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Original Article

# Prognostic factors for poor outcomes in patients with severe COVID-19 treated with remdesivir plus dexamethasone in Taiwan

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## KEYWORDS

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Remdesivir;  
Dexamethasone;  
Prognostic factors;  
Mortality

**Abstract** *Background:* Coronavirus disease-2019 (COVID-19) remains a global public health concern, and remdesivir plus dexamethasone combination therapy is suggested for patients with severe disease. However, the factors associated with poor outcomes in these patients remain unclear. We identified the factors associated with poor outcomes in Taiwanese patients with severe COVID-19 treated with remdesivir plus dexamethasone.

*Methods:* Adults with severe COVID-19 (oxygen saturation <94% on room air or requiring supplemental oxygen) treated with remdesivir and dexamethasone were identified between 1 May and 31 July 2021. The main outcomes were 14-day non-recovery, 28-day mortality, and progression to respiratory failure requiring invasive mechanical ventilation or death in initially non-ventilated patients. The prognostic factors associated with poor outcomes were analyzed by multivariate logistic regression and Cox regression.

*Results:* Of the 110 patients treated with remdesivir and dexamethasone, 57 (51.8%) recovered within 14 days and 6 (5.5%) died within 28 days. Of the 89 initially non-ventilated patients, 12 (13.5%) progressed to respiratory failure or death. Charlson Comorbidity Index, SOFA score, and admission to remdesivir treatment interval were associated with 14-day non-recovery.

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C-reactive protein level was associated with 28-day mortality. Pneumonia Severity Index and admission to remdesivir treatment interval were associated with progression to respiratory failure requiring invasive mechanical ventilation or death in initially non-ventilated patients. **Conclusion:** High disease severity on admission and delayed initiation of remdesivir therapy were associated with poor outcomes in COVID-19 patients treated with remdesivir and dexamethasone.

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## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global public health emergency.<sup>1</sup> Given the continual spread of COVID-19 worldwide, the Taiwanese government was able to prevent viral transmission in the community via border control, enforcement of social distancing, timely case detection and quarantine, and contact tracing.<sup>2</sup> After 18 months of successfully preventing COVID-19 in population, Taiwan experienced its first COVID-19 outbreak, caused by the alpha SARS-CoV-2 variants, in May 2021.<sup>3</sup> Our hospital played a central role in this domestic outbreak. During the COVID-19 surge in 2021, most Taiwanese patients were unvaccinated.<sup>3,4</sup>

Remdesivir administration within the first 10 days after symptoms onset was demonstrated to reduce the time to recovery in hospitalized COVID-19 patients requiring supplemental oxygen in the ACTT-1 trial.<sup>5</sup> The final report of the WHO Solidarity trial also suggests a minor beneficial effect of remdesivir treatment against death or progression to respiratory failure requiring invasive mechanical ventilation among hospitalized COVID-19 patients without mechanical ventilation.<sup>6</sup> In the RECOVERY trial, dexamethasone therapy has been shown to decrease mortality in patients requiring supplemental oxygen.<sup>7</sup> Therefore, both the National Institutes of Health (NIH) and the Infectious Diseases Society of America (IDSA) guidelines recommend dexamethasone for patients with severe COVID-19, defined as individuals who have SpO<sub>2</sub> < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) < 300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.<sup>8,9</sup> Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the combination therapy of dexamethasone plus remdesivir has become part of the NIH and IDSA guidelines for patients requiring supplemental oxygen.<sup>8</sup> However, the efficacy of this combination therapy has mostly only been evaluated in observational studies<sup>10–14</sup>; there have been very few reports regarding the prognostic factors for poor outcome in patients with severe COVID-19 under remdesivir plus dexamethasone therapy.<sup>15</sup> The national guidelines of the Taiwan Centers for Disease Control (CDC) refer to the international guidelines; dexamethasone plus remdesivir was widely used in patients requiring oxygen supplementation during the outbreak in 2021.<sup>16</sup>

Here, we aimed to investigate the efficacy of remdesivir plus dexamethasone in hospitalized patients with severe COVID-19 and to determine the prognostic factors for poor outcomes including non-recovery, disease progression, and mortality in these patients.

## Methods

### Study design

This retrospective study was conducted between May 1 2021 and July 31 2021 in a medical center in Taipei, Taiwan. Adult (≥20 years of age) COVID-19 patients admitted to the hospital were enrolled in the study. All patients were confirmed to have SARS-CoV-2 infection based on reverse transcription-polymerase chain reaction of nasopharyngeal samples. The patients' clinical data were retrieved from their electronic medical records. Ethics approval was obtained from the Institutional Review Board of the hospital. Informed consent was waived due to the retrospective nature of the study.

### Study population and treatment

The eligibility criteria for this study included hospitalized severe COVID-19 patients requiring supplemental oxygen who received a combination of remdesivir and dexamethasone (or dose-equivalent corticosteroid). Patients younger than 20 years of age and those with incomplete medical records were excluded. All patients received standard care according to the Taiwan CDC therapeutic guidelines.<sup>16</sup>

In Taiwan, remdesivir has been available since May 2020; its use has been regulated by the Taiwan CDC. All patients within 10 days of symptoms onset who had peripheral SpO<sub>2</sub> < 94% while breathing room air or needing supplemental oxygen were eligible to receive 200 mg intravenous remdesivir on day 1 as a loading dose, followed by a maintenance dose of 100 mg daily for a total of five days. Along with remdesivir, the aforementioned patients receive dexamethasone 6 mg per day for 10 days, or 20 mg per day for 5 days followed by a gradually tapering dose.<sup>7,17</sup> Dexamethasone may be discontinued early if the patient recovered clinically, was no longer in need of supplemental oxygen, and was discharged or remained admitted only for isolation purposes. Tocilizumab was prescribed for some patients with elevated C-reactive protein (CRP) levels

greater than 7.5 mg/dl, according to Taiwan CDC guidelines.<sup>16</sup> Antibiotic use was determined by the treating physicians.

### Data collection and outcome measures

Demographic data, including age, sex, comorbidities, COVID-19 vaccination status, laboratory and clinical parameters, treatment, and the admission to remdesivir treatment (ART) interval, were collected. Antibiotics prescribed within 7 days of admission and used for more than 48 h were documented. On admission, Sequential Organ Failure Assessment (SOFA) score,<sup>18</sup> Pneumonia Severity Index (PSI),<sup>19</sup> and the WHO eight-category ordinal scale were calculated to assess clinical severity.<sup>5</sup> The WHO eight-category ordinal scale was categorized as follows: category 1 as not hospitalized and no limitations of activities; category 2 as not hospitalized, with limitation of activities, home oxygen requirement, or both; category 3 as hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons); category 4 as hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions); category 5 as hospitalized, requiring any supplemental oxygen; category 6 as hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; category 7 as hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); category 8 as death. Moderate disease is identified as category 4. Severe disease is identified as category 5 and 6. Critical disease is identified as category 7.

The main objectives of this study included assessment of the 14-day clinical recovery, 28-day mortality, and progression to respiratory failure requiring invasive mechanical ventilation in initially non-ventilated patients. Patients were followed up until in-hospital death or discharge. Clinical recovery was defined as a reduction in the WHO eight-category ordinal scale by at least two scores.<sup>5</sup>

### Statistical analysis

Fisher's exact test was used to assess the differences between categorical variables. Mann–Whitney U test was used to assess the differences between continuous variables. Univariate and multivariate logistic regressions were used to evaluate factors associated with 14-day non-recovery. Univariate and multivariate Cox proportional hazards models were used to identify independent variables associated with 28-day mortality, and progression to respiratory failure requiring invasive mechanical ventilation or death in non-ventilated patients. Variables with  $p$  values  $< 0.2$  in univariate analyses, after checking for collinearity, were selected into the multivariate models. A stepwise backwards selection method was implemented for multivariate logistic regressions. All tests were two-tailed;  $p$  values  $< 0.05$  were considered statistically significant. Statistical analyses were performed using SPSS (v.23.0, SPSS Inc., Chicago, IL, USA) and R (v.3.6.2, R Core Team, Vienna, Austria).

## Results

### Clinical characteristics and outcomes of COVID-19 patients

From 1 May 2021 to 31 July 2021, 245 adult COVID-19 patients were admitted to our hospital. Of these, 76 patients who did not receive supplemental oxygen and 4 patients lacking complete medical records were excluded. In total, 165 patients meeting the definition of severe COVID-19 were further analyzed; 55 patients who did not receive remdesivir plus dexamethasone treatment were excluded. The reasons for not receiving standard therapy were a duration between the onset of symptoms and admission exceeding 10 days or the occurrence of death before the drug(s) could be administered. Finally, 110 patients who received remdesivir plus dexamethasone were included in the analysis. Fig. 1 shows the process of study patients enrollment.

The median age of these 110 patients was 65.5 (interquartile range [IQR], 59–74) years; 67 patients (60.9%) were male. The median Charlson Comorbidity Index (CCI) was 3 (IQR, 2–4). Only three patients (2.7%) had been vaccinated before contracting COVID-19, but their onset of symptoms occurred within two weeks of vaccination. Of the 110 patients, most patients ( $n = 84$ , 76.4%) received dexamethasone 6 mg per day, and the others ( $n = 26$ , 23.6%) received dexamethasone 20 mg/day for 5 days followed by a gradually tapering dose. Among the 84 patients who received dexamethasone 6 mg per day, 48 (57.1%) recovered within 14 days, and 5 (6%) died within 28 days; among the 26 patients who received dexamethasone 20 mg per day, 9 (34.6%) recovered within 14 days, and 1 (3.8%) died within 28 days. The 14-day clinical recovery and 28-day mortality rates were not different statistically

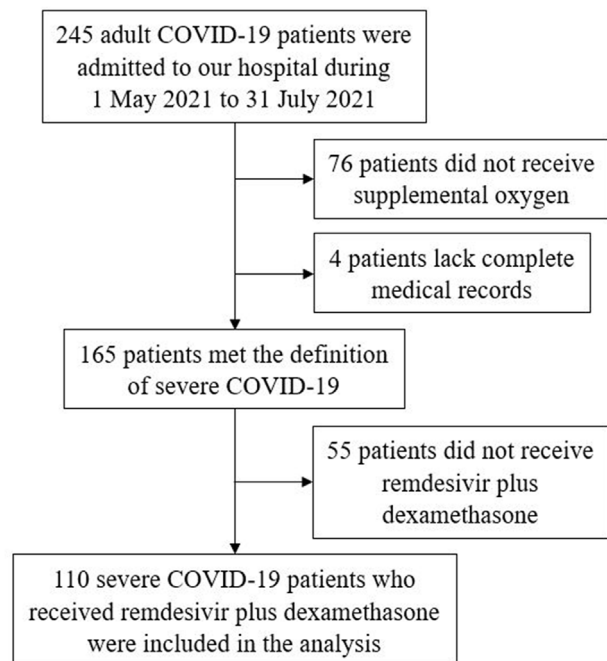


Figure 1. The enrollment of study patients.

between patients with the different dose of dexamethasone. For other therapies, 40 (36.4%) received tocilizumab; 81 (73.6%) received antibiotics within 7 days of admission.

Of the 110 patients, 57 (51.8%) recovered within 14 days; death from any cause within 28 days occurred in 6 patients (5.5%); 21 (19.1%) patients experienced respiratory failure before the initiation of remdesivir and dexamethasone and were intubated; the remaining 89 (80.9%) patients were initially non-ventilated. Of the 89 initial non-ventilated patients, 49 (55.1%) recovered within 14 days; 12 (13.5%) progressed to respiratory failure or death.

### Prognostic factors for 14-day non-recovery among patients treated with remdesivir plus dexamethasone

Table 1 lists the differences in the clinical characteristics between patients with and without 14-day recovery. Univariate analyses showed that factors associated with 14-day non-recovery include age, CCI, PSI, SOFA score, and tocilizumab use. Multivariate analysis showed that CCI (adjusted odds ratio, aOR = 1.327, 95% confidence interval, 95% CI = 1.083–1.626,  $p = 0.006$ ), SOFA score (aOR = 1.221, 95% CI = 1.05–1.419,  $p = 0.009$ ), and ART interval (aOR = 1.374, 95% CI = 1.065–1.772,  $p = 0.015$ ) were significantly associated with non-recovery within 14 days (Table 2).

### Prognostic factors for 28-day mortality among patients treated with remdesivir plus dexamethasone

Table 3 lists the clinical characteristics of 28-day survivors and non-survivors. Univariate analyses showed that factors associated with 28-day mortality included age, D-dimer, and CRP level. Multivariate analyses showed that CRP level (adjusted hazard ratio, aHR = 1.283, 95% CI = 1.044–1.576,  $p = 0.018$ ) was significantly associated with 28-day mortality (Table 4).

### Prognostic factors of 14-day non-recovery and progression to respiratory failure requiring invasive mechanical ventilation or death among initially non-ventilated patients treated with remdesivir plus dexamethasone

For initially non-ventilated patients, the factors significantly associated with 14-day non-recovery were CCI (aOR = 1.256, 95% CI = 1.015–1.553,  $p = 0.036$ ) and ART interval (aOR = 1.427, 95% CI = 1.07–1.902,  $p = 0.015$ ) (Supplementary Table 1 and Table 2); the factors significantly associated with progression to respiratory failure requiring invasive mechanical ventilation or death were PSI (aHR = 1.031, 95% CI = 1.002–1.062,  $p = 0.036$ ), and ART

**Table 1** Clinical characteristics of all patients with 14-day recovery or not.

Variables	Total (n = 110)	Recovery within 14 days (n = 57)	Non-recovery within 14 days (n = 53)	<i>P</i> value
Age	65.5 (59–74)	62 (55–72)	70 (62–78)	<b>0.004</b>
Male gender	67 (60.9)	37 (64.9)	30 (56.6)	0.436
Comorbidities				
Diabetes mellitus	34 (30.9)	17 (29.8)	17 (32.1)	0.839
Chronic obstructive pulmonary disease	3 (2.7)	2 (3.5)	1 (1.9)	>0.999
Chronic kidney disease	3 (2.7)	0 (0)	3 (5.7)	0.109
Chronic liver disease	6 (5.5)	3 (5.3)	3 (5.7)	>0.999
Active malignancy	17 (15.5)	6 (10.5)	11 (20.8)	0.188
Immunocompromised status	8 (7.3)	2 (3.5)	6 (11.3)	0.151
Charlson Comorbidity Index	3 (2–4)	2 (1–3)	4 (2–5)	<b>0.001</b>
Initial Disease Severity				
WHO ordinal scale at admission	5 (4.2–6)	5 (5–5)	5 (4–6)	0.699
Pneumonia Severity Index	109.5 (91–143.8)	102 (89–117)	126 (95–168)	<b>0.002</b>
SOFA score	3 (1.2–5)	2 (1–4)	4 (2–6)	<b>0.008</b>
Initial laboratory values				
NLR	5.2 (3.4–9.9)	5.2 (3.4–7.9)	5.1 (3.6–12.8)	0.270
D-dimer, mg/L	0.7 (0.4–1.2)	0.6 (0.4–1.2)	0.8 (0.5–1.4)	0.091
Ferritin, ng/mL	922.5 (566–1575.2)	938 (463–1576)	909 (635–1550)	0.704
CRP, mg/L	5.7 (2.8–10.2)	5.3 (2.9–10.2)	5.7 (2.7–10.1)	0.582
Admission to remdesivir treatment interval, days	2 (1–2.8)	1 (1–2)	2 (1–3)	0.105
Other treatment initiated within 7 days of hospitalization				
Tocilizumab	40 (36.4)	15 (26.3)	25 (47.2)	<b>0.029</b>
Antibiotics use	81 (73.6)	38 (66.7)	43 (81.1)	0.129

Data are presented as median (interquartile range) for continuous variables, and number (percent) for categorical variables. Categorical variables were evaluated using Fisher's exact test. Continuous variables were evaluated using Mann–Whitney U test. Statistically significant *P* values are highlighted in bold. NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

**Table 2** Prognostic factors of 14-day non-recovery in all patients treated with remdesivir plus dexamethasone.

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age	1.049 (1.015–1.085)	<b>0.004</b>	-	-
Chronic kidney disease	17,842,551.296 (0-Inf)	0.990	-	-
Active malignancy	2.226 (0.76–6.525)	0.145	-	-
Immunocompromised status	3.511 (0.676–18.225)	0.135	-	-
Charlson Comorbidity Index	1.346 (1.106–1.637)	<b>0.003</b>	1.327 (1.083–1.626)	<b>0.006</b>
Pneumonia Severity Index	1.019 (1.007–1.031)	<b>0.001</b>	-	-
SOFA score	1.231 (1.065–1.422)	<b>0.005</b>	1.221 (1.05–1.419)	<b>0.009</b>
D-dimer, mg/L	1.007 (0.953–1.064)	0.806	-	-
Admission to remdesivir treatment interval, days	1.234 (0.983–1.55)	0.070	1.374 (1.065–1.772)	<b>0.015</b>

Prognostic factors were evaluated using univariate and multivariate logistic regressions. Statistically significant *P* values are highlighted in bold. OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

**Table 3** Clinical characteristics of 28-day survivors and non-survivors.

Variables	Alive more than 28 days (n = 104)	Dead within 28 days (n = 6)	<i>P</i> value
Age	65 (58.8–73.2)	83.5 (69–87.5)	<b>0.023</b>
Male gender	62 (59.6)	5 (83.3)	0.401
Comorbidities			
Diabetes mellitus	34 (32.7)	0 (0)	0.174
Chronic obstructive pulmonary disease	3 (2.9)	0 (0)	>0.999
Chronic kidney disease	3 (2.9)	0 (0)	>0.999
Chronic liver disease	5 (4.8)	1 (16.7)	0.292
Active malignancy	15 (14.4)	2 (33.3)	0.232
Immunocompromised status	7 (6.7)	1 (16.7)	0.371
Charlson Comorbidity Index	3 (2–4)	4 (4–4.8)	0.077
Initial Disease Severity			
WHO ordinal scale at admission	5 (4–6)	5 (5–5.8)	0.658
Pneumonia Severity Index	107.5 (90.5–137.2)	162 (127.2–187.8)	0.052
SOFA score	2 (1–5)	4.5 (4–5.8)	0.109
Initial laboratory values			
NLR	5.1 (3.4–8.8)	9 (4.7–10.3)	0.308
D-dimer, mg/L	0.7 (0.4–1.2)	3.5 (0.9–11.8)	<b>0.025</b>
Ferritin, ng/mL	890.5 (541.2–1595)	1069 (1009.8–1093)	0.396
CRP, mg/L	5.3 (2.7–10)	17.2 (8.5–22.5)	<b>0.007</b>
Admission to remdesivir treatment interval, days	2 (1–2)	3 (1.2–4.8)	0.186
Other treatment initiated within 7 days of hospitalization			
Tocilizumab	36 (34.6)	4 (66.7)	0.188
Antibiotics use	75 (72.1)	6 (100)	0.338

Data are presented as median (interquartile range) for continuous variables, and number (percent) for categorical variables. Categorical variables were evaluated using Fisher's exact test. Continuous variables were evaluated using Mann–Whitney U test. Statistically significant *P* values are highlighted in bold. NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

interval (aHR = 1.446, 95% CI = 1.025–2.04, *p* = 0.036) (Supplementary Table 3 and Table 4).

## Discussion

In this study, the 28-day mortality rate was 5.5% in severe COVID-19 patients treated with remdesivir plus dexamethasone; CCI, SOFA score, and ART interval were independently associated with non-recovery within 14 days; CRP level on admission was associated with the 28-day

mortality; PSI and ART interval were associated with progression to respiratory failure requiring invasive mechanical ventilation or death in initially non-ventilated patients.

In a nationwide cohort study in Denmark from June through December 2020, severe COVID-19 treatment involving combined remdesivir and dexamethasone reduced the 30-day mortality rate compared to treatment with dexamethasone alone (12.6% versus 19.7%).<sup>10</sup> In another retrospective study in India, conducted between 25 June and 3 October 2020, the mortality of all hospitalized severe

**Table 4** Prognostic factors of 28-day mortality in all patients treated with remdesivir plus dexamethasone.

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	aHR (95% CI)	P value
Age	1.095 (1.021–1.176)	<b>0.012</b>	1.094 (0.975–1.228)	0.126
Diabetes mellitus	0 (0-Inf)	0.999	0 (0-Inf)	0.999
Charlson Comorbidity Index	1.203 (0.95–1.522)	0.125	1.359 (0.793–2.329)	0.265
Pneumonia Severity Index	1.021 (1.002–1.041)	<b>0.031</b>	0.999 (0.954–1.046)	0.958
SOFA score	1.085 (0.891–1.321)	0.418	1.032 (0.698–1.526)	0.874
D-dimer, mg/L	1.035 (0.98–1.094)	0.217	1.01 (0.823–1.24)	0.922
CRP, mg/L	1.161 (1.063–1.267)	<b>0.001</b>	1.283 (1.044–1.576)	<b>0.018</b>
Admission to remdesivir treatment interval, days	1.324 (0.953–1.84)	0.095	1.311 (0.691–2.484)	0.407

Prognostic factors were evaluated using univariate and multivariate Cox regressions. Statistically significant *P* values are highlighted in bold. HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein.

COVID-19 patients receiving remdesivir plus dexamethasone for five days was 22%.<sup>11</sup> A randomised controlled trial performed in Canada from 14 August 2020 to 1 April 2021 showed that the in-hospital mortality of hospitalized COVID-19 patients treated with remdesivir was 18.7%; most of them (87%) also received dexamethasone.<sup>20</sup> In a retrospective study in Germany between 1 July 2020 and 30 June 2021, COVID-19 patients under low-flow oxygen therapy treated with corticosteroids combined with early administration of remdesivir had lower 28-day mortality than those treated with corticosteroids alone (14.8% versus 22.2%).<sup>12</sup> A retrospective cohort study conducted in the USA between 1 March 2020 and 30 March 2021 reported no substantial reduction in mortality for dexamethasone and remdesivir combination therapy versus remdesivir treatment alone in all hospitalized COVID-19 patients (21.4% versus 21.6%).<sup>13</sup> Overall, combination therapy comprising remdesivir plus dexamethasone in severe COVID-19 resulted in mortality rates between 14.8% and 21.4% in the aforementioned studies.<sup>10–13,20</sup> In our study, we found that the 28-day mortality was 5.5% in severe COVID-19 patients treated with remdesivir plus dexamethasone, which was lower than that observed in previous studies. A recent report showed that only five countries, including Taiwan, had negative excess mortality during 2020 and 2021,<sup>21</sup> indicating that the Taiwanese healthcare system was well prepared during the COVID-19 pandemic. Our findings suggest that standard combination therapy with remdesivir and dexamethasone is effective in treating severely ill COVID-19 patients in an optimal healthcare system.

Notably, in a territory-wide study in Hong Kong conducted between 21 January 2020 and 31 January 2021, all hospitalized patients received dexamethasone irrespective of their disease severity, revealing that using remdesivir with dexamethasone in hospitalized COVID-19 patients was associated with a lower in-hospital death than for that seen using dexamethasone alone, with mortality rates of 7.7% and 11.6%, respectively.<sup>14</sup> The mortality in Hong Kong was lower than what has been reported previously.<sup>10–13</sup> However, most COVID-19 patients in Hong Kong did not require oxygen therapy on admission (66%), which is markedly different from our study, where all patients required oxygen therapy. This study, which focused on severe COVID-19, once again demonstrated the efficacy of standard therapy in these patients.

To the best of our knowledge, the prognostic factors for COVID-19 patient treated with remdesivir plus dexamethasone have only been touched on in a single conference abstract.<sup>15</sup> Gupta et al. showed that the 30-day mortality among severe COVID-19 patients treated with remdesivir plus dexamethasone at a center in Michigan between March and November 2020 was 15.3%; both age and quick SOFA score  $\geq 2$  were independent prognostic factors for 30-day mortality.<sup>15</sup> Our study further identified CRP level on admission as another prognostic factor for 28-day mortality. In addition to mortality, we also identified that disease severity and long ART interval were associated with a high risk of 14-day non-recovery. Given the broad use and efficacy of this regimen, we recommend that further studies are undertaken to investigate and validate the prognostic factors for poor outcomes in severe COVID-19 treated with remdesivir and dexamethasone.

Ali et al. showed remdesivir plus standard of care, including dexamethasone, decreased the need for mechanical ventilation compared to those assigned to standard of care alone (8.0% vs. 15.0%) in patients with severe COVID-19 in a randomised controlled study in Canada.<sup>20</sup> The global Solidarity trial also found that remdesivir plus standard care (67% with steroids) reduced death or progression to respiratory failure requiring invasive mechanical ventilation in hospitalized COVID-19 patients.<sup>6</sup> The aforementioned studies suggest that remdesivir plus dexamethasone reduces disease progression in patients without mechanical ventilation. However, we did not find any studies describing the prognostic factors for progression to respiratory failure requiring invasive mechanical ventilation or death among these patients. Our study showed that disease severity, indicated by PSI, was independently associated with progression to respiratory failure requiring invasive mechanical ventilation or death. Therefore, therapeutic strategies need to focus on patients with severe disease on presentation, even when treated with standard therapy.

Our study has some limitations. First, this was a retrospective study from a single medical center; thus, the power of the causal relationship between the influencing factors and outcomes might be limited. Second, the study was conducted during the outbreak of the alpha variant; the results may differ from the current omicron variant outbreak. Third, almost all patients were unvaccinated against COVID-19 during our study, which may not apply to

the current era in which most people have been fully vaccinated. However, our findings still offer insight regarding the prognostic factors for patients with severe COVID-19 receiving standard therapy in a fully functional healthcare system. Our findings have implications for managing severe COVID-19 patients, given that most Western countries are now well prepared for COVID-19.

In conclusion, our study showed that high disease severity on admission and delayed initiation of remdesivir therapy were associated with poor outcomes in COVID-19 patients treated with remdesivir and dexamethasone. Our findings enable the identification of patients at risk for poor outcomes, thereby highlighting the need to focus on therapeutic strategies for these patients.

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## References

- Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021 Mar;19(3):141–54.
- Chien-Jen C. Taiwan's pandemic vice-president - from lab bench to public office and back. *Nature* 2022 Mar;603(7900):203.
- Liu LT, Tsai JJ, Chang K, Chen CH, Lin PC, Tsai CY, et al. Identification and analysis of SARS-CoV-2 alpha variants in the largest Taiwan COVID-19 outbreak in 2021. *Front Med (Lausanne)* 2022 Apr 25;9:869818.
- Wang CJ, Ng CY, Brook RH. Response to COVID-19 in Taiwan: big data analytics, new technology, and proactive testing. *JAMA* 2020 Apr 14;323(14):1341–2.
- Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 - final report. *N Engl J Med* 2020 Nov 5;383(19):1813–26.
- WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet* 2022 May 21;399(10339):1941–53.
- RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021 Feb 25;384(8):693–704.
- COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. <https://www.covid19treatmentguidelines.nih.gov>. Accessed 23 January 2023.
- Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious diseases society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis* 2020;1–13. ciaa478. Last updated 2 Nov 2022, <https://www.idsociety.org/COVID19guidelines>. [Accessed 23 January 2023].
- Benfield T, Bodilsen J, Brieghel C, Harboe ZB, Helleberg M, Holm C, et al. Improved survival among hospitalized patients with coronavirus disease 2019 (COVID-19) treated with remdesivir and dexamethasone. A nationwide population-based cohort study. *Clin Infect Dis* 2021;73(11):2031–6.
- Mehta RM, Bansal S, Bysani S, Kalpakam H. A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: a real-world analysis. *Int J Infect Dis* 2021 May;106:71–7.
- Marx K, Gončarova K, Fedders D, Kalbitz S, Kellner N, Fedders M, et al. Clinical outcomes of hospitalized COVID-19 patients treated with remdesivir: a retrospective analysis of a large tertiary care center in Germany. *Infection* 2022 May 12: 1–12.
- Kuno T, Miyamoto Y, Iwagami M, Ishimaru M, Takahashi M, Egorova NN. The association of remdesivir and in-hospital outcomes for COVID-19 patients treated with steroids. *J Antimicrob Chemother* 2021 Sep 15;76(10):2690–6.
- Wong CKH, Lau KTK, Au ICH, Xiong X, Chung MSH, Lau EHY, et al. Optimal timing of remdesivir initiation in hospitalized patients with coronavirus disease 2019 (COVID-19) administered with dexamethasone. *Clin Infect Dis* 2022 Aug 24;75(1): e499–508.
- Gupta K, Monday L, Kaushik M, Alangaden GJ, Brar I. Risk factors associated with 30-day mortality in a large cohort of patients who received remdesivir and corticosteroids for severe COVID-19. *Open Forum Infect Dis* 2021;(8 Suppl 1): S375–6. Dec 4; 2021.
- Taiwan Centers for Disease Control. SARS-CoV-2 infection clinical management guideline. 19th ed. 2022 May 26. <https://www.cdc.gov.tw/File/Get/3Uk4nSt0rUlJiOh7czgiWw>. [Accessed 23 January 2023].
- Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020 Oct 6;324(13):1307–16.
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Intensive Care Med* 1996 Jul;22(7):707–10.
- Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997 Jan 23;336(4):243–50.
- Ali K, Azher T, Baqi M, Binnie A, Borgia S, Carrier FM, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ (Can Med Assoc J)* 2022 Feb 22;194(7):E242–51.
- COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *Lancet* 2022 Apr 16; 399(10334):1513–36.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jmii.2023.08.008>.