ORIGINAL ARTICLE

A Double-blind Multicenter Two-arm Randomized Placebo-controlled Phase-III Clinical Study to Evaluate the Effectiveness and Safety of Thymosin α1 as an Add-on Treatment to Existing Standard of Care Treatment in Moderate-to-severe COVID-19 Patients

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Abstract

Background: From an epidemic outbreak, coronavirus disease-2019 (COVID-19) has quickly developed. Thymosin α1 (Tα1) has the ability to boost the T-cell numbers, support T-cell differentiation, maturation, and reduce cell apoptosis. In this study, we have investigated the efficacy and safety of Tα1 in moderate-to-severe COVID-19 patients.

Patients and methods: In this double-blind, multicenter, two-arm, randomized, placebo-controlled, phase III clinical study, patients were randomized to receive either Tα1 or placebo in combination with standard of care (SOC). The data on all-cause mortality, clinical progression/ deterioration, duration of hospital/intensive care unit (ICU) stay, and safety data were collected. The patients were telephonically followed up on Day 28.

Results: A total of ($n = 105$) COVID-19 patients were included in the study, of which 40 and 65 were severe and moderate, respectively. Thymosin arm (11.1%) had a statistically lower death rate in comparison to the placebo arm (38.5%). A total of 67 adverse events were reported in 42 patients among 105 dosed patients during the study. Among them, 43 adverse events were of mild in nature, 16 adverse events were of moderate in nature, and 8 serious adverse events (death) occurred during the study.

Conclusion: This study provides evidence that Tα1 can lower death rate in severe COVID-19 patients, reduce the load on hospitals by shortening the required number of days of hospitalization and help in abbreviating the requirement of oxygen support by positively impacting the recovery rate and time taken for recovery.

Keywords: Coronavirus disease-2019, Mortality, Thymosin α1.

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Introduction

The COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly developed from an epidemic outbreak in Wuhan, China.[1] In the last few months, it has spread all over China and near 213 other countries worldwide having 5,683,802 confirmed COVID-19 cases till the date. The emerging data suggest that COVID-19 should be viewed as a systemic disease involving multiple systems, including the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems, despite the fact that it is well known that COVID-19 primarily manifests as a respiratory tract infection.[2,3]

Thymic epithelial cells generate a type of polypeptide hormone called thymosin 1 (T1), which has the ability to significantly boost T cell counts, assist T-cell development and maturation, and lower cell death.[4,5] Thus, T1 has been successfully employed in clinical practice to treat individuals who have hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency viruses (HIV). Pathological observation has also supported T1's usefulness.[6–8] Additionally, 76 critically ill COVID-19 cases who were admitted to the General Hospital of the Central Theatre Command and Wuhan Pulmonary Hospital in Wuhan from December 2019 to March 2020 and whose clinical data were retrospectively analyzed provide a preliminary demonstration that T1 benefits COVID-19 patients, particularly those with severe lymphocytopenia, and that it lowers the mortality of severe COVID-19 patients compared to the untreated group. Thus, Tα1 may be a potential treatment that can be dosed in combination with SOC in patients with COVID-19.[9]

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In this double-blind, multicenter, two-arm, randomized, placebo-controlled, phase III clinical study, we have evaluated and compared the efficacy of Tα1 in combination with SOC and SOC alone, in moderate-to severe COVID-19 patients. Additionally, we also evaluated and compared the efficacy of Tα1 in combination with SOC vs placebo with SOC on associated clinical response. Furthermore, the safety of study formulations in moderate-to-severe COVID-19 patients was evaluated.

Materials and Methods

Study Design and Study Population

This multicenter, two-arm, randomized, placebo-controlled, double-blind study was done in male and female patients with moderate and severe COVID-19 symptoms. The DCGI (CT/SND/80/2020) and all institutional ethics committees at trial sites gave their approval to the protocol, which was then registered in the Clinical Trial Registry of India (CTRI/2020/10/028277). The Good Clinical Practice recommendations and the principles of the Declaration of Helsinki were followed during the study's execution. According to the Consolidated Standards of Reporting Trials, the study was reported (CONSORT 2017).

Patient Recruitment

After obtaining written informed consent from the study patients, the participants were recruited according to the inclusion/exclusion criteria. The study was done in two separate cohorts comprising moderate and severe COVID-19 patients. We included both male and female whose age was above or18 years with moderate and SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) test/any other confirmatory tests. For the patients with moderate symptoms, the patient presented with any one of the following features: Respiratory rate, ≥24 breaths/min; oxygen saturation (SpO_2), from >90 to ≤94% on room air. For patients with severe symptoms, the patient presented with any one of the following features: Respiratory distress with respiratory rate, ≥30 breath/min; SpO_2, ≤90% on room air; arterial blood oxygen partial pressure (PaO_2)/fraction of inspired oxygen (FiO_2), ≤200 mm Hg (1 mm Hg = 0.133 kPa); and patient presented with respiratory failure requiring mechanical ventilation support. All patients who had participated in any other clinical trial of an experimental treatment for COVID-19 or those with pre-existing illness or those who had participated in another trial with an investigational drug within 1 month prior to this trial were excluded. Additionally, female patients who were breast feeding, pregnant, or intended to become pregnant during the study were also excluded.

Study Interventions

Patients with moderate symptoms of COVID-19 were administered two subcutaneous injections of active treatment (containing 1.6-mg Tα1) or placebo along with SOC in the morning and two subcutaneous injections of active treatment (containing 1.6-mg Tα1) or placebo in the evening along with SOC as per randomization schedule from Day 1 to Day 7.

Patients with severe symptoms of COVID-19 were administered two subcutaneous injection of active treatment (containing 1.6-mg Tα1) or placebo thrice daily—in the morning, afternoon, and evening—along with SOC as per randomization schedule from Day 1 to Day 7.

Standard of care was according to the Revised Guidelines on Clinical Management of COVID-19, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. The following were received by the patients: Steroids, $N = 57$; antivirals: $N = 16$; and other disease-modulating drugs such as HCQ, tocilizumab, etc., $N = 2$.

Study Procedure

All patients were made to undergo the screening procedure to determine whether they are meeting the required inclusion and exclusion criteria. The patients were randomized to receive either active (Tα1 1.6-mg injection + SOC) or placebo (placebo injection + SOC) arm using a computer-generated randomization sequence using Random Allocation software, v.2.0. Block randomization was used and the block size was six and the allocation ratio was 2:1. Interactive web response system (IWRS) was used to maintain allocation concealment. The duration of each patient's participation in the study was 7 days of treatment period and follow-up till Day 28. The patients' medical/surgical history, including the concomitant medications was documented. The patient's demographics, physical examination including vital signs [blood pressure (BP), pulse rate, respiration rate, oxygen (O_2) saturation, and chest X- ray] were recorded. All patients were made to undergo clinical laboratory tests for biomarkers and for safety. Female patients of childbearing age underwent a urine pregnancy test. The clinical assessment of COVID-19 infection was done by the investigator (e.g., checking the ordinal score, respiratory symptoms assessment). All patients were hospitalized. The WHO 8-point ordinal scale has been described previously. The below mentioned details were collected prospectively:

- *Incidences of All-cause Hospital Mortality:* Time frame—from the date of drug administered until the date of hospital discharge or date of death from any cause, whichever came first, assessed up to 28 days.
- *Evaluation of Clinical Progression/Deterioration*: Based on 8-point ordinal scale (recommended by the World Health Organization: Coronavirus disease-2019 R&D) (time frame up to 7 days) on Day 1, screening, and end of the treatment (EOT) (Day 7).
- *Investigations Done on Day 1 and Day 7:* During hospitalization, the patient's physical examination was done once daily. Vital sign assessments (BP, pulse rate, respiration rate, and O_2 saturation) were recorded twice a day. Assessment of respiratory and constitutional symptoms were done twice a day. The following biomarkers, namely, total lymphocytes count; CD4 and CD8 count; ferritin levels; interleukin 6 (IL-6); lactate dehydrogenase (LDH); C-reactive protein (CRP) and D-dimer were assessed. The patients were telephonically called for a follow-up on Day 28.

Adverse Event and Concomitant Medication Assessment

Adverse events occurring during the study period were monitored until satisfactory resolution or stabilization. It was recorded in case record form (CRF) and managed appropriately. Concomitant medication assessment was done and recorded in CRFs during the study.

Statistical Analysis

Assuming that the treatment difference of 20% with respect to all-cause mortality in 28 days, a total of approximately 105 subjects (70 subjects per Tα1 + SOC arm, and 35 in the placebo + SOC arm using a 2:1 ratio) are required to achieve at least 80% of power with the type I error of 0.05, a total of approximately

Table 1: Baseline characteristics of the study patients

	Moderate			*Severe*		
Characteristics	*Active (n = 48)*	*Placebo (n = 17)*	*p-value*	*Active (n = 27)*	*Placebo (n = 13)*	*p-value*
Age (years)	49 (38–62)	44 (31–52)	0.63	48 (35–58)	55 (40–72)	0.17
Gender						
Male	33 (69%)	13 (77%)	0.54	16 (59%)	9 (69%)	0.54
Female	15 (31%)	4 (23%)		11 (41%)	4 (31%)	
Hospital stay (days)	7 (7–8)	9 (8–10)	0.0001	12 (10–13)	15 (11–19)	0.01
ICU stay (days)	None	None		10 (8–12)	15 (11–19)	0.001

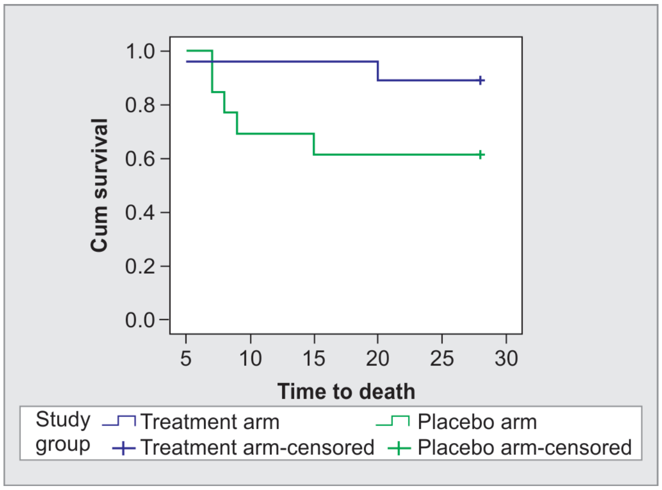


Fig. 1: Kaplan–Maier graph on all-cause mortality among severe COVID-19 patients

120 subjects will be randomized into the study if a dropout rate of 10% is assumed. A total of approximately 120 subjects were randomized into the study assuming a 10% dropout rate. Our assumptions on the estimates of the treatment difference were based on the results published in the research articles. Continuous variables were summarized as mean SD or median interquartile range (IQR), and percentages and frequencies were used to express categorical data. The Chi-squared test was used to assess differences between groups in the categorical variables. Depending on how the data were distributed, either parametric or non-parametric tests were utilized. The differences in the primary outcomes were measured using paired Student's *t* test or Wilcoxon signed rank–sum test. The differences in continuous variables between the groups were analyzed with Mann–Whitney *U* test or independent samples *t*-test. Kaplan–Maier curve with log rank test was used to plot the difference in outcomes across the study period between the two groups. All statistical analyses were performed with SPSS software, v.16.0 (SPSS Inc., Chicago, IL). Also, $p < 0.05$ were considered statistically significant.

Results

Baseline Characteristics of the Study Patients

A total of ($n = 105$) COVID-19 patients were included in the study, of which 40 were severe and 65 were of moderate nature. Among the patients with moderate COVID-19, the number of patients randomized to active and placebo drugs were ($n = 48$) and ($n = 17$), respectively. Among the patients with severe COVID-19, the number of patients randomized to active and placebo drugs were ($n = 27$) and ($n = 13$), respectively. There were no statistical differences in the baseline characteristics such as age and gender between the two groups of patients (Table 1). The baseline characteristics of patients including the presence of comorbidities were as follows: The total number of patients with comorbidity was 31 and the number of patients more than one comorbidity was 8. About 67 patients received oxygen, where the mode of oxygen therapies were nasal prongs, NRBM, HFNO, etc., and 15 patients received NIV or invasive mechanical ventilation. The median duration of illness prior to giving the study drug was 3 (2–7) days.

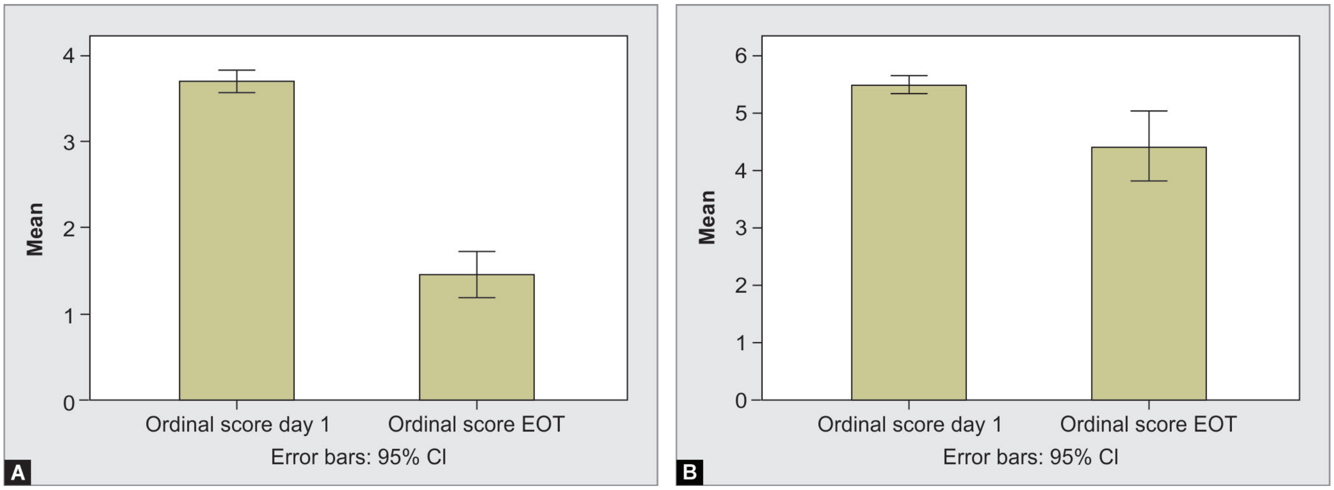
Effect of Thymosin on All-cause Mortality, Clinical Progression/Deterioration, and Hospitalization

There was a statistically significant ($p = 0.03$) difference between two arms with respect to all-cause mortality, where thymosin arm had 11.1% death rate compared to 38.5% in placebo arm, with absolute difference of 27.4% (Fig. 1). A total of 96% of the patients in study arm have shown progression/improvement after 7 days of treatment with Tα1 along with SOC in WHO 8-point ordinal score vs 57% in placebo arm in moderate group (Fig. 2). There was a significant decrease in the WHO ordinal scale in the thymosin arm compared to placebo arm for both moderate ($p = 0.0001$) and severe patients ($p = 0.0001$) (Table 2). The SPO_2 levels significantly improved in the study group in comparison to the placebo group (for moderate, p-value = 0.005; for severe, $p = 0.0001$). The median number of ventilator days were more in the placebo group in comparison to the treatment group [11 vs 7 days ($p = 0.002$)]. For moderate, no subjects have been on ventilator and thus the data is not applicable (Table 2).

Among the patients with moderate disease, the median number of days of hospitalization was significantly lesser in the study arm in comparison to the placebo arm [7 vs 9 days ($p = 0.0001$)]. This similar pattern was also seen in severe disease between both groups [12 vs 15 days ($p = 0.01$)] (Fig. 3). The median duration of ICU stay was significantly lesser in the study group (10 days) in comparison to the placebo group (15 days); ($p = 0.001$) (Table 1). During disease progression, the number of patients who required advanced respiratory support, mechanical ventilation, vasopressors, and dialysis were 11, 2, 5, and none, respectively.

Effect of Thymosin on the Immune Microenvironment and Cytokines

In moderate COVID-19 patients, there was a significant increase in the expression of CD4 ($p = 0.01$) and CD8 ($p = 0.01$) in the T cells in study arm in comparison to the placebo arm. Additionally, the levels of D-dimer significantly reduced in the study arm in comparison to the placebo arm ($p = 0.04$) (Table 3). Among the



Figs 2A and B: Effect on thymosin on *8-point ordinal scale

Table 2: Effect of thymosin on clinical progression/deterioration among patients

	Active arm		*Placebo arm*		**p-value*
Moderate patients					
*8-point ordinal scale	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	4	1	4	3	**0.0001**
IQR	3–4	(1–1)	3–4	2–3	
SPO_2					
Median	92	98	92	96	**0.005**
IQR	91–93	97–99	91–93	95–97	
Severe patients					
*8-point ordinal scale	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	6	3	5	6	**0.0001**
IQR	5–6	3–4	5–5	5–8	
SPO_2					
Median	88	94	88	86	**0.0001**
IQR	86–89	93–95	86–90	79–89	

*p value denotes the change in the 8-point ordinal scale and SPO_2 from day 1 to EOT between active arm and placebo arm; IQR, interquartile range

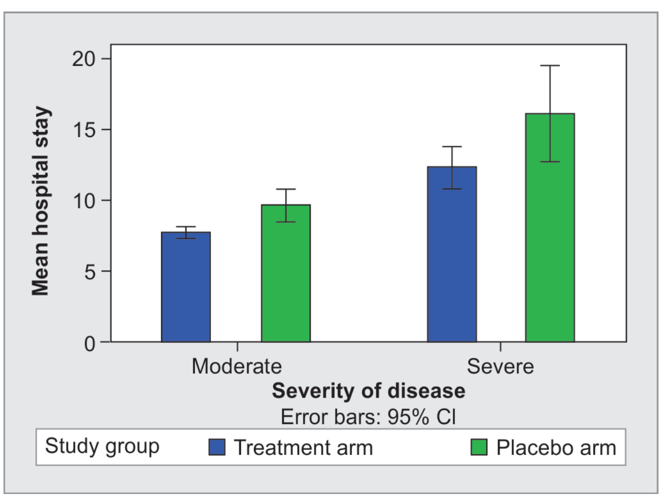


Fig. 3: Effect on thymosin on hospital days

patients with severe disease, there was a significant increase in the expression of CD4 (p = 0.0001), CD8 (p = 0.005), and total leukocyte count (TLC) (p = 0.0001) in study arm in comparison to the placebo arm. A significant decrease in the levels of D-dimer (p = 0.002), IL-6 (p = 0.0001), CRP (p = 0.0001), and ferritin (p = 0.002) was seen (Table 4).

Adverse Events

A total of 67 adverse events were reported in 42 patients among 105 dosed patients during the study. Forty-three adverse events were of mild in nature. Sixteen adverse events were of moderate in nature. Eight serious adverse events (death) occurred during the study. All 67 adverse events were "not related" to the study drug. The administration of Tα1 along with SOC to the patients with moderate-to-severe COVID-19 appears to have acceptable safety.

Discussion

In this double-blind, multicenter, two- arm, randomized, placebo-controlled, phase III clinical study, we have investigated the safety and efficacy of Tα1 in combination with SOC and SOC alone, in moderate-to-severe COVID-19 patients. The major findings of the study were as follows: (i) The addition of Tα1 significantly reduced the mortality rates, reduced the median number of hospital/ICU days, WHO ordinal score and SPO_2. (ii) Furthermore, there was a significant reduction in the biomarkers D-dimer, CRP, LDH, ferritin, IL-6, and an increase in the CD4, CD8 T cells, and TLC.

It has been reported that Tα1 enhances the immune responses of severe acute respiratory syndrome (SARS) patients and helps to limit the spread of SARS and treat patients infected with HBV, HCV, and HIV. Being a polypeptide hormone produced by thymic epithelial cells, this can effectively increase T-cell production, support T-cell differentiation, maturation, and reduce cellular apoptosis. Moreover, prior retrospective studies have shown that treatment with Tα1 reduced the mortality rates among severe COVID-19 patients.[9–11] To the best of our knowledge, this is the first randomized controlled study reporting the beneficial effects of Tα1 by reducing the mortality rates and improving the ordinal scores. Based on these assumptions, Tα1 seems to be a potential treatment that can be dosed in combination with SOC in patients with COVID-19 by enhancing the cellular immunity for the resistance of viral infection.

Table 3: Effect of thymosin on laboratory investigations among moderate patients

Parameters	*Active arm*		*Placebo arm*		*p-value
CD4	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	219	372	346	216	**0.01**
IQR	134–357	234–552	164–470	193–446	
CD8	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	211	385	291	247	**0.01**
IQR	127–324	214–467	134–434	171–402	
Ferritin levels	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	288	268	127	168	0.61
IQR	98–390	167–369	46–229	98–234	
IL-6	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	36	15	45	28	0.44
IQR	8–98	6–34	4–209	3–151	
LDH	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	226	248	197	278	0.14
IQR	172–351	205–312	140–273	181–365	
CRP	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	8.6	5.8	10	7	0.57
IQR	3.6–21	3.1–9.4	4–21	3–13	
D-dimer	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	838	532	987	721	**0.04**
IQR	600–1250	217–775	461–1333	512–1484	
TLC	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	596	893	650	871	0.22
IQR	385–874	604–1238	431–1026	356–1303	

**p* value: Change in the laboratory investigations from Day 1 to EOT between active arm and placebo arm; LDH, lactate dehydrogenase; IQR, interquartile range; TLC, total leukocyte count

The earlier studies that have investigated the role of immune mediators in COVID-19 patients have shown that critically ill COVID-19 patients develop uncontrolled inflammatory activation, resulting in the increase in neutrophils and decrease in the total number of lymphocytes. Lymphocytes play a key role in the antiviral processes by balancing the fight against pathogens and risk, and decreased lymphocytes is related to poor prognosis in several diseases.[12,13] This study is in line with previous studies demonstrating that supplementation of Tα1 increased the production of CD4, CD8, and TLC among severe to moderate COVID-19 patients. Thymosin α1 activates the toll-like receptor (TLR), leading to stimulation of the nuclear factor kappa B (NF-κB) and p38 mitogen-activated protein kinase (MAPK) pathways, playing a critical role in cell maturation. Other biomarker candidates that mediate inflammation in COVID-19 has been the IL-6, which is a cytokine produced by macrophages inducing a proinflammatory response an is often found to be elevated in COVID-19 patients. The activation of IL-6 leads to the production of acute phase proteins, such as these proteins are CRP, serum amyloid A (SAA), fibrinogen, haptoglobin, and a1-antichymotrypsin in the initial stage of inflammation. *In vitro* studies have shown that the treatment with Tα1 mitigated the cytokine release syndrome suggesting a potential role of Ta1 in modulating the immune response homeostasis and the cytokine storm.[14] In an earlier study, it was seen that Tα1-mediated inhibition of IL-6 accompanied by the induction and maintenance of high levels of IL-10, a cytokine that is well known as a master regulator of immune responses.[15,16] Similar findings were seen in this study which showed that administration of Tα1 downregulated the levels inflammatory mediators such as D-dimer, CRP, LDH, ferritin, and IL-6 which are known markers of poor prognosis. These findings suggest the potential use of Tα1 in modulating the immune response homeostasis and the cytokine storm *in vivo*.

Thymosin α should be given as early as possible as it has shown benefit in both moderate and severe COVID-19 patients. In the viral replication phase, it can prevent cytokine storm and prevent from moving to severe category, in the inflammatory phase it causes immune homeostasis. Molnupiravir and nirmatrelvir was not approved during the trial phase of thymosin α in India. These drugs are indicated for patients with mild COVID-19 who are not hospitalized. We suggest based on our data that thymosin is a suitable drug that could be best utilized for patients with moderate and severe COVID-19 who have a greater risk of poor outcomes. High-risk patients may have a less chance of poor outcomes if on thymosin.

Table 4: Effect of thymosin on laboratory investigations among severe patients

Parameters	*Active arm*		*Placebo arm*		*p-value
CD4	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	183	434	147	198	**0.0001**
IQR	108–258	273–615	121–298	64–275	
CD8	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	179	431	187	181	**0.005**
IQR	138–256	157–742	99–257	104–213	
Ferritin levels	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	878	488	1045	1437	**0.002**
IQR	523–1578	282–727	694–2203	798–2000	
IL-6	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	178	77	325	487	**0.0001**
IQR	99–241	22–137	161–422	276–657	
LDH	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	362	252	543	794	0.12
IQR	207–609	160–459	189–1100	330–955	
CRP	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	49	21	58	75	**0.0001**
IQR	23–95	6–47	21–84	25–143	
D-dimer	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	2000	1253	1456	1577	**0.002**
IQR	958–3577	504–2067	894–2127	980–4615	
TLC	*Day 1*	*EOT*	*Day 1*	*EOT*	
Median	373	759	1345	913	**0.0001**
IQR	273–675	573–1005	514–1678	426–1126	

**p* value: Change in the laboratory investigations from Day 1 to EOT between active arm and placebo arm; EOT, end of the treatment; LDH, lactate dehydrogenase; IQR, interquartile range; TLC, total leukocyte count

Strengths and Limitations

The main strength of this study was that it was a randomized, blinded, placebo-controlled design, with high adherence to the study protocol, and rigorous monitoring for safety events and adverse events. Moreover, the primary outcome was patient-centered and hard end point, capturing data related to clinically meaningful ordinal scale, mortality, and morbidity related to COVID-19.

Conclusion

Our study showed that thymosin has a superior effect with respect to key parameters such as all-cause mortality, WHO 8-point ordinal scale, SPO_2, and days of hospitalization. This was also accompanied by a distinctly significant improvement in most of the biomarkers assessed such as TLC, CD4, CD8, CRP, LDH, and IL-6 levels in all patients after treatment with Tα1 for 7 consecutive days. Thymosin α1 looks to be a formidable treatment that can be dosed in combination with SOC in patients with severe COVID-19. This study provides evidence that it can lower death rate in severe COVID-19 patients, reduce the load on hospitals by shortening the required number of days of hospitalization and help in abbreviating the requirement of oxygen support by positively impacting the recovery rate and time taken for recovery.

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