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Original Article

# The COVIDTW2 study: Role of COVID-19 vaccination in intubated patients with COVID-19-related acute respiratory distress syndrome in Taiwan

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ABSTRACT

*Background:* COVID-19 vaccines have reduced the risk of disease progression to respiratory failure or death. However, in patients with breakthrough infections requiring invasive mechanical ventilation, the effect of prior COVID-19 vaccination on mortality remains inconclusive.
*Method:* We retrospectively analyzed data on patients intubated due to COVID-19 pneumonia between May 1, 2022 and October 31, 2022. Receipt of two or more doses of vaccine were considered as fully vaccinated. The primary outcome was the time from intubation to all-cause intensive care unit (ICU) mortality.
*Result:* A total of 84 patients were included (40 fully vaccinated versus 44 controls). The baseline characteristics, including age, comorbidities, and Sequential Organ Failure Assessment (SOFA) score on the day of intubation were similar between the two groups. The difference in ICU mortality rate between the fully vaccinated and control groups was not significant (35 % vs. 25 %, P = 0.317; hazard ratio with 95 % confidence interval = 1.246 (0.575–2.666), P = 0.571). The SOFA score (hazard ratio: 1.319, P = 0.001) and body mass index (BMI) (hazard ratio: 0.883, P = 0.022) were significantly associated with ICU mortality.
*Conclusion:* Being fully vaccinated was not associated with a mortality benefit in intubated patients with COVID-19. A higher SOFA score on the day of intubation and lower BMI were poor prognostic factors.

## 1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic began in China in December 2019. By the end of February 2023, more than 758 million confirmed cases and 6.8 million deaths had been reported globally [1]. The response to the COVID-19 pandemic has lasted for more than 3 years. COVID-19 vaccine is one of the most effective methods to lower the risk of infection and the mortality rate. COVID-19 vaccines reduce the risk of hospitalization, intensive care unit (ICU) admission, and disease progression to mechanical ventilation or death [2–4]. However, a small proportion of vaccinated patients with breakthrough severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection develop respiratory failure and require invasive mechanical ventilation. The benefits of vaccination in reducing mortality in intubated patients remain unclear. Several studies have investigated the impact of vaccination on critically ill patients (intubated or non-intubated upon ICU admission) [3,5,6]. To the best of our knowledge, only one multi-center study in Greece had evaluated the effect of COVID-19 vaccination on mortality in exclusively intubated patients with COVID-19 pneumonia (all patients were intubated at ICU admission) [7]. In addition, previous studies that investigated the effectiveness of vaccination in critically ill patients with COVID-19 were conducted during the period when the Delta variant was predominant [3,5–7]. Limited data are available on the effectiveness of vaccination in patients infected with the Omicron variant.

The first wave of the COVID-19 epidemic in Taiwan last from May to July 2021. According to data from the Taiwan Centers for Disease Control, approximately 14,000 patients were diagnosed with COVID-19 during the first wave [8]. Owing to robust public health policy, the second wave of the COVID-19 epidemic in Taiwan began in May 2022

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(approximately 10 months after the end of the first wave). The second wave was much larger than the first wave. The highest number of newly confirmed cases in a single day was 80,845 on May 28, 2022 (approximately six times as many as the total cases in the first wave). By the end of February 2023, approximately 10,000,000 cumulative cases of COVID-19 had been reported in Taiwan. Since early 2022, the predominant COVID-19 variant in Taiwan has been the Omicron variant [8]. We have previously published the COVIDTW study on the first wave of the COVID-19 epidemic (Alpha variant predominant) in Taiwan [9]. The current study analyzed the second wave of COVID-19 epidemic (Omicron variant predominant) in Taiwan. Thus, it was named the COVIDTW2 study. We aimed to investigate the impact of COVID-19 vaccines on mechanically ventilated patients infected with the Omicron variant.

## 2. Materials and methods

We retrospectively reviewed the records of patients hospitalized with COVID-19 at Taipei Tzu Chi Hospital between May 1 and October 31, 2022. For each patient, the maximum follow-up duration was 4 months. All patients had COVID-19 confirmed by polymerase chain reaction. We focused on mechanically ventilated patients with COVID-19-related acute respiratory distress syndrome (ARDS) and excluded (1) patients <18 years and (2) patients who did not receive intubation and invasive mechanical ventilation. Patients who underwent invasive mechanical ventilation for major surgical procedures were also excluded. The day of intubation was considered as DAY 1 in the COVIDTW2 study. The COVIDTW2 adhered to the STROBE guidelines for observational studies.

We defined the fully vaccinated group as patients who received at least two doses of COVID-19 vaccine at least 14 days before intubation. Patients who were unvaccinated or had received only one dose of COVID-19 vaccine formed the control group. In the vaccination group, we calculated the interval from the last dose of vaccine to the day of intubation. During the study period, four types of COVID-19 vaccines {ChAdOx1-S (AstraZeneca), MVC-COV1901 (Medigen), mRNA-1273 (Moderna), and BNT162b2 (Pfizer-BioNTech)} were available in Taiwan. The vaccines were categorized into three platforms: 1. replication-deficient chimpanzee adenovirus: ChAdOx1-S (AstraZeneca), 2. RNA-based vaccines: mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech), and 3. protein subunit vaccine: MVC-COV1901 (Medigen) [10]. Patients in this study received various doses of different vaccine combinations according to the guidelines of the Taiwan Centers for Disease Control [8]. Therefore, the fully vaccinated group received different vaccine doses with different combinations of vaccine platforms. Among these vaccines, Moderna, AstraZeneca, and Pfizer-BioNTech have substantial evidence of their efficacy. The MVC-COV1901 (Medigen) vaccine has been approved in four countries, including Taiwan. The interim results of a phase 3 trial revealed that the MVC-COV1901 (Medigen) vaccine has a higher neutralizing antibody and seroconversion rate, similar to that of the ChAdOx1-S (AstraZeneca) vaccine [11].

We collected data including age, sex, body mass index (BMI), smoking history, education level (the bachelor's degree or higher versus senior high school or lower), use of oral anti-viral agents {nirmatrelvir and ritonavir (Paxlovid) or molnupiravir} prior to intubation, use of systemic corticosteroid (dexamethasone 6 mg once daily for up to 10 days), use of remdesivir prior to intubation, use of tocilizumab, bedridden status, comorbidities, the Sequential Organ Failure Assessment (SOFA) score on DAY 1, laboratory data on DAY 1, and ventilator parameters on DAY 1. Comorbidities included chronic lung disease, cardiovascular disease, stroke, end-stage renal disease (ESRD), advanced malignancy, autoimmune disease, diabetes mellitus, and hypertension. The comorbidities are described in detail in Appendix 1.

After intubation, patients typically underwent several blood tests within the first 24 h. To calculate the SOFA score on DAY 1, we utilized the most recent record available (i.e., data closet to day 2). BMI was classified into the following categories: underweight (<18.5 kg/m$^2$), healthy weight (18.5–24.9 kg/m$^2$), overweight (25–29.9 kg/m$^2$), obesity class I (30–34.9 kg/m$^2$), obesity class II (35–39.9 kg/m$^2$), and obesity class III (>40 kg/m$^2$).

The primary endpoint was the time from day of intubation to all-cause ICU mortality. The secondary endpoints were the time since the day of intubation to all-cause in-hospital mortality, all-cause ICU mortality, all-cause in-hospital mortality, length of ICU and hospital stay among survivors, duration of IMV among survivors, bacteremia, use of neuromuscular blocking agents, sedative agents, and vasopressors. Sedative agents included continuous intravenous infusion of benzodiazepines and opioids. Vasopressors included norepinephrine, vasopressin, and dopamine.

## 3. Statistical analysis

P values $< 0.05$ were considered statistically significant. Data were expressed as median with interquartile range (IQR) or number with percentage. We also computed the 95 % confidence interval (CI) of the odds ratio (OR) or hazard ratio (HR). The Mann-Whitney *U* test was used to compare the distributions of continuous variables. The Chi-square test or Fisher's exact test were used to compare proportions of categorical variables, as appropriate.

We plotted the Kaplan-Meier survival curves of the fully vaccinated and control groups. The log-rank test was used to compare the survival probabilities of the two groups. We used the Cox proportional hazards regression model to plot the estimated survival curve and calculate the adjusted HR. The covariates in the multivariate Cox model included vaccination status, age, sex, SOFA score on DAY 1, BMI, number of comorbidities, and bedridden status. GraphPad Prism Version 9.5.1. (GraphPad Software, San Diego, CA, USA) was used to perform the analysis.

## 4. Ethical statements

The Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, approved the study (protocol number: 11-X-075) and waived the requirement for informed consent.

## 5. Results

Fig. 1 shows the enrollment and in-hospital mortality in the COVIDTW2 study. A total of 1558 patients were admitted to the hospital with COVID-19 during the study period. A total of 358 patients were aged <18 years. Among the 1200 adult patients, 106 were transferred to the ICU, and 1094 were treated in the general ward. The all-cause in-hospital mortality rate in the general ward was 6.85 % (75/1,094). Among the 106 patients admitted to the ICU, we excluded 10 patients who were not intubated and 12 patients who received intubation for major surgical procedures. A total of 84 patients intubated due to COVID-19 pneumonia were included in the analysis, of whom 40 patients were fully vaccinated, and the other 44 patients were assigned to the control group. The all-cause in-hospital mortality rates of the fully vaccinated (16/40 = 40 %) and control groups (17/44 = 39 %) did not differ significantly (P = 0.898).

In the control group (n = 44), 40 patients were unvaccinated, and 4 patients had received only one dose of vaccine. The number of doses of vaccine is reported in detail in Appendix-2. The number of doses of vaccine received was not associated with ICU mortality or in-hospital mortality (Appendix-3).

Table 1 shows the baseline characteristics of the fully vaccinated and control groups. In the fully vaccinated group, the median time from receiving the last dose of vaccine to endotracheal intubation was 129 days. There were no statistically significant differences between the two groups in age, sex, BMI, smoking, education, use of oral antiviral medications, systemic corticosteroids, remdesivir, and tocilizumab,

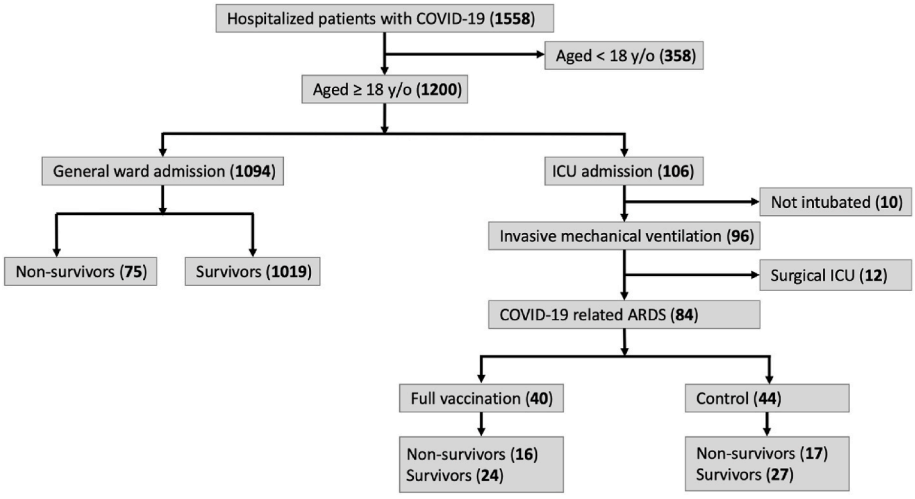


**Fig. 1.** Study enrollment and outcomes We enrolled patients with COVID-19 who were hospitalized between May 1 and October 31, 2022. Patients aged <18 years were excluded. Among 106 patients admitted to the intensive care unit, 10 patients did not receive endotracheal intubation and 12 patients were admitted to the surgical intensive care unit for reasons other than pneumonia. The measure of survival was based on in-hospital mortality.

bedridden status, comorbidities, SOFA score on DAY 1, laboratory data on DAY 1, and ventilator parameters on DAY 1 except for the respiratory rate. The median respiratory rate of the fully vaccinated group was significantly lower than that of the control group (16 breaths/min versus 18 breaths/min; P = 0.026).

Table 2 shows the result of the Cox proportional hazards regression model of ICU survival. The difference in survival between the fully vaccinated and control groups was not statistically significant (HR: 1.246, 95 % CI: 0.575–2.666, P = 0.571). A higher SOFA score on DAY 1 and lower BMI were significantly associated with an increased risks of ICU mortality.

Table 3 shows the secondary outcomes. None of the secondary outcomes differed significantly between the two groups. The all-cause ICU mortality rates of the fully vaccinated and control groups were 35 % and 25 %, respectively (P = 0.317). The fully vaccinated group had a lower rate of bacteremia than the control group (however, not statistically significant). For survivors, there was a trend that the fully vaccinated group had a shorter length of ICU stay, hospital stay, and IMV treatment than the control group.

Fig. 2A shows the Kaplan-Meier plot of the ICU survival curve of the fully vaccinated and control groups. The P value of the log-rank test was 0.796. Fig. 2B shows the estimated ICU survival curve by Cox proportional hazards regression model. The covariates in the Cox model included vaccination status, age, sex, SOFA score on DAY 1, BMI, number of comorbidities, and bedridden status. The HR of the fully vaccinated group relative to the control group was 1.246 (95 % CI: 0.575–2.666; P = 0.571). Fig. 3A shows the Kaplan-Meier plot of the in-hospital survival curve of the fully vaccinated and control groups. The P value of the log-rank test was 0.760. Fig. 3B shows the estimated in-hospital survival curve obtained using the Cox proportional hazards regression model. The hazard ratio of the fully vaccinated group relative to the control group was 1.231 (95 % CI: 0.595–2.549; P = 0.572).

The Appendix-4 shows the proportion of patients by BMI class and the corresponding vaccination status and in-hospital mortality rates. None of the patients had a BMI $\geq$35 kg/m$^2$ (obesity class II or III).

Six different vaccine combinations were administered to the fully vaccinated group. The corresponding mortality rates for different vaccine combinations are summarized in Appendix-5. The effect of different combinations of vaccine platforms on mortality was not statistically significant (P = 0.127).

## 6. Discussion

The COVIDTW2 study investigated the second wave of the COVID-19 epidemic (Omicron variant) in Taiwan from May 1 to October 31, 2022. The COVIDTW2 study showed that: (1) full vaccination did not improve all-cause ICU mortality of mechanically ventilated patients with COVID-19 pneumonia compared with the control group; (2) a higher SOFA score on the day of intubation and lower BMI were associated with higher mortality. To the best of our knowledge, only two studies (COVIDTW2 and a multi-center study from Greece [7]) have evaluated the association between vaccination status and mortality in exclusively intubated patients with COVID-19 pneumonia (all patients were intubated at ICU admission).

The effect of vaccination on the mortality of patients with COVID-19-related ARDS remains unclear. Three studies have reported that the vaccination status was not associated with improved mortality in critically ill patients (intubated and non-intubated at ICU admission) [3,5,6]. Despite both the Greek study conducted by Graspa et al. [7] and our study focused only mechanically ventilated patients upon ICU admission, our study demonstrated that a full vaccination status did not provide a significant survival benefit. In contrast, a multi-center study conducted in Greece by Graspa et al. found that a full vaccination status was associated with lower all-cause ICU mortality [7]. In that study, Grapsa et al. reported that the fully vaccinated group were older and had more comorbidities than the control group [7]. After adjusting for these unfavorable factors, vaccination still provided a survival advantage. The reasons for the different conclusions of these two studies are unclear. However, there are several differences in the study populations. First, the predominant SARS-CoV-2 variants were Delta and Omicron in the Greek study and the COVIDTW2 study, respectively. An English study found that the Omicron variant was less virulent and that patients had a lower rate of severe outcomes than those infected with the Delta variant [12]. Second, patients in the COVIDTW2 study had a higher SOFA score on the day of intubation (median: 7 versus 5), an older age (median: 78 versus 66 years), and a higher prevalence of comorbidities (88 % versus 69 %) than patients in the Greek study. Age [6,7,12], SOFA score [7], and comorbidities [6] are risk factors for severe outcomes. These confounding factors may have affected the mortality outcomes.

In this study, the fully vaccinated and control groups had similar baseline characteristics. In contrast, in studies conducted in Western countries among critically ill or intubated patients with COVID-19, fully vaccinated patients are generally older and have more comorbidities than those in the control group [3,4,6,7]. The relatively small sample

**Table 1**
Baseline characteristics of mechanically ventilated patients with COVID-19 pneumonia.

| Characteristics | All n = 84 (100 %) | Fully vaccinated group n = 40 (48 %) | Control group n = 44 (52 %) | P value |
|---|---|---|---|---|
| Time from the last dose of COVID-19 vaccine to intubation, median (IQR), days | N/A | 129 (109–226) | N/A | N/A |
| Age, median (IQR), years old | 78 (68–85) | 78 (63–86) | 78 (70–85) | 0.321 |
| Sex (male), No. (%) | 42 (50) | 20 (50) | 22 (50) | 1.000 |
| Body Mass Index, median (IQR) | 22 (19–26) | 23 (19–27) | 22 (19–25) | 0.401 |
| Smoking, No. (%) | 17 (20) | 10 (25) | 7 (16) | 0.416 |
| Education, No. (%) @ | 10 (12) | 4 (10) | 6 (14) | 0.741 |
| Use of oral antiviral agents, No. (%) & | 8 (10) | 4 (10) | 4 (9) | 1.000 |
| Use of systemic corticosteroid, No. (%) | 77 (92) | 36 (90) | 41 (93) | 0.704 |
| Use of Remdesivir, No. (%) | 80 (95) | 39 (98) | 41 (93) | 0.618 |
| Use of Tocilizumab, No. (%) | 26 (31) | 13 (33) | 13 (30) | 0.770 |
| Bedridden status, No. (%) | 6 (7) | 3 (8) | 3 (7) | 1.000 |
| Comorbidities, No. (%) # | | | | |
| Any | 74 (88) | 37 (93) | 37 (84) | 0.319 |
| Numbers of comorbidities, median (IQR) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 0.982 |
| Chronic lung disease [a] | 13 (15) | 7 (18) | 6 (14) | 0.765 |
| Cardiovascular disease [b] | 25 (30) | 11 (28) | 14 (32) | 0.666 |
| Stroke [c] | 20 (24) | 8 (20) | 12 (27) | 0.456 |
| ESRD [d] | 9 (11) | 7 (18) | 2 (4) | 0.166 |
| Advanced malignancy [e] | 8 (10) | 5 (13) | 3 (7) | 0.469 |
| Autoimmune disease [f] | 3 (4) | 1 (3) | 2 (5) | 1.000 |
| Diabetes mellitus | 35 (42) | 13 (33) | 22 (50) | 0.104 |
| Hypertension | 44 (52) | 22 (55) | 22 (50) | 0.647 |
| SOFA score on DAY 1 + | 7 (5–10) | 7 (5–9) | 7 (5–10) | 0.849 |
| Respiration | 1 (0–2) | 1 (0–2) | 1 (0–2) | 0.356 |
| Coagulation | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0.475 |
| Liver | 0 (0–1) | 0 (0–0) | 0 (0–0) | 0.428 |
| Cardiovascular | 1 (0–2) | 1 (0–2) | 1 (0–2) | 0.585 |
| GCS | 3 (2–3) | 3 (2–4) | 3 (2–3) | 0.469 |
| Kidney | 1 (0–2) | 1 (0–3) | 1 (0–2) | 0.682 |
| Laboratory data on DAY 1 + | | | | |
| WBC, median (IQR), $*10^3/\mu L$ | 10.9 (7.2–15.1) | 10.8 (7.2–15.1) | 11.4 (7.0–15.0) | 0.906 |
| Neutrophil, median (IQR), % | 87 (79–91) | 88 (78–91) | 85 (76–92) | 0.511 |
| Lymphocyte, median (IQR), % | 6 (2–12) | 5 (2–9) | 6 (3–13) | 0.310 |
| NL ratio, median (IQR) | 16 (7–46) | 17 (7–48) | 14 (6–32) | 0.453 |
| Platelet, median (IQR), $*10^3/\mu L$ | 196 (120–283) | 232 (141–284) | 188 (111–282) | 0.260 |
| CRP, median (IQR), mg/dL | 9 (2–14) | 6 (2–14) | 9 (2–17) | 0.434 |
| Lactate, median (IQR), mmol/L | 2.1 (1.2–3.2) | 2 (1.1–3.5) | 2.2 (1.2–3.1) | 0.470 |
| D-dimer, median (IQR), mmol/L | 2247 (1215–5150) | 1742 (1250–3590) | 2789 (1079–6019) | 0.316 |
| hs Troponin-I, median (IQR), pg/mL | 55 (24–269) | 41 (23–129) | 100 (27–350) | 0.122 |
| Ventilator parameters on DAY 1 + | | | | |
| FiO2, median (IQR), % | 60 (40–93) | 43 (40–54) | 45 (36–60) | 0.759 |
| PH, median (IQR) | 7.42 (7.36–7.46) | 7.42 (7.37–7.46) | 7.42 (7.34–7.45) | 0.864 |
| PaO2, median (IQR), mmHg | 172 (120–225) | 163 (111–216) | 180 (124–233) | 0.339 |
| PaO2:FiO2, median (IQR) | 288 (191–383) | 272 (194–381) | 308 (182–385) | 0.807 |
| PaCO2, median (IQR), mmHg | 35 (30–41) | 36 (31–40) | 35 (27–42) | 0.594 |
| HCO3, median (IQR), mmHg | 22.2 (19–25.4) | 23 (20–27) | 21 (18–25) | 0.138 |
| Tidal volume, median (IQR), mL | 509 (450–583) | 512 (447–582) | 505 (437–587) | 0.760 |
| RR, median (IQR), breath/min | 18 (15–21) | 16 (14–20) | 18 (16–20) | 0.026 |
| PEEP, median (IQR), cm H2O | 8 (6–8) | 8 (6–8) | 8 (8–8) | 0.363 |
| PC level, median (IQR), cm H2O | 18 (14–20) | 16 (14–19) | 18 (16–20) | 0.107 |
| PIP, median (IQR), cm H2O | 25 (22–28) | 24 (21–28) | 26 (24–28) | 0.149 |
| Pmean, median (IQR), cm H2O | 12 (11–15) | 12 (11–15) | 13 (12–15) | 0.230 |
| Cdyn, median (IQR), mL/cmH2O | 43 (30–53) | 39 (29–50) | 45 (30–55) | 0.374 |

Abbreviations: IQR, interquartile range; N/A, not applicable; ESRD, end-stage renal disease; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Score; WBC, white blood cell; NL ratio, neutrophil to lymphocyte ratio; CRP, C-reactive protein; hs, high sensitivity; FiO2, fraction of inspiratory oxygen; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; RR, respiratory rate; PEEP, positive end expiratory pressure; PC, pressure control; PIP, peak inspiratory pressure; Pmean, mean airway pressure; Cdyn, dynamic compliance.

Data are presented as median ± interquartile range or number (percentage).

@: Bachelor's degree or higher.

&: Oral antiviral agents include nirmatrelvir and ritonavir (Paxlovid) and molnupiravir.

#: The comorbidities are expressed as number (percentage), except for the number of comorbidities.

+: DAY 1 was defined as the day of intubation.

[a] Chronic lung disease includes chronic obstructive pulmonary disease and asthma.

[b] Cardiovascular disease includes congestive heart failure, coronary artery disease status post percutaneous coronary intervention or coronary artery bypass graft, valvular heart disease status post operation, and arrhythmia (atrial fibrillation, atrial flutter, and sick sinus syndrome).

[c] Stroke includes ischemic and hemorrhagic stroke.

[d] ESRD denotes end-stage renal disease requiring renal replacement therapy.

[e] Advanced malignancy includes malignancy (colon cancer, cholangiocarcinoma, lung cancer, hepatocellular carcinoma, pancreatic cancer, and renal cancer) with local invasion or distant metastasis.

[f] Autoimmune disease includes systemic lupus erythematosus, bullous pemphigoid, and myasthenia gravis.

**Table 2**
Cox proportional hazards regression model analysis of survival after admission to the intensive care unit.

| Risk factors | Hazard ratio with 95 % CI | P value |
|---|---|---|
| Full vaccination status vs Control | 1.246 (0.575–2.666) | 0.571 |
| Age | 0.976 (0.943–1.010) | 0.150 |
| Sex (female vs male) | 1.108 (0.516–2.365) | 0.789 |
| SOFA score on DAY 1 | 1.319 (1.150–1.526) | 0.001 |
| Body mass index | 0.883 (0.790–0.978) | 0.022 |
| Number of comorbidities | 1.108 (0.803–1.524) | 0.527 |
| Bedridden status | 2.135 (0.469–7.016) | 0.256 |

Abbreviations: SOFA, sequential organ failure assessment.

**Table 3**
Secondary outcomes.

| Outcomes | All n = 84 (100 %) | Fully vaccinated group n = 40 (48 %) | Control group n = 44 (52 %) | P value |
|---|---|---|---|---|
| ICU mortality, No. (%) | 25 (30) | 14 (35) | 11 (25) | 0.317 |
| In-hospital mortality, No. (%) | 33 (39) | 16 (41) | 17 (38) | 0.898 |
| Length of ICU stay among survivors, median (IQR), days | 23 (11–34) | 15 (9–33) | 30 (13–35) | 0.134 |
| Length of hospital stay among survivors, median (IQR), days | 36 (17–59) | 34 (17–56) | 39 (23–66) | 0.406 |
| Duration of IMV among survivors, median (IQR), days | 17 (9–35) | 14 (8–32) | 22 (9–35) | 0.473 |
| Bacteremia, No. (%) | 17 (20.2) | 5 (12.5) | 12 (27.2) | 0.110 |
| Use of NMBA, No. (%) | 24 (28.6) | 10 (25.0) | 14 (31.8) | 0.490 |
| Use of sedative agents, No. (%) | 58 (69) | 27 (67.5) | 31 (70.5) | 0.770 |
| Use of vasopressors, No. (%) | 54 (64.3) | 26 (65.0) | 28 (63.6) | 0.896 |

Abbreviations: IMV, invasive mechanical ventilation; NMBA, neuromuscular blocking agents.
Sedative agents include continuous intravenous infusion of benzodiazepines and opioids.
Vasopressors include norepinephrine, vasopressin, and dopamine.

size of the COVIDTW2 study, purely Asian population, and relatively high full vaccination rate (85.8 %) in Taiwan [13] may explain why the results of the COVIDTW2 study differ from those of previous studies. At the beginning of study enrollment, the full vaccination rates in different countries were 12.5 % [14], 22.8 % [14], 53.9 % [14], and 64.3 % [3] in the United States [4], Greece [7], Italy [6], and Switzerland [3], respectively. Globally, health policy has prioritized high-risk people with older age and multiple comorbidities to receive vaccination. A lower vaccination rate may result in more low-risk unvaccinated patients requiring IMV and ICU admission.

The current study found that a lower BMI and higher SOFA score on the day of intubation were associated with a higher mortality rate. Obesity is a well-established risk factor for severe COVID-19 outcomes. In addition to obesity, being underweight is also associated with COVID-19 mortality. Two review articles (conducted before initiation of mass vaccination) found a J-shaped relationship between BMI and mortality in unvaccinated patients suggesting that underweight and obese patients with COVID-19 have a higher risk of mortality than those with a healthy weight [15,16]. A population-based (9 million people) study in England also observed a J-shaped association between BMI and COVID-19 mortality in vaccinated patients [17]. Moreover, vaccine protection against severe outcomes (hospitalization or death) is less effective in underweight patients [17]. In the COVIDTW2 study, a large proportion of patients were underweight or had a healthy weight, and no patients had a BMI $\geq$35 kg/m$^2$. Hence, the mortality risk was skewed toward a lower

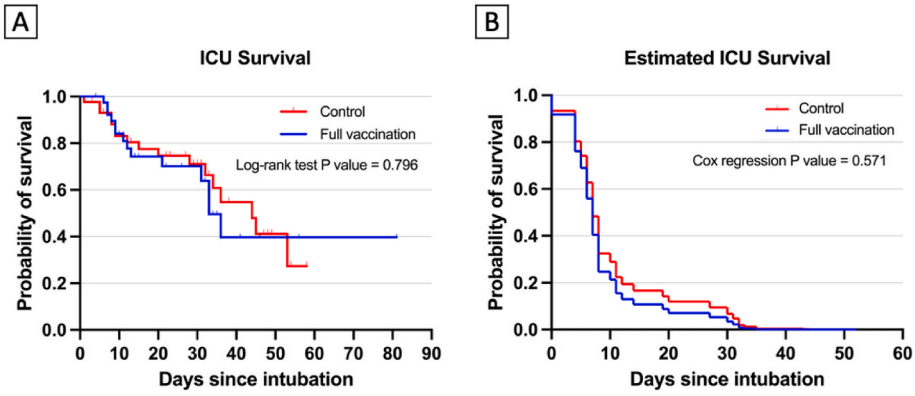


**Fig. 2.** Kaplan-Meier survival curve and estimated survival curve after admission to the intensive care unit (A) We used Kaplan-Meier analysis to plot the time since intubation to all-cause intensive care unit mortality in the fully vaccinated and control group. The P value of log-rank test was 0.796. (B) We used the Cox proportional hazards regression model to plot the estimated survival curves of the time since intubation to all-cause intensive care unit mortality of the two groups. The hazard ratio of the fully vaccinated group relative to control group was 1.246 (95 % confidence interval: 0.575–2.666; P = 0.571).

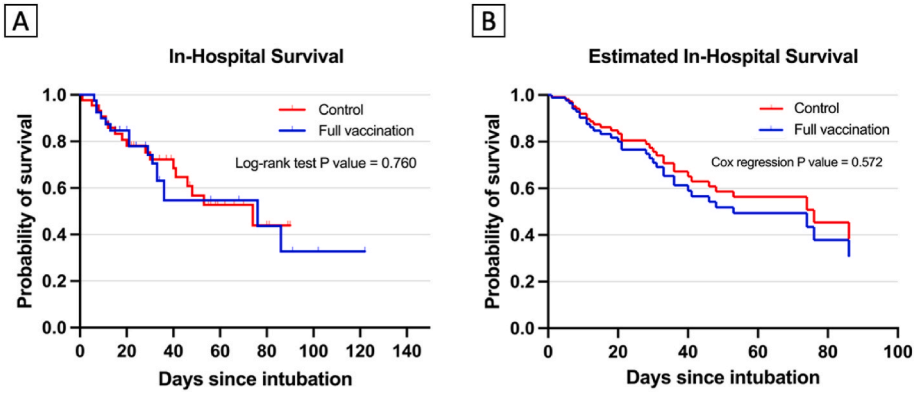


**Fig. 3.** Kaplan-Meier survival curve and estimated survival curve of in-hospital mortality (A) We used Kaplan-Meier analysis to plot the time since intubation to all-cause in-hospital mortality of the fully vaccinated and control group. The P value of log-rank test was 0.760. (B) We used the Cox proportional hazards regression model to plot the estimated survival curves of the time since intubation to all-cause in-hospital mortality between the two groups. The hazard ratio of the fully vaccinated group relative to control group was 1.231 (95 % confidence interval: 0.595–2.549; P = 0.572).

BMI. However, the prognostic value of the SOFA score in COVID-19 remains inconclusive [7,18–20]. Most research has shown a positive correlation between the SOFA score and mortality [7,19,20], but a multi-center ICU study conducted in the United States found that SOFA score did not have good prognostic value in patients with COVID-19 [18]. Previous studies have diverse enrollment criteria and recording time of the SOFA score [7,18–20]. In intubated patients with COVID-19-related ARDS, this study and the Greek study by Graspa et al. [7] both found that the SOFA score on the day of intubation was positively associated with mortality risk. Further research is required to assess the effect of the SOFA score on COVID-19 mortality.

In our study, we observed that the fully vaccinated group exhibited a lower respiratory rate upon ICU admission than that of the control group. An increased respiratory rate at admission was identified as a significant predictor of COVID-19 mortality [21]. However, few studies have investigated the relationship between respiratory rate and vaccination status in patients with COVID-19. Notably, in healthy participants receiving the Pfizer-BioNTech vaccine, the respiratory rate did not change significantly for up to 6 days following vaccination [22]. An Italian study [23] reported a similar finding as that of the COVIDTW2 study. Chiumello et al. observed that patients with COVID-19 who received vaccination exhibited a lower respiratory rate at admission than that of unvaccinated patients; however, the difference was not statistically significant [23]. Further studies are needed to investigate the underlying mechanism of the interaction between vaccination status and respiratory rate in patients with COVID-19.

## 7. Limitations

This study has some limitations. First, this study had the innate disadvantage of being a retrospective study. Second, the overall sample size in the COVIDTW2 study was relatively small. We did not observe a significant difference in the efficacy of multiple vaccine combinations. Therefore, a large-scale study is required to compare the efficacy of the combinations of multiple vaccine types in terms of survival. Third, there was a moderate time (approximately 4 months) from the last COVID-19 vaccine to intubation. Based on prior reports of the duration of vaccine effectiveness, this study did not define a time threshold for vaccine effectiveness. Tenfode et al. [4] reported that two doses of mRNA vaccine had an 84 % effectiveness at preventing IMV or death after 150 days. A study from Lombardy, Italy found that two doses of mRNA vaccine had an effectiveness of 79 %–91 % at preventing ICU admission after 120 days [6]. Another study from Qatar found that vaccination provided 94 % effectiveness at preventing ICU admission 12 months after two doses of mRNA vaccine [24].

## 8. Conclusions

This study found that (1) in mechanically ventilated patients with COVID-19 pneumonia, fully vaccinated patients did not have a lower all-cause ICU mortality compared with the control group; (2) a lower BMI and higher SOFA score on the day of intubation were significant risk factors for mortality.

## Declaration of competing interest

The authors declare no conflicts of interest.

The authors declare that the material contained in the manuscript has not been previously published and is not being concurrently submitted elsewhere.

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## Appendixes

*Appendix-1. Details of comorbidities*

a: Chronic lung disease includes chronic obstructive pulmonary disease and asthma.
b: Cardiovascular disease includes congestive heart failure, coronary artery disease status post percutaneous coronary intervention or coronary artery bypass graft, valvular heart disease status post operation, and arrhythmia (atrial fibrillation, atrial flutter, and sick sinus syndrome).
c: Stroke includes ischemic and hemorrhagic stroke.
d: ESRD denotes end-stage renal disease requiring renal replacement therapy.
e: Advanced malignancy includes malignancy (colon cancer, cholangiocarcinoma, lung cancer, hepatocellular carcinoma, pancreatic cancer, and renal cancer) with local invasion or distant metastasis.
f: Autoimmune disease includes systemic lupus erythematosus, bullous pemphigoid, and myasthenia gravis.

*Appendix-2. Number of doses of vaccine received*

| Doses of vaccine received | 0 | 1 | 2 | 3 | 4 | Total |
|---|---|---|---|---|---|---|
| Number of patients | 40 | 4 | 18 | 19 | 3 | 84 |
| Proportion | 40/84 (47.6 %) | 4/84 (4.8 %) | 18/84 (21.4 %) | 19/84 (22.6 %) | 3/84 (3.6 %) | 84/84 (100 %) |

*Appendix-3. The intensive care unit and in-hospital mortality rate according to the number of vaccine doses received*

| Doses of vaccine received | 0 | 1 | 2 | 3 | 4 | P value |
|---|---|---|---|---|---|---|
| ICU mortality rate | 10/40 (25 %) | 1/4 (25 %) | 6/18 (33 %) | 6/19 (32 %) | 2/3 (66 %) | 0.6318 |
| In-hospital mortality rate | 15/40 (38 %) | 2/4 (50 %) | 6/18 (33 %) | 8/19 (42 %) | 2/3 (66 %) | 0.8232 |

*Appendix-4. Proportion of patients by body mass index class and the corresponding full vaccination rate and in-hospital mortality rate*

| BMI classification; Total number = 84 | Underweight (<18.5 kg/m$^2$) | Healthy weight (18.5–24.9 kg/m$^2$) | Overweight (25.0–29.9 kg/m$^2$) | Obesity class I (30.0–34.9 kg/m$^2$) |
|---|---|---|---|---|
| No./total number (%) | 15/84 (18) | 45/84 (54) | 16/84 (19) | 8/84 (10) |
| Full vaccination rate (%) | 7/15 (47) | 20/45 (42) | 8/16 (50) | 5/8 (63) |
| In-hospital mortality rate (%) | 8/15 (47) | 18/45 (38) | 7/16 (44) | 0/8 (0) |

*Appendix-5. Vaccine platforms and corresponding ICU mortality rates in the fully vaccinated group*

| Vaccine types | AV | R | S | AV + R | AV + S | R + S | Total |
|---|---|---|---|---|---|---|---|
| Number of patients | 6 | 19 | 2 | 11 | 1 | 1 | 40 |
| ICU mortality, No. (%) | 0 (0) | 7 (37) | 0 (0) | 6 (55) | 1 (100) | 0 (0) | 14 (35) |

AV = adenovirus platform.
R= RNA-based platform.
S = protein subunit platform.
AV + R = adenovirus platform combined with RNA-based platform.
AV + S = adenovirus platform combined with protein subunit platform.
R + S = RNA-based platform combined with protein subunit platform.

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