Higher Survival Rate Associated with Thymosin Alpha 1 use in Critical COVID-19: A Retrospective Multicenter Cohort Study

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Research Article
Abstract

Background
Currently no satisfactory pharmaceutical intervention is available for COVID-19. This retrospective study aimed to determine the therapeutic effect of thymosin alpha1 in critical COVID-19.

Results
We enrolled 109 critically ill severe acute respiratory syndrome-related coronavirus-2 RNA positive patients from 15 hospitals. The mortality rate in critical patients treated with thymosin alpha1 was 11%, compared to 56% in critical patients not treated with thymosin alpha1. With confounding factors adjusted in multivariate logistic regression, thymosin alpha1 treatment was identified as a protective factor for critical COVID-19.

Conclusion
Our observation advocates the treatment of critical COVID-19 with thymosin alpha1.

Introduction
The clinical presentations of the Coronavirus Disease 2019 (COVID-19) have two conflicting sides. On one side, the excessive response of the immune system, represented by high levels of proinflammatory cytokines and chemokines, is considered the major mechanism for critical illness and mortality of COVID-19[1, 2]. For this reason, suppression of patients’ immune system with glucocorticoid has been common in the management of COVID-19[3–5]. On the other side, severe lymphocytopenia was frequently observed in COVID-19, especially in aged and severe cases[1, 6]. Recently, Liu et al. reported that thymosin alpha 1 (Ta1) may benefit COVID-19 patients by restoring their immune capacity[7]. However, this study did not address the potential influences of the confounding factors.

To determine the therapeutic effect of Ta1 in critical COVID-19, we conducted a retrospective cohort study and found that use of Ta1 caused beneficial outcomes including a much lower mortality rate.

Methods
We reviewed the medical records of 410 suspected COVID-19 patients. Excluding 56 records for negative RNA test, 24 for duplicated records, 219 for non-critical condition, and 2 for the lack of relevant data, we enrolled 109 critically ill[8] severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) RNA positive patients hospitalized at 15 hospitals in Jingzhou and Dongguan, China, from January 16 to March 30, 2020 (Fig. 1).

Treatment of COVID-19 followed the Diagnosis and Treatment Guideline for COVID-19, National Health Commission of the People's Republic of China. Most patients were treated with oxygen supplementation,
respiratory support, antibiotics, usually Moxifloxacin, and antivirus drugs, usually Lopinavir and Ritonavir. Mechanical ventilation was conducted when indicated by exacerbating or persistent hypoxemia and dyspnea after non-invasive oxygen supplementation. Based on physician's preference, 18 of the critical patients exhibiting persistent positive results for SARS-CoV-2 RNA or lymphocyte count < $1.5 \times 10^9$/L were treated with Ta1 (Ta1 group) at a dosage of 1.6 mg per 12 or 24hr subcutaneously for the length of critical illness. The other 91 critical patients were not treated with Ta1 (non-Ta1 group).

Multivariate logistic regressions were performed to identify clinical features and treatments associated with Ta1 treatment and mortality, respectively, and were adjusted with potential confounders identified from univariate regressions.

**Results**

Eighteen of the 109 critically ill COVID-19 patients (17%) were treated with Ta1. Compared to the 91 critical patients not treated with Ta1, the Ta1 treated patients were more often from Dongguan People's Hospital (Guangdong Province) (Table 1), exhibited a lower serum procalcitonin level on admission (Table 2), and more often treated with immunoglobulin and albumin (Table 1).
Table 1: Demographics and clinical characteristics of COVID-19 patients on admission

|                      | Critically ill (n = 109) | p value |
|----------------------|--------------------------|---------|
|                      | Thymosin treatment (n = 18) | No thymosin treatment (n = 91) |         |
| Age, years           |                          |         |
| ≥ 60                 | 11 (61%)                 | 62 (68%) | 0.563   |
| Sex                  |                          |         |
| Female               | 6 (33%)                  | 38 (42%) | 0.506   |
| Male                 | 12 (67%)                 | 53 (58%) |         |
| Location             |                          |         |
| Dongguan, Guangdong  | 9 (50%)                  | 4 (4%)   | < 0.001 |
| Jingzhou, Hubei      | 9 (50%)                  | 87 (96%) |         |
| Signs and symptoms   |                          |         |
| Fever (≥ 37.3°C)     | 15 (83%)                 | 72 (79%) | 0.932   |
| Cough                | 12 (67%)                 | 67 (74%) | 0.546   |
| Dyspnea              | 10 (56%)                 | 43 (47%) | 0.520   |
| Sputum               | 7 (39%)                  | 26 (29%) | 0.384   |
| Myalgia              | 3 (17%)                  | 19 (21%) | 0.932   |
| Diarrhoea            | 2 (11%)                  | 13 (14%) | 1.000   |
| Cephalalgia          | 1 (6%)                   | 12 (13%) | 0.607   |
| Hemoptysis           | 0                        | 2 (2%)   | 1.000   |
| Comorbidities        |                          |         |
| Hypertension         | 9 (50%)                  | 40 (44%) | 0.638   |
| Diabetes             | 3 (17%)                  | 16 (18%) | 1.000   |
| Digestive tract disease | 2 (11%)             | 8 (9%)   | 1.000   |
| Cardiovascular disease | 0                        | 10 (11%) | 0.209   |
| Cerebrovascular disease | 1 (6%)                | 4 (4%)   | 1.000   |
| Malignancy           | 1 (6%)                   | 4 (4%)   | 1.000   |
| Liver disease        | 1 (6%)                   | 5 (5%)   | 1.000   |
|                              | Critically ill (n = 109) | p value |
|------------------------------|--------------------------|---------|
| Chronic lung disease         | 1 (6%)                   | 6 (7%)  | 1.000  |
| Treatments                   |                          |         |        |
| Antiviral treatment          | 15 (83%)                 | 84 (92%)| 0.448  |
| Interferon                   | 1 (6%)                   | 16 (18%)| 0.353  |
| Antibiotics                  | 15 (83%)                 | 83 (91%)| 0.558  |
| Corticosteroids              | 11 (61%)                 | 61 (67%)| 0.628  |
| Immunoglobulin               | 8 (44%)                  | 18 (20%)| 0.025  |
| Albumin                      | 8 (44%)                  | 3 (3%)  | < 0.001|
| Supplemental oxygen          | 18 (100%)                | 89 (98%)| 1.000  |
| Outcomes                     |                          |         |        |
| ARDS                         | 9 (50%)                  | 54 (59%)| 0.463  |
| Mechanical ventilation       | 3 (17%)                  | 43 (47%)| 0.032  |
| ECMO                         | 1 (6%)                   | 3 (3%)  | 1.000  |
| ICU admission                | 18 (100%)                | 61 (67%)| 0.003  |
| Mortality                    | 2 (11%)                  | 51 (56%)| 0.001  |
| Length of hospital stay (survival),days | 27.5 (17.3–31.5) | 19.0 (15.0–25.0) | 0.309  |

Data are median (IQR) or n (%). p values comparing thymosin treatment and non-thymosin treatment are from Mann-Whitney U test, Chi-Square test, or Fisher’s exact test, as appropriate. COVID-19 = Coronavirus Disease 2019. ECMO = extracorporeal membrane oxygenation. ARDS = acute respiratory distress syndrome. ICU = intensive care unit.
|                        | Reference values | Critically ill (n = 109) | p value |
|------------------------|------------------|--------------------------|---------|
|                        |                  | Thymosin treatment (n = 18) | No thymosin treatment (n = 91) |
| White blood cell count (X10^9/L) | 4.00–10.00 | 6.60 (4.41–8.75) | 7.73 (5.12–11.11) | 0.121 |
| Lymphocyte count (X10^9/L) | 1.50-4.00 | 0.76 (0.42–1.09) | 0.85 (0.65–1.20) | 0.119 |
| Neutrophil count (X10^9/L) | 2.00–7.00 | 5.45 (2.57–7.17) | 5.74 (3.55–8.80) | 0.215 |
| NLR | 0.78–3.53 | 8.14 (2.02–16.76) | 5.44 (3.27–10.56) | 0.862 |
| Monocyte count (X10^9/L) | 0.12-1.00 | 0.34 (0.22–0.46) | 0.37 (0.23–0.58) | 0.118 |
| Platelet count (X10^9/L) | 99.00-303.00 | 187.00 (161.75–218.50) | 190.00 (154.00-273.00) | 0.317 |
| APTT(s) | 21.00–37.00 | 34.20 (31.98–38.53) | 31.40 (24.59–36.43) | 0.198 |
| fibrinogen (g/L) | 2.00–4.00 | 3.70 (3.22–5.19) | 3.48 (2.65–4.66) | 0.137 |
| D-dimer (µg/mL) | 0.00-0.55 | 1.15 (0.35–1.71) | 0.57 (0.37–1.11) | 0.592 |
| Procalcitonin (ng/mL) | 0.00-0.50 | 0.11 (0.10–0.28) | 0.29 (0.15–0.44) | < 0.001 |
| CRP(mg/L) | 0.00–10.00 | 34.86 (6.01–103.90) | 24.28 (7.68–76.69) | 0.979 |
| ESR (mm/1 h) | 0.00–30.00 | 28.00 (19.00–66.00) | 34.00 (26.00-64.20) | 0.469 |
| Creatine kinase (U/L) | 25.00-200.00 | 68.60 (39.95-132.05) | 147.35 (66.50-179.75) | 0.768 |
| Lactate dehydrogenase (U/L) | 91.00-230.00 | 223.00 (192.15–311.70) | 226.00 (167.00-331.00) | 0.975 |
| Creatinine (µmol/L) | 44.00-112.00 | 67.40 (50.48–75.20) | 83.00 (65.70-110.40) | 0.107 |
| BUN (mmol/L) | 2.50–7.10 | 5.41 (4.70–9.35) | 6.36 (4.77–9.56) | 0.616 |
| AST (U/L) | 0.00–40.00 | 28.10 (20.63-38.00) | 38.00 (28.40–57.00) | 0.282 |
| ALT (U/L) | 0.00–50.00 | 23.00 (18.60-50.03) | 41.80 (28.00–61.00) | 0.230 |
| Total bilirubin (µmol/L) | 3.00–21.00 | 18.10 (8.73–20.95) | 19.70 (13.90–28.50) | 0.053 |
| Reference values | Critically ill (n = 109) | p value |
|------------------|-------------------------|---------|
|                  |                         |         |

Data are median (IQR). p values comparing thymosin treatment and non-thymosin treatment are from Mann-Whitney U test or Student's t test, as appropriate. NLR = neutrophil-to-lymphocyte ratio. APTT = activated partial thromboplastin time. ESR = Erythrocyte sedimentation rate. CRP = C-reactive protein. BUN = blood urea nitrogen. AST = aspartate transaminase. ALT = alanine aminotransferase.

Two patients (11%) in the Ta1 died compared to 51 patients (56%) in the non-Ta1 group. Similarly, 3 patients (17%) in the Ta1 group required mechanical ventilation, compared to 43 patients (47%) in the non-Ta1 group (Table 1). After adjusting for potential confounding factors including age, gender, location of the hospitals, comorbidities, treatment with immunoglobulin and albumin, Ta1 treatment was identified as a protective factor for mortality, with an adjusted odds ratio of 0.02 (95%CI: 0.00-0.35) (Table 3). However, no correlation was observed between Ta1 treatment and the requirement for mechanical ventilation after adjustment for confounding factors (Table 4).
Table 3, Logistic univariate and multivariate regression analyses on the association between the mortality rate and the clinical features

|                        | Univariable OR (95%CI) | p value | Multivariable OR (95%CI) | p value | Adjust factors                                                                 |
|------------------------|------------------------|---------|--------------------------|---------|-------------------------------------------------------------------------------|
| **Age ≥ 60 years**     | 1.28 (0.81–2.03)       | 0.293   | 0.02 (0.00–0.35)         | 0.009   | age, sex, hypertension, diabetes, antiviral treatment, interferon, antibiotics, corticosteroids, intravenous immunoglobulin, albumin, region, procalcitonin (on admission) |
| **Sex**                | 0.86 (0.53–1.40)       | 0.536   |                          |         |                                                                               |
| **Comorbidities**      |                        |         |                          |         |                                                                               |
| Hypertension           | 1.45 (0.82–2.56)       | 0.201   |                          |         |                                                                               |
| Diabetes               | 1.11 (0.45–2.73)       | 0.819   |                          |         |                                                                               |
| **Treatments**         |                        |         |                          |         |                                                                               |
| Thymosin α1            | 0.13 (0.03–0.54)       | 0.006   | 0.02 (0.00–0.35)         | 0.009   | age, sex, hypertension, diabetes, thymosin α1, interferon, antibiotics, corticosteroids, intravenous immunoglobulin, albumin, region, procalcitonin (on admission) |
| Antiviral treatment    | 0.94 (0.64–1.40)       | 0.763   | 0.70 (0.12–4.21)         | 0.696   | age, sex, hypertension, diabetes, thymosin α1, interferon, antibiotics, corticosteroids, intravenous immunoglobulin, albumin, region, procalcitonin (on admission) |
| Interferon             | 7.50 (1.72–32.80)      | 0.007   | 1.31 (0.17–10.00)        | 0.792   | age, sex, hypertension, diabetes, thymosin α1, antiviral treatment, antibiotics, corticosteroids, intravenous immunoglobulin, albumin, region, procalcitonin (on admission) |
| Antibiotics            | 0.92 (0.62–1.37)       | 0.686   | 0.67 (0.11–4.10)         | 0.667   | age, sex, hypertension, diabetes, thymosin α1, antiviral treatment, interferon, corticosteroids, intravenous immunoglobulin, albumin, region, procalcitonin (on admission) |
|                  | Univariable OR (95%CI) | p value | Multivariable OR (95%CI) | p value | Adjust factors                                                                 |
|------------------|------------------------|---------|--------------------------|---------|-------------------------------------------------------------------------------|
| Corticosteroids  | 1.88 (1.16–3.05)       | 0.011   | 8.61 (2.27–32.61)        | 0.002   | age, sex, hypertension, diabetes, thymosin α1, antiviral treatment, interferon, antibiotics, intravenous immunoglobin, albumin, region, procalcitonin (on admission) |
| Intravenous      | 2.25 (0.98–5.18)       | 0.056   | 2.97 (0.29–30.27)        | 0.359   | age, sex, hypertension, diabetes, thymosin α1, antiviral treatment, interferon, antibiotics, corticosteroids, albumin, region, procalcitonin (on admission) |
| immunoglobulin   |                        |         |                          |         |                                                                               |
| Albumin          | 0.57 (0.17–1.95)       | 0.372   | 2.99 (0.16–56.31)        | 0.465   | age, sex, hypertension, diabetes, thymosin α1, antiviral treatment, interferon, antibiotics, corticosteroids, intravenous immunoglobin, albumin, region, procalcitonin (on admission) |
| ARDS             | 2.00 (1.19–3.38)       | 0.009   | 4.08 (1.76–9.48)         | 0.001   | age, sex, comorbidities                                                       |
| Location         | 0.07 (0.01–0.56)       | 0.012   | 0.05 (0.00–0.53)         | 0.014   | age, sex, comorbidities                                                       |
| (Dongguan)       |                        |         |                          |         |                                                                               |
| Procalcitonin    | 1.44 (0.84–2.46)       | 0.186   |                          |         |                                                                               |
| (on admission)   |                        |         |                          |         |                                                                               |

OR = odds ratio. CI = confidence interval. ARDS = acute respiratory distress syndrome.
Table 4  
Logistic univariate and multivariate regression analyses on the association between the mechanical ventilation and the clinical features

|                                      | Univariable OR (95%CI) | p value | Multivariable OR (95%CI) | p value | Adjust factors                                                                 |
|--------------------------------------|------------------------|---------|--------------------------|---------|---------------------------------------------------------------------|
| Age ≥ 60 years                       | 0.87 (0.55–1.38)       | 0.559   |                          |         |                                                                    |
| Sex                                  | 0.81 (0.49–1.31)       | 0.386   |                          |         |                                                                    |
| Comorbidities                        |                        |         |                          |         |                                                                    |
| Hypertension                         | 0.82 (0.46–1.43)       | 0.476   |                          |         |                                                                    |
| Diabetes                             | 0.90 (0.37–2.22)       | 0.819   |                          |         |                                                                    |
| Treatments                           |                        |         |                          |         |                                                                    |
| Thymosin α1                          | 0.20 (0.06–0.69)       | 0.011   | 0.23 (0.03–1.87)         | 0.168   | age, sex, hypertension, diabetes, antiviral treatment, interferon, antibiotics, corticosteroids, intravenous immunoglobulin, albumin, region, procalcitonin (on admission) |
| Antiviral treatment                  | 0.68 (0.45–1.01)       | 0.058   |                          |         |                                                                    |
| Interferon                           | 1.43 (0.54–3.75)       | 0.469   |                          |         |                                                                    |
| Antibiotics                          | 0.75 (0.50–1.12)       | 0.159   |                          |         |                                                                    |
| Corticosteroids                      | 1.00 (0.63–1.59)       | 1.000   |                          |         |                                                                    |
| Intravenous immunoglobulin           | 1.00 (0.46–2.16)       | 1.000   |                          |         |                                                                    |
| Albumin                              | 0.38 (0.10–1.41)       | 0.147   |                          |         |                                                                    |
| Condition | Univariable OR (95%CI) | p value | Multivariable OR (95%CI) | p value | Adjust factors |
|-----------|------------------------|---------|---------------------------|---------|----------------|
| ARDS      | 1.63 (0.98–2.70)       | 0.061   |                           |         |                |

OR = odds ratio. CI = confidence interval. ARDS = acute respiratory distress syndrome.

Most of the critical patient in both study groups exhibited similarly severe lymphocytopenia on admission. Before discharge, the lymphocyte counts of many patients treated with Ta1 were restored to the normal range, and were significantly higher than those in the non-Ta1 group (Table 2, 5).
Table 5
Laboratory findings of critical COVID-19 patients before discharge

|                          | Reference values | Critically ill (n = 109) | p value |
|--------------------------|------------------|--------------------------|---------|
|                          |                  | Thymosin treatment (n = 18) | No thymosin treatment (n = 91) |
| White blood cell count (X10^9/L) | 4.00–10.00 | 5.50 (3.77–9.56) | 7.90 (5.87–11.64) | 0.125 |
| Lymphocyte count (X10^9/L) | 1.50–4.00 | 1.14 (0.97–1.84) | 0.73 (0.53–1.11) | 0.026 |
| Neutrophil count (X10^9/L) | 2.00–7.00 | 3.01 (1.51–6.23) | 5.92 (3.85–8.58) | 0.044 |
| NLR                      | 0.78–3.53 | 2.59 (1.47–4.32) | 8.30 (4.38–13.53) | < 0.001 |
| Monocyte count (X10^9/L) | 0.12–1.00 | 0.34 (0.19–0.65) | 0.48 (0.29–0.65) | 0.191 |
| Platelet count (X10^9/L) | 99.00–303.00 | 209.50 (155.00–285.25) | 196.00 (128.00–275.00) | 0.737 |
| APTT(s)                  | 21.00–37.00 | 34.00 (31.80–36.08) | 35.20 (27.15–42.55) | 0.453 |
| fibrinogen (g/L)         | 2.00–4.00 | 3.71 (2.76–4.69) | 3.27 (2.05–4.33) | 0.164 |
| D-dimer (µg/mL)          | 0.00–0.55 | 0.95 (0.40–2.43) | 0.87 (0.38–5.50) | 0.795 |
| Procalcitonin (ng/mL)    | 0.00–0.50 | 0.10 (0.10–0.30) | 0.32 (0.21–0.48) | 0.351 |
| CRP (mg/L)               | 0.00–10.00 | 22.33 (5.00–74.18) | 49.45 (16.91–135.83) | 0.004 |
| ESR (mm/1 h)             | 0.00–30.00 | 40.50 (12.00–59.00) | 46.00 (32.00–83.00) | 0.231 |
| Creatine kinase (U/L)    | 25.00–200.00 | 32.00 (23.60–60.00) | 180.00 (54.15–365.50) | 0.514 |
| Lactate dehydrogenase (U/L) | 91.00–230.00 | 241.30 (175.93–312.00) | 313.00 (203.75–541.50) | 0.335 |
| Creatinine (µmol/L)      | 44.00–112.00 | 60.65 (41.00–78.98) | 83.00 (65.95–142.45) | 0.063 |
| BUN (mmol/L)             | 2.50–7.10 | 5.90 (4.08–7.86) | 7.63 (5.39–17.93) | 0.203 |
| AST (U/L)                | 0.00–40.00 | 36.20 (26.23–68.75) | 64.00 (43.25–109.00) | 0.266 |
| ALT (U/L)                | 0.00–50.00 | 36.75 (23.13–98.75) | 65.50 (43.55–136.65) | 0.121 |
| Total bilirubin (µmol/L) | 3.00–21.00 | 15.30 (9.78–21.28) | 27.00 (19.40–33.88) | 0.628 |
| Reference values | Critically ill (n = 109) | p value |
|------------------|-------------------------|---------|
| SOFA             | 4.00 (3.00-6.25)        | 9.00 (4.00–13.00) | <0.001 |

Data are median (IQR). p values comparing thymosin treatment and non-thymosin treatment are from Mann-Whitney U test or Student’s t test, as appropriate. NLR = neutrophil-to-lymphocyte ratio. APTT = activated partial thromboplastin time. ESR = Erythrocyte sedimentation rate. CRP = C-reactive protein. BUN = blood urea nitrogen. AST = aspartate transaminase. ALT = alanine aminotransferase. SOFA = Sequential Organ Failure Assessment.

The laboratory results before discharge were similar to those on admission in that both study groups exhibited elevated inflammatory markers such as C-reactive protein (CRP) and Erythrocyte sedimentation rate (Table 2, 5). Importantly, the CRP level was significantly lower in the Ta1 group compared to the non-Ta1 group before discharge. Similarly, other inflammatory markers such as the neutrophil count and the neutrophil-to-lymphocyte ratio fell into the normal range in all patients treated with Ta1 (Table 5). Before discharge, markers of tissue damage for liver, kidney, and muscle in the Ta1 group exhibited a trend of decreased level compared to the non-Ta1 group, in line with the lower Sequential Organ Failure Assessment (SOFA) score in Ta1 group (Table 5).

**Discussion**

With our patients, Ta1 is the best pharmaceutical intervention for critical COVID-19 achieving a much reduced mortality rate (11%), compared to the mortality rate in the non-Ta1 group (56%). Our data also indicated that the reduced mortality rate by Ta1 is linked with the increased counts of lymphocytes and the prevention of infections and injuries of multiple organs. Therefore, Ta1 may have protected the patients by boosting the antiviral capacity of the immune system.

Our observations are in concert with a recent report that Ta1 increased lymphocyte counts and thymus output, and reversed T cell exhaustion in severe COVID-19[7]. Similar outcomes were observed with influenza virus infected mice. When treated with Ta1, these mice exhibited increased NK-cell activity, CD4 and CD8 cell counts and activity in the lung, reduced viral titers and increased survival[9]. Besides viral infection, Ta1 has been successful in the treatment of severe sepsis, a condition known for high mortality rate. Patients with severe sepsis often present multi-organ failure in septic shock characterized by over-stimulation of the immune system in response to infection, and are commonly treated with immune suppressive drugs such as glucocorticoids. Counter-intuitively, several studies have demonstrated benefits of Ta1 in the treatment of severe sepsis, including higher survival rates[10].

The timing of the Ta1 treatment may be critical, because evidence has been presented for over-active immune system in causing the critical illness and mortality in COVID-19[1, 2]. Our patients received Ta1 at times when severe symptoms presented with persistent viral infection or lymphocytopenia, likely in a status of immune exhaustion. Monitoring serum cytokine levels may provide additional help in making the decision on whether to use and when to use Ta1.
The therapeutic mechanism of Ta1 remains largely unknown. Through up-regulation of TLR2 and TLR9 expression, the pleiotropic effects of Ta1 include not only enhanced functions of NK cells, CD4+ and CD8+ T cells[9, 11], but also FoxP3+ Treg cells that promotes immune tolerance[12–14]. Before further evidence from mechanistic study is available, we cannot rule out the possibility that the benefits of Ta1 in critical COVID-19 was mediated by the Ta1 stimulation of the proliferation of FoxP3+ Treg cells, which consequently led to a more balanced immune activity.

**Limitations**

Our study has several limitations. Firstly, this is a retrospective study based on chart review, wherein the validity of the diagnosis and the evaluation factors might have led to information bias. Secondly, COVID-19 is a sudden epidemic, the supply of medical resources might affect the treatment which may led to selection bias. Thirdly, there was a relatively small sample size in Ta1 group. Thus, further research is necessary to evaluate the external validation and applicability with a larger sample size.

**Abbreviations**

COVID-19, Coronavirus Disease 2019;

CRP, C-reactive protein;

SARS-CoV-2, severe acute respiratory syndrome-related coronavirus-2;

SOFA, Sequential Organ Failure Assessment;

Ta1, Thymosin alpha 1.

**Declarations**

**Ethics approval, guidelines and consent to participate**

This study was approved by the Institutional Review Boards of Sun Yat-sen University and the participating hospitals. The study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Informed consent was waived by the Clinical Research Ethics Committee of The Sixth Affiliated Hospital of Sun Yat-sen University since this study was a retrospective chart review and did not involve any patient tissue or interview.

**Consent for publication**

Not applicable.
Availability of data and materials

Data set is available on a reasonable requests from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LZ, GY, YZ and RZ conceived and designed this study. YL, SC, JK, JL, LS, RF, JG, YH and LZ collected data. YL, SC, JK, NJ and LZ prepared the first draft. All authors critically revised the manuscript and approved the final version.

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**Figures**

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**Figure 1**

Study flow diagram. Medical records of COVID-19 patients included for the study of the thymosin alpha 1 effects were accessed from Jingzhou Hospital of Traditional Chinese Medicine (61 cases), Jianli Hospital...
of Traditional Chinese Medicine (44 cases), Dongguan People's Hospital (13 cases), Jingzhou First Hospital (9 cases), Jingzhou Central Hospital (29 cases), Jingzhou First People's Hospital (11 cases), Jingzhou Chest Hospital (9 cases), Gongan People's Hospital (8 cases), Honghu People's Hospital (10 cases), Honghu Hospital for the Control of Schistosomiasis (3 cases), Honghu Central Hospital (2 cases), Jianli People's Hospital (3 cases), Jiangling People's Hospital (2 cases), Shishou Hospital of Traditional Chinese Medicine (5 cases), and Songzi People's Hospital (6 cases).