A Comparison Study of COVID-19 Outcomes based on Vaccination Status among Hospitalized Patients in Wangaya General Hospital Denpasar, Bali

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Abstract: _Background: Background: COVID-19 infections continuously spreading and impact the global health and economic system despite rigorous public health protocols. There is evidence that vaccines may reduce transmission, symptomatic infection, and severity of illness, with 70 - 90% vaccine effectiveness. This report provides a comparative analysis of the severity and mortality of COVID-19 infection between vaccinated and unvaccinated individuals who were hospitalized in Wangaya General Hospital Denpasar, Bali. Method: We conducted a retrospective observational study with a case - control design. The data were collected using secondary data from the medical records that were hospitalized in Wangaya General Hospital Denpasar from the last June 2021 through August 2021. The data that met the inclusion criteria were then analyzed with SPSS 22.0. Result: On bivariate analysis showed there is a significant correlation between vaccination status with outcome of COVID-19 infections (p= 0, 032) and the severity of illness (p= 0, 017). The multivariate analysis was done at the variables that showed significant result in bivariate analysis. The binary logistic regression was done. The result showed that age (p= 0, 045; 95% CI 1, 002 - 1, 209), D - dimer level (p= 0, 006; 95% CI 1, 000 - 1, 001), length of stay (p= 0, 006; 95% CI 0, 386 - 0, 855), and vaccination status (p= 0, 048; 95% CI 1, 025 - 564, 786) significantly correlated with the outcome. While only gender (p= 0, 032; 95% CI 0, 118 - 0, 909) and D - dimer level (p= 0, 001; 95% CI 1, 000 - 1, 001) has strong correlation with severity of illness. However, vaccination had protective effect against severe - critical illness (OR=0.318; p= 0.017) and mortality (OR= 0.20; p=0.032) when infected by SARS - CoV - 2. Conclusion: COVID-19 vaccines play a critical role in this devastating pandemic situation. Vaccinated patients have shown good outcomes when infected by SARS - CoV - 2 compared with unvaccinated patients._

Keywords: COVID-19, SARS - CoV - 2, COVID-19 vaccine, vaccinated, unvaccinated

1. Background

COVID-19 infections continuously spreading and impact the global health and economic system despite with rigorous public health protocols, such as wear a mask, physical distancing, stay at home, and school closures.1 As of September 6, 2021, the COVID-19 pandemic has reached 220 million cases and 4.5 million death globally, including 4 million confirmed cases and 136 thousand death in Indonesia[2]. However, despite continued public health protocols, the second wave showed to be greatly increase, this shows that a safe and effective vaccine is importance to control this pandemic[1].

COVID-19 vaccine emergency use authorization was announced by the Food and Drug Administration (FDA) on October 2020[3]. Several vaccines with relatively high efficacy in clinical trials have been approved[1]. It is almost 11% of the world's population had received COVID-19 vaccine for at least one dose on early June, 2021[4].

The immunity and protection following COVID-19 vaccination does not occur immediately. Vaccines are not expected to offer protection in the first two weeks after the first dose administration, as it takes time to develop imunity[5]. It is estimated that Pfizer, Moderna, or AstraZeneca vaccines had 60 - 80% Vaccine Effectiveness (VE) for preventing COVID-19 infection 3 - 4 weeks after receiving the first dose, and increase greater than 85% after the second dose[6]. There is evidence that vaccine may reduce transmission, symptomatic infection, and severity of illness, with 70 - 90% vaccine effectiveness for prevention of serious outcomes for hospitalizations and intensive care unit (ICU) admission[7].

Even though vaccination has provides protection from COVID-19 infection with high efficacy, but there is no vaccine with a 100% effectiveness, hence it is expected that a small proportion of vaccinated individuals may become infected[5, 6]. This report provides comparison analysis on the severity and mortality of COVID-19 infection between vaccinated and unvaccinated individuals who were hospitalized in Wangaya General Hospital Denpasar, Bali.

2. Method

We conducted a retrospective observational study with a case control design. The data were collected using secondary data from medical record. The inclusion criteria included patient with positive RT - PCR for COVID-19 that hospitalized in Wangaya General Hospital Denpasar since the last June 2021 through August 2021, age 18 years or older, and a known history of vaccinated or unvaccinated for COVID-19. Patients that didn't meet the inclusion criteria were excluded from the study.

The data was analyzed with Mann - Whitney test, Chi - square test, and Fisher exact test using SPSS 22.0 to analyzed factors that correlated with severity of illness and outcomes. The factors that correlated with severity of illness and outcomes then analyzed with multivariate analysis. The binary logistic regression was done to analyze the correlation between the factors with severity of illness and outcomes.

3. Result

Of the 105 patients were included in this study, 60 patients were not vaccinated and 45 patients have vaccinated. The characteristic of the subject was shown on table 1. The median age was 52 years old (21 - 86 years old) with no significant differences between female and male gender. The most common symptom was cough (84.8%), fever (71.4%) and dyspnea (60%). Almost all of the subject has comorbidity and only 33.3% without comorbidity, the comorbidities includes heart disease (18.1%), diabetes mellitus (17.1%), hypertension (15.2%), kidney disease (12.4%), pregnancy (5.7%), asthma (1.9%), stroke (1%) and others diseases (39%). On chest X - ray showed the majority has bilateral pneumonia (54.3%). On laboratory findings revealed a median of CT - value 19.4 (0 - 36.27), median of D - dimer level was 557.6 (0 - 10.000), median of CRP level was 40 (0 - 200). The median of length of stay was 8 days (1 - 20 days).

About 42.9% of the patients have been vaccinated and 57.1% were unvaccinated. The majority of patients have a good outcome with 87.6% were survivor and only 12.4% were non - survivor. The severity of illness in this study was classified into 2 category such as moderate illness and severe - critical illness. The majority of patients have moderate illness (72.1%) and about 27.6% with severe - critical illness.

Table 1: The Characteristic of subjects

Characteristic	Frequency	Percent (%)
Age (years), median (min - max)	52 (21 - 86)	
Gender		
Male	49	46, 7
Female	56	53, 3
Symptoms		
Fever	75	71, 4
Cough	89	84, 8
Fatigue	49	46, 7
Sore throat	7	6, 7
Runny nose	7	6, 7
Dyspnea	63	60, 0
Nausea/vomiting	41	39, 0
Anosmia	36	34, 3
Diarrhea	7	6, 7
Headache	5	4, 8
Anorexia	8	7, 6
Other symptoms	9	8, 6
Comorbidity		
Without comorbid	35	33, 3
Diabetes mellitus	18	17, 1
Hypertension	16	15, 2
Heart disease	19	18, 1
Stroke	1	1, 0
Kidney disease	13	12, 4
Pregnancy	6	5, 7
Asthma	2	1, 9
Other diseases	41	39, 0
Chest X - ray		
Non - pneumonia	30	28, 6
Unilateral pneumonia	18	17, 1
Bilateral pneumonia	57	54, 3
History of COVID-19 Vaccination		
Vaccinated	45	42, 9
Unvaccinated	60	57, 1
CT Value, median (min - max)	19, 4 (0 - 36, 27)	
D - dimer, median (min - max)	557, 6 (0 - 10.000)	
CRP, median (min - max)	40 (0 - 200)	
Length of stay, median (min - max)	8 (1 - 20)	
Outcome		
Survivor	92	87, 6
Non - survivor	13	12, 4
Severity		
Moderate illness	76	72, 4
Severe - critical illness	29	27, 6

Correlation between vaccination status with severity of illness and outcome
There is a significant correlation between vaccination status and outcome of COVID-19 infections (table 2). The unvaccinated group mostly non - survivor (84.6%) and about 53.3% were survivor. Vaccination will prevent mortality in COVID-19 patient (OR= 0.20; *p*= 0.032).

Table 2: The correlation of vaccination status with outcomes

Vaccination status	Outcome		*p* value	OR
	Survivor (n=91)	*Non - survivor* (n=13)		
Vaccinated	43 (46, 7%)	2 (15, 4%)		0.20
Unvaccinated	49 (53, 3%)	11 (84, 6%)	0, 032	

There is significant correlation between vaccination status with severity of illness (table 3). The majority of severe - critical illness infection was unvaccinated (75.9%) and about 50% of survivor group was unvaccinated. Vaccination will prevent severe - critical illness in COVID-19 patient (OR= 0.318; *p*= 0.017).

Table 3: The correlation of vaccination status with severity of illness

Vaccination status	Severity of illness		*p* value	OR
	Moderate illness (n=76)	Severe - critical illness (n=29)		
Vaccinated	38 (50%)	7 (24, 1%)		0.318
Unvaccinated	38 (50%)	22 (75, 9%)	0, 017	

Factors that correlated with outcomes
The data was analyzed with Mann - Whitney test, it showed a significant differences from age, D - dimer, CRP, and length of stay between survivor group and non - survivor group. The non - survivor group has older median of age, higher median of D - dimer level and CRP level, and shorter length of stay in comparison with the survivor group. All of non - survivor group has comorbid, whereas about 62% of the survivor group has comorbid. The majority of non - survivor group has comorbidity of diabetes mellitus, heart disease, and kidney disease. There is significant correlation between comorbidity of diabetes mellitus, heart disease, and kidney disease with outcome of COVID-19 infections.

Table 4: The characteristic of patients based on the outcome

Characteristic	Outcome		p value
	Survivor (n=91)	Non - survivor (n=13)	
Age	51, 5 (21 - 86)	64 (22 - 78)	**0, 005[a]**
Gender Male Female	42 (54, 7%) 50 (54, 3%)	7 (53, 8%) 6 (46, 2%)	0, 579[b]
Comorbidity No Yes	35 (38%) 57 (62%)	0 (0%) 13 (100%)	**0, 004[c]**
CT Value D - dimer CRP Length of stay	19, 26 (0 - 36, 27) 537, 55 (0 - 10.000) 25 (0 - 200) 9 (1 - 20)	19, 79 (14, 61 - 34, 51) 3.522, 4 (3.72,6-10.000) 74 (20 - 150) 6 (1 - 10)	0, 395[a] **0, 001[a]** **0, 003[a]** **0, 001[a]**

Note: [a]Mann - whitney test; [b]Chi - Square test; [c]Fisher exact test

Table 5: Comorbidity of the patient based on the outcome

Comorbidity (N=70)	Outcome		p value
	Survivor	Non - survivor	
DM No Yes	79 (85, 9%) 13 (14, 1%)	8 (61, 5%) 5 (38, 5%)	0, 045[c]
Hypertension No Yes	78 (84, 8%) 14 (15, 2%)	11 (84, 6%) 2 (15, 4%)	1, 000[c]
Heart disease No Yes	79 (85, 9%) 13 (14, 1%)	7 (53, 8%) 6 (46, 2%)	0, 012[c]
Stroke No Yes	92 (100%) 0 (0%)	12 (92, 3%) 1 (7, 7%)	0, 124[c]
Kidney disease No Yes	84 (91, 3%) 8 (8, 7%)	8 (61, 5%) 5 (38, 5%)	0, 010[c]
Pregnancy No Yes	86 (93, 5%) 6 (6, 5%)	13 (100%) 0 (0%)	1, 000[c]
Asthma No Yes	90 (97, 8%) 2 (2, 2%)	13 (100%) 0 (0%)	1, 000[c]

Factors that contributed to severity of illness

There is significant correlation between gender, comorbid of diabetes mellitus, and D - dimer level with the severity of illness in COVID-19 infections. The majority of patients with severe - critical illness were male (65.5%) and most of the patient with moderate illness were female (60.5%). The proportion of diabetes mellitus in patient with severe - critical illness significantly higher compared with patient with moderate illness. The D - dimer level in patient with severe - critical illness significantly higher compared with the patient with moderate illness ($p<0.05$).

Table 6: The characteristic of patient based on the severity of illness

Characteristic	Severity		p value
	Moderate illness (n=76)	Severe - Critical illness (n=29)	
Age	52 (22 - 86)	55 (21 - 74)	0, 259[a]
Gender Male Female	30 (39, 5%) 46 (60, 5%)	19 (65, 5%) 10 (34, 5%)	**0, 017[b]**
Comorbidity No Yes	28 (36, 8%) 48 (63, 2%)	7 (24, 1%) 22 (75, 9%)	0, 217[b]

	CT Value D - dimer CRP Length of stay	19, 265 (0 - 36, 27) 513 (0 - 7170, 60) 23, 5 (0 - 130) 8 (1 - 19)	19, 79 (0 - 31, 89) 1214, 8 (0 - 10.000) 63 (0 - 200) 7 (1 - 20)	0, 986[a] **0, 001[a]** 0, 13[a] 0, 623[a]

Note: [a]Mann - whitney test; [b]Chi - Square test; [c]Fisher exact test

Table 7: Comorbidity based on the severity of illness

Comorbidity (N=70)	Severity		p value
	Moderate illness (n=76)	Severe - critical illness N= (29)	
DM No Yes	79 (85, 9%) 13 (14, 1%)	8 (62, 9%) 5 (38, 5%)	0, 045[c]
Hypertension No Yes	67 (88, 2%) 9 (11, 8%)	22 (75, 9%) 7 (24, 1%)	0, 135[c]
Heart disease No Yes	64 (84, 2%) 12 (15, 8%)	22 (75, 9%) 7 (24, 1%)	0, 320[b]
Stroke No Yes	76 (100%) 0 (0%)	28 (96, 6%) 1 (3, 4%)	0, 276[c]
Kidney disease No Yes	67 (88, 2%) 9 (11, 8%)	25 (86, 2%) 4 (13, 8%)	0, 750[c]
Pregnancy No Yes	70 (92, 1%) 6 (7, 9%)	29 (100%) 0 (0%)	0, 184[c]
Asthma No Yes	74 (97, 4%) 2 (2, 6%)	29 (100%) 0 (0%)	1, 000[c]

Multivariate Analysis

The multivariate analysis was done at the variables that showed significant result in bivariate analysis. The binary logistic regression was done as seen in table 8. The result showed that age, D - dimer level, length of stay, and vaccination status significantly correlated with the outcome. The vaccinated patient has the chance of 24 times higher to have a good outcome when infected by the SARS - CoV - 2 compared with unvaccinated patient.

Table 8: The binary logistic regression of the factors that correlated with the outcome

Variable	p value	Exp (B)	95% CI
Age	0, 045*	1, 101	1, 002 - 1, 209
D - dimer	0, 006*	1, 001	1, 000 - 1, 001
CRP	0, 225	1, 013	0, 992 - 1, 035
Length of stay	0, 006*	0, 574	0, 386 - 0, 855
Diabetes Mellitus	0, 103	10, 297	0, 624 - 169, 923
Heart disease	0, 926	1, 117	0, 109 - 11, 451
Kidney disease	0, 121	6, 462	0, 613 - 68, 168
Vaccination status	0, 048*	24, 061	1, 025 - 564, 786

The binary logistic regression was also done to show the factors that correlated with the severity of illness (table 9). The result showed gender and D - dimer level correlated with the severity of illness. Male has the chance of 0.327 times to survive compared with female, or the chance of male to be a non - survivor higher than female.

Table 9: The binary logistic regression of factors that correlated to severity of illness

Variable	p value	Exp (B)	95% CI
Vaccination status	0, 230	1, 925	0, 661 - 5, 610
Diabetes mellitus	0, 722	1, 253	0, 361 - 4, 351
D - dimer	0, 001*	1, 000	1, 000 - 1, 001
Gender	0, 032*	0, 327	0, 118 - 0, 909

4. Discussion

The immune response to SARS - CoV - 2 infection includes innate immune activation and specific responses of B and T cells. Protection from viral infections usually acquired when virus - neutralizing antibodies achieved by adaptive immune response due to infection or vaccination. These antibodies blocked the receptor of the virus on the cell host or by preventing the fusion of virus with the cell membrane[8].

Titer neutralizing antibodies were significantly increased parallel with the severity of clinical manifestations. The inflammatory response progresses with the more antibodies are produced, hence the highest titer of neutralizing response observed in a patient hospitalized in intensive care unit. At the time when reinfection occur the antigenic - specific memory B cells rapidly arise as it improving the immunological efficiency[9].

The level of plasma viremia was associated with disease severity and mortality. Systemic circulation of SARS - CoV - 2 virions may contribute to extra - pulmonary and vascular complications. In addition, some patients may have severe to a life - threatening manifestation as a result of overactive immune response which is more destructive than the infection it self. Activation of innate and adaptive immunity caused production of pro - inflammatory cytokines and chemokine. In some occasion, this immune activation becomes massive and resulting in cytokine storm that caused thrombotic tendency, multi organ failure, and eventually death[10, 11, 12].

Some proposed predisposing factors for cytokine storm in COVID-19 are (1) Impaired viral clearance as the virus may have some strategies to avoid host defense mechanism; (2) Low levels of type I interferon. Type I interferon is crucial for anti viral response and viral clearance as it play a role at recognizing viral nucleic acid; (3) Increased neutrophil extracellular traps (NETs); (4) Miscellaneous other mechanism. Pyroptosis lead to massive release of inflammatory cytokines as the caused of rapid viral replication[11, 12].

In a study conducted by Trimaille *et al.* showed D - dimer levels reflected the severity of illness in COVID-19 patient, in accordance to our result that D - dimer levels are strongly correlated with the severity of illness (p= 0.001; 95% CI: 1.000 - 1.001) and outcomes (p= 0.006; 95% CI: 1.000 - 1.001) in COVID-19 patients regardless of vaccination status. In line with the study conducted by Atmaja, K. S. *et al.* in Wangaya General Hospital Denpasar, found that D - dimer level was strongly correlated with others inflammatory biomarker in COVID-19 such as CRP level and NLR (Neutrophil to Lymphocyte Ratio) with mean concentration of 2709 ng/mL. Vascular endothelial injury or damage due to binding of viral and ACE - 2 receptor proposed as the thrombotic tendency in COVID-19 infection. Alveolar capillary micro - thrombi are higher in COVID-19 lungs. It may lead to clinical manifestation mimicking disseminated intravascular coagulopathy (DIC) with elevated D - dimer levels[11, 13, 14, 15].

In our study, the vaccination group patient has received the vaccine of CoronaVac and ChAdOx1 nCoV - 19. The patient who received CoronaVac vaccine were fully vaccinated with 2 doses, and patient who received ChAdOx1 nCoV - 19 vaccine were only have the first dose. We found that vaccination status was significantly correlated with the outcomes (p= 0, 048; 95% CI: 1, 025 - 564, 786; OR= 0.20). Patient who have been vaccinated are 24 times higher to survive when infected by SARS - CoV - 2 compared with unvaccinated. On bivariate analysis there is a significant correlation between vaccination status with severity of illness (p= 0.017), but in multivariate anlysis there is no significant corelation between vaccination status and severity of illness. However, vaccination have a protective effect against severe - critical illness (OR=0.318; p= 0.017) and mortality (OR= 0.20; p=0.032) when infected by SARS - CoV - 2.

The vaccines used several mechanism of action to trigger immune responses. ChAdOx1 nCov - 19 is based on adenovirus vectors vaccine. It is a non - replicating viral vectors and it may boost the immune response without adjuvants. This vector will raise immune response and mimicking the real infection by expression of transgene products. The use of non - replicating viral vectors will allow the signaling pathways such as antibody development and a potent T cell cytotoxic response to kill infected cells. The epitopes of the vector presented by APC with MHC class I and II. The induction of T cell memory is by reactivation of anti - adenovirus effector memory cells, as the fact that most of the adults have been infected by several adenoviruses[16, 17].

CoronaVac is an inactivated vaccine, where the virus is non infective while maintaining the immunogenicity with high quality antigens to generate immune response. The mechanism of immune activation was similar to ChAdOx1 nCov - 19. Activation of monocyte generate IFN expression which activates CD4+ T cells, increase antibody secretion by B cell activation, and activates CD8+ cells which will promote killing the infected cells. Sero - conversion following CoronaVac vaccines achieve in 92.4% of participants after 2 weeks and 97.4% 4 weeks after the second dose. The titer of antibodies found to be high in 6 weeks after administration[17].

In a large observational study conducted by Alejandro Jara *et. al.* in Chile with 10.2 million subject found that CoronaVac vaccine effectiveness among fully vaccinated person is 72.9% for prevention of COVID-19 infection, 89.2% for prevention of hospitalization, 91.6% for the prevention of ICU admission and 87.8% for prevention of COVID-19 related death[18]. In a study that conducted by Vasileiou *et. al.* in Scotland found that vaccine effectiveness of ChAdOx1 at 28 - 34 days for preventing hospital admissions was 88% after receiving the first dose in general

population[19]. A study in the UK found that vaccine effectiveness of general population after receiving first dose of ChAdOx1 is 65 - 73% for preventing SARS - CoV - 2 infection[20].

However, SARS - CoV - 2 is known to mutate, particularly in the S glycoprotein which is the key of antibody epitopes, arising in different virus variants, therefore the immune protection may be compromised[9]. Bernal, J. L. et al. found that effectiveness of ChAdOx1 nCoV - 19 vaccine among patients with alpha variant and delta variant was 74.5% and 67.0% after the second dose, respectively. Whereas, in any vaccine, the effectiveness after first dose administration was 48.7% among person infected with alpha variant and 30.7% with delta variant. Vaccine effectiveness of CoronaVac after two doses administration during gamma variant epidemic in Brazil was found to be 47% against symptomatic COVID-19, 56% against hospital admission, and 61% against COVID-19 death in patient aged $\geq$ 70 years old[21, 22].

Our study had several limitations. We measured vaccine effect against COVID-19 among hospitalized patients. Our government policy limits the hospitalized patient only for moderate to severe - critical diseases. Therefore, patient with asymptomatic or mild diseases were not included in this study. Furthermore, this study was conducted with limited period of time, besides some of the data was not completed with history of vaccination status, these may resulted in potential bias.

5. Conclusion

COVID-19 vaccines play a critical role in this devastating pandemic situation. Vaccinated patients have shown good outcomes when infected by SARS - CoV - 2 compared with the unvaccinated patients. Even though in this study, the vaccination status revealed no significant correlation with the severity of illness, but it showed strong correlation with the outcomes. Several studies showed high vaccine effectiveness for preventing hospital admission, severe disease and COVID-19 related death. In line with our study, vaccination had preventive effect against severe - critical illness and mortality when infected by SARS - CoV - 2.

6. Ethical Clearance

Our study was approved by ethical committee of Wangaya General Hospital, Denpasar, Bali.

7. Author Contribution Statement

All of author contributed equally.

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