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ORIGINAL RESEARCH

Comparison of Clinical Characteristics and Mortality Outcome in Critical COVID-19 Patients Infected with Alpha and Omicron Variants

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Objective: Early reports have indicated that the Omicron variant of coronavirus disease 2019 (COVID-19) may be associated with low mortality. However, the mortality rate of critical patients in Taiwan with COVID-19 caused by different variants has not been well described.

Methods: This retrospective cohort study was conducted at the Linkou Branch of Chang Gung Memorial Hospital, Taiwan, from April 2020 to September 2022. Critically ill patients who had confirmed SARS-CoV-2 infection and were on mechanical ventilation (MV) were enrolled. Demographic data, laboratory results, and treatment information were collected and analyzed. In addition, clinical outcomes for different SARS-CoV-2 variants were analyzed.

Results: This study included 110 critical patients with COVID-19 who required intubation and intensive care unit (ICU) admission. Among these patients, 46 (41.8%) required intensive care during Alpha predominance period and 64 (58.2%) during the Omicron predominance period. The Alpha group had a higher body mass index, had a longer ICU stay, and included more patients with acute respiratory distress syndrome, and the Omicron group included more active smokers, had more comorbidities, had worse initial laboratory data (including higher white blood cell counts, prothrombin time [PT], activated partial prothrombin time, blood urine nitrogen levels, and creatine levels), and had higher in-hospital mortality rates (40.6% vs 15.2%, $p = 0.004$). The independent risk factors for in-hospital mortality, were Charlson Comorbidity Index (CCI) ≥ 3 and higher PT and creatine levels.

Conclusion: Our study discovered that CCI ≥ 3, elevated serum creatine levels, and prolonged PT were independently associated with a high mortality rate in patients with critical COVID-19. Patients with those risk factors may require intensive monitoring during their treatment course.

Keywords: COVID-19, intensive care, CCI, Charlson Comorbidity Index, mortality

Background

Coronavirus disease 2019 (COVID-19), the outbreak of which was declared a pandemic by the World Health Organization on March 11, 2020, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of December 17, 2023, more than 772 million cases of COVID-19 have been confirmed worldwide, and the pandemic has resulted in more than 7 million deaths.[1] Since the emergence of the ancestral strains of SARS-CoV-2, five variants of concern have been identified: Alpha, Beta, Gamma, Delta, and Omicron. In Taiwan, three waves of COVID-19 occurred before 2023; these waves involved the Alpha and Omicron variants. The Alpha variant was the dominant variant from April to August 2021; the Delta variant caused only sporadic outbreaks between June and December 2021.[2] The Omicron

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variant led to two sustained waves of community transmission from January to December 2022.[3] The pandemic considerably affected health systems in Taiwan. As of March 2023, Taiwan has experienced >10 million confirmed COVID-19 cases and >19,000 associated deaths.[3]

Reports indicate that the Omicron variant is more transmissible and resistant to vaccine neutralization than other variants are.[4] Several studies have demonstrated that the Omicron variant is associated with significantly lower disease severity than other variants are in terms of hospitalization, oxygen requirements, mechanical ventilation, and death.[4] However, a substantial number of Omicron-infected patients exhibit severe COVID-19 symptoms and require intensive care support. Studies on patients admitted to ICUs for severe COVID-19 have reported no difference in in-ICU mortality or 28-day mortality between the Delta and Omicron variants.[5,6] By contrast, a study reported a higher mortality rate for Omicron-infected patients than for Alpha-infected patients.[5] In addition to the differences in the mortality rates among patients with severe COVID-19 who are infected with the Alpha and Omicron variants, evidence has indicated that these two variants differ in terms of the pathogenesis leading to severe disease.[7] However, little is known regarding the comorbid factors and clinical conditions related to the severity of different COVID-19 variants.

In an investigation of the risk factors for severe COVID-19 infection, older age, multiple or significant comorbidities, and a lack of immunization against SARS-CoV-2 were determined to be predictors of severe disease and unfavorable outcomes.[8] A study reported that having a higher number of comorbidities is linked to higher mortality.[9] In addition, the study reported that compared with patients infected with other variants, Omicron-infected patients had a higher rate of vaccination. Another study reported that patients hospitalized for COVID-19 during the Omicron wave were older and had more comorbidities than patients hospitalized for infection with other variants did.[10] A study also reported that the Omicron variant mostly causes severe disease in patients with impaired health status, and the Alpha variant can lead to severe disease in young patients without significant comorbidities.[11] These findings suggest distinct pathogeneses for these two SARS-CoV-2 variants. Nonetheless, there are limited studies directly comparing their mortality rates. The effects of underlying health conditions and baseline statuses have not been thoroughly explored. Therefore, there is a need for studies aiming to determine the impacts of underlying health condition and comorbidity on mortality outcomes of SARS-CoV-2 variants.

The present study compared the characteristics of critical patients hospitalized for COVID-19 during the Alpha- and Omicron-predominant periods of the pandemic in Taiwan and investigated possible predictors of mortality in patients with critical COVID-19 who are infected with these variants.

Materials and Methods

Study Design and Patient Selection

This retrospective cohort study was conducted at the Linkou Branch of Chang Gung Memorial Hospital in Taoyuan, Taiwan. The study period was April 2020 to September 2022, which covered the periods of the outbreaks of the Alpha (April to June 2021) and Omicron (from April 2022) variants in Taiwan. This study consecutively enrolled critical patients with PCR-confirmed SARS-CoV-2 infection. All patients were admitted to a specialized ICU for quarantine for COVID-19 infection. Patients were admitted to the ICU who (1) had acute respiratory failure requiring mechanical ventilation; (2) had elevated oxygen demand (requiring oxygen supplementation of simple mask 10 L per minute or higher, non-rebreathing mask or high-flow nasal oxygen) and were at risk of respiratory failure; (3) had dysfunction of at least one organ and required invasive care because of, for example, acute myocardial infarction, cerebral infarction, or intracranial hemorrhage; (4) underwent an operation and required intensive care; and (5) had hemodynamic instability requiring the use of vasopressors.[12] Prior to admission, each patient was evaluated by a pulmonologist to maintain consistency with the principles of clinical practice. Patients were excluded from this study if they were younger than 18 years or had a concurrent human immunodeficiency virus infection. The study was conducted in accordance with the Declaration of Helsinki. This retrospective evaluation of archived, anonymized patient data was approval by the Institutional Review Board of the Chang Gung Medical Foundation (IRB No. 202400546B0). The requirement for informed consent was waived because this was a retrospective study. Data were collected from electronic medical records and included laboratory data obtained within 24 hours of admission; these data served as the baseline data (day 0).

COVID-19 Management Protocol

The strategies employed for managing COVID-19 adhered to the Interim Guidelines for Clinical Management of SARS-CoV-2 Infection.[13] The strategies involved regular monitoring of vital signs and oxygen saturation (continuous monitoring for severe cases), providing enhanced supportive treatment, ensuring adequate caloric intake, and maintaining the stability of the internal environment (eg, ensuring sufficient water and electrolyte intake and acid–base balance). In patients presenting with hypoxemia, supplemental oxygen therapy was immediately administered. The target for oxygen saturation was a pulse oxygen saturation of 90%. If standard oxygen therapy failed, high-flow nasal catheter oxygen or noninvasive ventilation was used. If noninvasive mechanical ventilation did not yield benefits, invasive mechanical ventilation was initiated. Antiviral therapy and anti-inflammatory agents were administered in accordance with standardized guidelines. Remdesivir was administered to patients with an SpO_2 of 94% under room air or supplied oxygen. Low-dose dexamethasone (6 mg per day for no more than 10 days) was administered to patients with an SPO_2 of 94% under room air or supplied oxygen, those with respiratory failure, and those on extracorporeal membrane oxygenation. Tocilizumab was administered to patients with an SPO_2 of less than 94% under room air or supplied oxygen as well as those with respiratory failure or receiving extracorporeal membrane oxygenation. Antimicrobial agents (oral or intravenous) were prescribed according to the patient's condition. All medical expenses were covered by the National Health Insurance program in Taiwan. Antiviral and anti-inflammatory agents were supplied by the Taiwanese Centers for Disease Control and were administered in accordance with standard guidelines. Thus, the medical interventions across hospitals were highly homogeneous and consistently adhered to standard guidelines.

Data Collection and Measurement

We collected data from electronic medical records by using a case report form. We collected demographic data, including age, sex, underlying diseases, and laboratory data. Treatment information, such as the use of tocilizumab, remdesivir, dexamethasone, nirmatrelvir-ritonavir (Paxlovid), molnupiravir, and antibiotics, was also recorded. This study analyzed the clinical course and outcomes for each patient, including the use of mechanical ventilation; the occurrence of acute kidney injury, cardiac injury, and acute respiratory distress syndrome (ARDS); the length of ICU stay; the length of hospital stay; and in-hospital mortality. Fully vaccinated adults were defined as those who were not immunocompromised and had received the second dose of a two-dose COVID-19 vaccine series ≥14 days before receiving the positive SARS-CoV-2 test result associated with their hospitalization. Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes criteria.[14] ARDS was diagnosed by a pulmonologist on the basis of the Berlin definition.[15] Cardiac injury was defined on the basis of at least one assay revealing elevated high-sensitivity troponin-I levels.[16] The reason for admission was reviewed by 2 independent physicians. For admissions due to a positive SARS-CoV-2 RT-PCR result, COVID-19 was determined to be the reason for admission if the admitting provider confirmed COVID-19 infection or, in the absence of explicit confirmation, if the reviewers could not identify a clear alternative reason for admission that was not plausibly linked to SARS-CoV-2 infection. Alternative reasons for admission included uncomplicated labor, surgical procedure, trauma, psychiatric care, or medical diagnosis not plausibly linked to COVID-19 (eg, cellulitis, gastrointestinal bleeding, small bowel obstruction, osteomyelitis, and intra-abdominal infection). Exacerbations of chronic conditions (eg, congestive heart failure, chronic obstructive pulmonary disease, and asthma) were attributed to COVID-19. Any positive RT-PCR test result ≥7 days after the initial negative test result on admission was considered to indicate nosocomial SARS-CoV-2 infection; therefore, the admission was not attributed to COVID-19.

Statistical Analysis

The study results are presented as means with standard deviations or as numbers with percentages where appropriate. The independent Student's *t* test was used to compare continuous variables with a normal distribution. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables. Variables with a p value of less than 0.1 were included in univariate and multivariate logistic regression analyses conducted to identify the factors independently predicting in-hospital mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic regression model. Significance was determined by $p < 0.05$. Kaplan–Meier curves were constructed, and Log rank tests

were performed to assess the mortality rates for patients with high and low Charlson Comorbidity Index (CCI) values. Two-tailed tests were used, and $p < 0.05$ was considered to indicate significance. Receiver operating characteristic (ROC) curves for day 1 creatinine levels and PT values were plotted to predict the mortality outcome, and the respective areas under the ROC curves (AUROC) were calculated. Cut-off values were derived by the ROC curves using threshold values maximizing the sum of sensitivity and specificity. All statistical analyses were performed using IBM SPSS Statistics for Windows/Macintosh, version 27.0 (IBM, Armonk, NY, USA). All curves were generated using GraphPad Prism for Windows, version 9.0 (GraphPad Software, Boston, MA, USA).

Results

During the study period, 110 patients with COVID-19 met the inclusion criteria. Among these patients, 46 (41.8%) were infected with the Alpha variant, and 64 (58.2%) were infected with the Omicron variant. The average age was 66.39 ± 14.36 years, and 61.8% of the patients were men. Twenty-three patients (20.9%) were active smokers. Thirty-four patients (30.9%) had received adequate vaccination (two or more doses); however, none of the patients with Omicron infection had received vaccination because vaccines were not widely available in Taiwan until the end of June 2021. Forty-two patients (38.2%) were given a diagnosis of respiratory failure upon admission. Hypertension was the most common comorbidity, affecting 50.9% of patients. The majority of the patients (93.6%) received antibiotic treatment, and approximately half (56.4%) received remdesivir.

Clinical Outcomes

The results revealed an overall mortality rate of 30% (Table 1). The mortality rate was significantly higher in the Omicron group than in the Alpha group (40.6% vs 15.2%, OR: 3.81, 95% CI: 1.48–9.82, $p = 0.004$). In addition, 44 patients (40%) were given a diagnosis of acute kidney injury, and 11 patients (10%) had cardiac injury. The length of ICU stay was significantly longer in the Alpha group than in the Omicron group, averaging 28.63 ± 26.79 days versus 17.31 ± 16.44 days ($p = 0.013$). All patients infected with the Alpha variant were admitted due to COVID-19, whereas approximately half of patients in the Omicron group (31 patients, 48.4%) were admitted for COVID-19-related pneumonia; the remaining patients were admitted for other reasons, such as acute myocardial infarction, intracranial hemorrhage, and trauma. No significant differences were noted in the occurrence of respiratory failure or subsequent ARDS, AKI, or cardiac injury or the length of hospital stay between the Alpha and Omicron groups (Table 1).

Table 1 Clinical Outcomes Among Patients with COVID-19

	Total Cohort N=110	Omicron n=64	Alpha n=46	Relative Risk	95% C.I.	P value
High flow nasal cannula	16 (14.5)	9 (14.1)	7 (15.2)	0.91	0.31–2.66	0.865
Respiratory failure	93 (84.5)	47 (73.4)	46 (100)	1.36	1.18–1.58	<0.001*
ARDS	34 (30.9)	10 (15.6)	24 (52.2)	0.17	0.07–0.41	<0.001*
Acute kidney injury	44 (40.0)	26 (40.6)	18 (39.1)	1.06	0.49–2.31	0.875
Cardiac injury	11 (10.0)	6 (9.4)	5 (10.9)	0.85	0.24–2.97	0.797
Mortality	33 (30.0)	26 (40.6)	7 (15.2)	3.81	1.48–9.82	0.004*
Length of hospital stay, days	40.88±45.97	41.14±53.57	40.52±33.18			0.945
Length of ICU stay, days	22.05±22.00	17.31±16.44	28.63±26.79			0.013*
PCR CT No. >30 in 10 days	38 (34.5)	20 (31.3)	18 (39.1)	0.71	0.32–1.56	0.391
COVID related admission	77 (70.0)	31 (48.4)	46 (100)	2.07	1.60–2.66	<0.001*

Note: Data are expressed as *n* (%) and median (IQR).
Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; Ct, cycle threshold; * Significant.

Survival versus Fatality

Because of the heterogeneity of the two groups, we reclassified them into a survival group and a deceased group (Table 2). A comparison between the two groups revealed that the Omicron variant was significantly more prevalent in the deceased group than in the survival group (49.4% vs 78.8%, p = 0.004). Patients who were adequately vaccinated had a significantly higher mortality rate (23.4% vs 48.5%, p = 0.009). The deceased group also had more comorbidities and higher CCI values. Nearly all patients (30 patients, 90.9%) in the deceased group had a CCI value of 5 or more. By contrast, only 64.9% of the patients in the survival group had a CCI value of 5 or more. Compared with the survival group, the deceased group had higher PTs and higher D-dimer, blood urea nitrogen, and creatinine levels. Additionally, the use of dexamethasone and tocilizumab appeared to be protective factors against mortality (79.2% vs 60.6%, p = 0.042 and 35.1% vs 6.1%, p = 0.002, respectively).

Univariate and Multivariate Logistic Regression

For the Omicron variant, factors such as male sex, COVID-19-related hospitalization, a CCI value of 3 or more, adequate vaccination, hypertension, creatinine levels, PT, and administration of dexamethasone and tocilizumab were selected in the univariate analysis. In multivariate binary logistic regression (Table 3), a CCI value of 3 or higher (adjusted OR =

Table 2 Baseline Characteristics of Critical Patients with COVID-19

	Survival n=77	**Deceased n=33**	**P value**
Omicron variants	38(49.4)	26(78.8)	0.004*
Age, yr	65.00±14.91	69.64±12.61	0.121
Male gender, no. (%)	52(67.5)	16(48.5)	0.060
BMI	23.88±4.88	24.09±5.21	0.848
Adequately vaccinated	18(23.4)	16(48.5)	0.009*
Active smoker	15(19.5)	8(24.2)	0.574
Respiratory failure on admission	31(40.3)	11(33.3)	0.493
COVID related hospitalization	58(75.3)	19(57.6)	0.063
Comorbidities			
Hypertension	34(44.2)	22(66.7)	0.030*
CAD	8(10.4)	10(30.3)	0.010*
Heart failure	5(6.5)	8(24.2)	0.008*
Af	7(9.1)	3(9.1)	1.000
CVA	13(16.9)	6(18.2)	0.869
DM	28(36.4)	17(51.5)	0.139
CKD	8(10.4)	5(15.2)	0.478
COPD	5(6.5)	2(6.1)	0.932
Autoimmune disease	5(6.5)	0(0.0)	0.134
Malignant solid cancer	8(10.4)	10(30.3)	0.010*
Number of comorbidities	1.57±1.31	2.52±1.66	0.002*
Charlson Comorbidity Index	3.83±2.59	5.39±2.79	0.006*
Charlson Comorbidity Index ≥3	50(64.9)	30(90.9)	0.005*

(*Continued*)

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Table 2 (Continued).

	Survival n=77	Deceased n=33	P value
Laboratory findings			
WBC, 10000/μL	9111.69±5397.25	12,642.42±13,272.03	0.148
Lymphocyte count, 1000/μL	1072.48±2029.36	1055.47±923.24	0.963
Neutrophil-lymphocyte ratio ≥5	57(74.0)	23(69.7)	0.640
Platelet, 1000/μL	213.06±116.14	236.65±108.12	0.333
Prothrombin time, second	13.356±2.13	15.944±5.83	0.032*
aPTT, second	30.92±6.03	35.50±10.83	0.059
BUN, mg/dL	27.29±23.34	38.43±29.94	0.042*
Creatinine, mg/dL	1.44±2.01	2.67±2.98	0.035*
AST, U/L	46.46±32.48	95.50±177.40	0.191
ALT, U/L	55.21±129.10	97.84±247.96	0.363
Total bilirubin, mg/dL	0.84±0.87	1.70±2.71	0.182
CRP, mg/L	106.17±106.87	121.11±99.07	0.509
Day1Ct value	21.62±7.13	21.52±6.76	0.948
Day9 Ct value	28.69±6.88	24.81±3.41	0.224
Treatment			
Antimicrobial agents	73(94.8)	30(90.9)	0.443
Remdesivir	46(59.7)	16(48.5)	0.275
Dexamethasone	61(79.2)	20(60.6)	0.042*
Tocilizumab	27(35.1)	2(6.1)	0.002*

Note: Data are expressed as *n* (%) and median (IQR).
Abbreviations: COVID-19, coronavirus disease 2019; BMI, body mass index; CAD, coronary arterial disease; Af, atrial fibrillation; CVA, cerebrovascular accident; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; PT, prothrombin time; aPTT, activated partial prothrombin time; BUN, blood urine nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; CRP, C-reactive protein; * Significant.

7.00, 95% CI = 1.31–37.31, p = 0.023), PT (adjusted OR = 1.19, 95% CI = 1.02–1.38, p = 0.032), and creatine levels (adjusted OR = 1.21, 95% CI = 1.01–1.46, p = 0.044) were identified as positive predictors of COVID-19-related mortality.

AUROC revealed that creatinine levels and PT values had modest discriminative powers pertaining to the mortality outcome (0.712, 95% CI 0.597–0.827, p = 0.001; and 0.673, 95% CI 0.545–0.820, p =0.008, respectively). The cutoff values for creatinine and PT in predicting mortality were 1.12 mg/dL (sensitivity, 70.4%; specificity, 64.8%) and 13.45 second (sensitivity, 66.7%; specificity,67.6%), respectively. The Kaplan–Meier survival curve (Figure 1) used to compare the mortality rates between the groups with higher and lower CCI values revealed significantly higher mortality in the group with higher CCI values than in group with lower CCI values (HR = 4.54, reference: lower CCI group; 95% CI = 2.17–9.47, Log rank test p = 0.005).

Discussion

Our research revealed that patients with severe COVID-19 caused by the Omicron variant had a higher mortality rate compared to those infected with the Alpha variant. Nonetheless, when we conducted a multivariate analysis accounting

Table 3 Risk Factors Associated with in-Hospital Mortality

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Omicron variant	2.91	1.26–6.70	0.012*			
Male gender	0.50	0.25–0.99	0.047*			
COVID related hospitalization	0.534	0.27–1.07	0.076			
CCI ≥3	3.56	1.08–11.66	0.036*	7.00	1.31–37.31	0.023*
Hypertension	1.954	0.95–4.03	0.062			
CAD	2.44	1.15–5.16	0.02*			
Heart failure	2.35	1.06–5.22	0.035*			
Malignant solid cancer	2.358	1.12–4.96	0.024*			
Creatinine,	0.82	0.68–0.98	0.032*	1.21	1.01–1.46	0.044*
Prothrombin time, seconds	0.82	0.70–0.96	0.011*	1.19	1.02–1.38	0.032*
Dexamethasone	0.42	0.21–0.86	0.016*			
Tocilizumab	0.16	0.04–0.66	0.011*			
ARDS	0.29	0.11–0.76	0.012*			

Abbreviations: CCI, Charlson's Comorbidity Index; COVID, coronavirus disease 2019; CAD, coronary arterial disease; ARDS, acute respiratory distress syndrome; * Significant.

for underlying comorbidities, severity of illness, vaccination status, treatment, and laboratory biomarkers, infection with Omicron variant did not emerge as an independent risk factor for mortality. In the patients with critical COVID-19, the independent predictors of mortality were CCI value higher than 3, prothrombin time, and baseline creatinine levels.

The results of this study revealed a significantly higher mortality rate in patients with the Omicron variant. Many studies have investigated the contribution of Omicron variants to the mortality rate among patients with severe COVID-19. However, their results have been inconclusive. For example, a retrospective cohort study in England reported that compared with that from the Delta variant, the adjusted HR of mortality from the Omicron variant was 0.31 (95% C.I.; 0.26–0.37).[17] In addition, a report from the United States Department of Health and Human Services/Centers for Disease Control and Prevention revealed that the crude mortality risk (deaths per 100 patients hospitalized primarily for COVID-19) was lower during the Omicron-predominant period than during the Delta-predominant period.[18] Consistent with our results, a study reported a higher mortality rate for the Omicron variant than that for the Alpha variant (47% vs 25%, p =

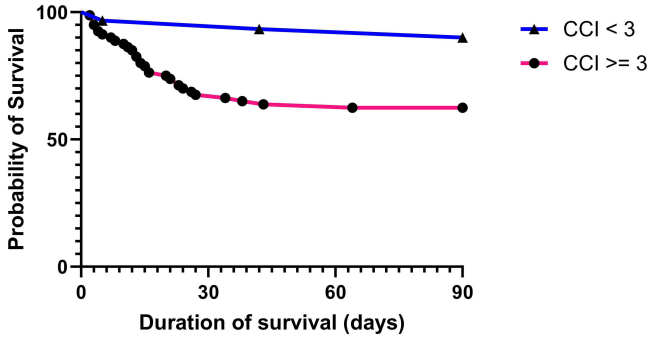

Figure 1 Survival curves for patients with COVID-19 with Charlson comorbidity index (CCI) ≥ 3 versus CCI < 3; hazard Ratio: 4.54; 95% confidence interval: 2.17–9.47, Log rank test p = 0.005.

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0.047).[5] The lower mortality rate for the Alpha variant may be attributed to the adequacy of medical resources, policy of quarantine, vaccination status, and local prevalence of the Alpha outbreak. The adequacy of medical resources for controlling outbreaks in Taiwan during the Alpha-predominant period may have contributed to the current study's finding of a lower mortality rate in patients infected with this variant. A public health surveillance report on COVID-19 in Taiwan revealed that only 14,620 cases were diagnosed before December 2021; that is, only 0.066% of Taiwan's population was infected prior to that month.[3] In addition, the higher prevalence of comorbidities[5] and different immune responses to the Omicron variant may have affected the mortality outcomes in patients with Omicron infection. This could clarify why our research found a higher mortality rate in patients with Omicron variants.

The association of comorbidities with the clinical outcomes of patients with COVID-19 has been extensively investigated.[19,20] The CCI, which was developed by Dr. Charlson in 1987, has been widely used to evaluate patient prognosis.[21,22] In addition, the CCI has frequently been applied for predicting mortality among patients with COVID-19.[19,20] Previous studies have also used the CCI to predict the in-hospital mortality of patients with critical COVID-19.[23,24] In line with previous research,[19,20,25] our study demonstrated that a higher CCI value is an independent risk factor for in-hospital mortality. Impaired organ function and immune response in patients with more comorbidities are key contributors to poor COVID-19 outcomes. The findings of this study indicate that the cutoff value of CCI ≥ 3 can be used to identify high-risk patients on admission.

This study discovered renal insufficiency to be an independent risk factor for mortality in patients with critical COVID-19. Research reported that poor renal function upon admission is linked to a higher mortality rate.[26] The possible causes of impaired baseline renal function are underlying chronic renal insufficiency or COVID-19-related acute kidney injury. A renal histopathological study discovered significant acute tubular injury in all included patients with acute kidney injury.[27] The acute kidney injury may be due to direct cytopathic effects on kidney tissue or may be secondary to SARS-CoV-2 virus-induced cytotoxic effects. Chronic kidney injury can serve as a marker of severity for other diseases, such as diabetes or hypertension.[28] Consequently, baseline chronic kidney injury may indicate end-organ dysfunction caused by severe comorbidities, making it an independent factor associated with high mortality.

In line with those of a previous study,[29] our findings revealed that a prolonged PT is an independent risk factor for mortality. Coagulation disorders and thrombotic complications were reported in COVID-19 patients,[30] and coagulopathy is associated with a poor prognosis in hospitalized patients with severe COVID-19.[31] COVID-19 induced injury of lung tissue and endothelial cell system may activate platelets, resulting in aggregation and formation of microthrombi and eventually leading to coagulopathy with prolonged PT.[18] In addition, COVID-19-caused damage to pulmonary endothelial cells and subsequent fibrinolysis system dysfunction play significant roles in the subsequent abnormal in coagulation system.[32]

Reliable biomarkers of COVID-19 disease outcomes are urgently required to enable identification of high-risk patients; because the disease spreads rapidly, patients must be immediately identified to ensure optimal resource allocation. This study demonstrated that CCI ≥ 3, an increased baseline creatine level, and prolonged PT are strong predictors of mortality outcomes, and patients presenting with these factors should be given priority in terms of the allocation of resources. By determination of the cut-off value of CCI, creatinine, and PT levels, future COVID-19 patients presenting with these risk factors may need intensively monitoring and treatment to prevent mortality outcome. Furthermore, future research should incorporate these variables into clinical and laboratory algorithms. Studies have reported comorbidities to be associated with abnormal renal function and PT levels. The present study investigated the role of these biomarkers in patients with severe COVID-19 who were infected with different variants. To ensure improved disease outcomes, patients with critical COVID-19 who are at high risk should be closely monitored.

One major limitation of this study is its retrospective nature, which may have introduced selection bias. Additionally, because of the small sample size, the results should be interpreted with caution. In Taiwan, all patients with confirmed cases received treatment in accordance with guidelines from the Taiwanese Centers for Disease Control. This enabled longitudinal follow-up and ensured consistent treatment regimens across hospitals. Additionally, no genomic analysis was conducted in our study; classification into Alpha and Omicron variants was based on the predominant strains announced by the Taiwan Center for Disease Control. Therefore, the results should be interpreted with caution. Furthermore, patients with asymptomatic or mild Omicron variant infection were either quarantined at home or admitted

to collective quarantine sites. Only those with moderate or severe infection were hospitalized to hospitals. In contrast, during the pandemic of alpha variant infection, all the PCR-confirmed COVID-19 patients were hospitalized. Therefore, certain bias may exist between the 2 cohorts.

In conclusion, in patients with critical COVID-19, CCI $\geq$ 3, elevated serum creatine levels, and prolonged PT were independently associated with a high mortality rate. Patients with those risk factors may require intensive monitoring during their treatment course.

Data Sharing Statement

The datasets analyzed in this study are available from the corresponding author upon reasonable request.

Ethical Approval Statement

The study was approved by the Institutional Review Board of the Chang Gung Memorial Foundation (IRB No. 202400546B0).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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