older than those who survived, even though the data was not significantly correlated (P=0.953). An epidemiological analysis showed that 77.8% of COVID-19 patients were in the age range of 30 to 69 years with the highest proportion in the age of 50 to 60 years.

The infection rate in children was considered relatively low. High severity happens in patients aged >60 years old, living in nursing homes or long-term care facilities, and had chronic diseases. Male patients dominated (56.9%) cases. The highest mortality rate happens in patients aged >70 years old, regardless of the presence of a chronic medical condition, such as 32% of cardiovascular disease, 30% of DM, and 18% of chronic lung disease. Other conditions that put people at high risk were cancer, obesity, kidney disease, sickle cell disease, and other immunocompromised conditions.[2,21–23]

LIMITATION

There were some limitations of the study. First, it was a retrospective cohort research in which observations were made indirectly by relying on medically recorded data only. Thus, we could not control the data quality. In addition, indirect observations made it difficult to accurately determine the effective time of the vaccine. Second, this study did not rule out the type and the onset of the vaccine. The effect of antibodies after their administration might affect the outcome of moderate, severe, and critical COVID-19 patients. Research over a longer period is also required to determine the development of the subject's condition and diagnosis.

CONCLUSION

Vaccination, especially the 2nd dose, was significantly associated with the cure rate of moderate to critically severe COVID-19 patients with hypertension and without comorbidities. Hence, it is important to diagnose controlled hypertension early. Diabetes is an independent risk factor for the prognosis of COVID-19. More attention should be paid to the prevention and treatment of diabetic patients, especially those who require insulin therapy. Further prospective research is needed on the type of COVID-19 vaccines to see the success rate of vaccination in people with comorbidities.

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CONFLICT OF INTEREST

None.

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