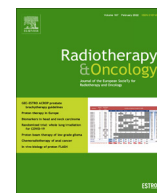




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## Original Article

## Whole lung irradiation as a novel treatment for COVID-19: Final results of the prospective randomized trial (WINCOVID trial)



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## ABSTRACT

**Background and purpose:** The ability of low dose radiotherapy (LDRT) to control the unprecedented cytokine release associated with COVID-19 pathogenesis has been an area of widespread research since the COVID pandemic. It has not been studied adequately whether the anti-inflammatory effect of LDRT provides additional benefit when used concurrently with steroids amongst other standard pharmacologic therapy.

**Material and methods:** 51 RT-PCR positive COVID-19 patients were recruited between November 2020 and July 2021. 34 patients were allotted to receive 0.5 Gy single session LDRT along with standard pharmacologic therapy while 17 patients received standard pharmacologic therapy alone. All had SpO<sub>2</sub> <94% on room air, respiratory frequency >24/min and SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio between >89 but <357. All patients underwent a baseline CT scan. They were followed up for 28 days during when serial SF ratio, blood biomarkers (CRP, Serum ferritin, IL-6), Absolute lymphocyte count (ALC), repeat CT scan were performed at pre-defined time points.

**Results:** LDRT showed a statistically significant early improvement in oxygenation, an early time to clinical recovery, early hospital discharge and better radiological resolution compared to control group. There was no statistically significant difference between the two groups with respect to ALC or blood biomarkers at any of the measured time points. The 28-day mortality rate did not show statistically significant difference between the two groups.

**Conclusion:** LDRT can be considered for selected oxygen-dependent moderate to severe COVID-19 patients for rapid relief of respiratory distress. It can be safely combined with standard pharmacologic treatment in such patients for added clinical benefit.

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The emergence of new variants leading to outbreaks, slow vaccination rates, growing costs of pharmacological therapies, shortage of beds and supplemental oxygen in hospitals are some of the challenges faced by several countries across the world in the fight against COVID-19 pandemic. The probability of future outbreaks cannot be entirely ruled out, especially in densely populated countries. There remains a need for a widely available, non-toxic, cost-effective treatment approach for patients with moderate to severe COVID-19.

Low dose radiotherapy (LDRT) is being evaluated across many institutions around the world as an anti-inflammatory/immunomodulatory approach against moderate to severe COVID-19. There has been recent advancement in understanding the underlying mechanism of action of LDRT. Calabrese et al proposed that the clinical benefit from LDRT was derived from various subcellular effects mediated by activation of nuclear factor erythroid 2-related transcription factor (Nrf-2) resulting in anti-oxidant responses and subsequent polarization shift of macrophages from pro-inflammatory (M1) to anti-inflammatory (M2) phenotype. This could not only help in resolving inflammation, but also in suppressing the cytokine storm, promoting tissue repair thereby preventing COVID-19 related mortality [1].

As per our preliminary observations, LDRT appeared to be a promising modality for selected patients with moderate to severe COVID-19 [2]. In this manuscript, we discuss the final results from

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our single-institutional experience in treating COVID-19 patients with low dose whole-lung radiotherapy.

## Material and methods

### Study design

This prospective, randomized, parallel group active-controlled clinical trial was approved by the Institutional Ethics committee registered with the Central Drugs Standard Control Organization, India (Registration number ECR/926/Inst/TN/2017/RR-20). The study protocol was registered in Clinical Trial Registry of India (CTRI/2020/10/028597), available at [www.ctri.nic.in](http://www.ctri.nic.in).

The study was done to evaluate bilateral whole lung LDRT using a Linear Accelerator (6 MV), as a treatment for interstitial pneumonia in patients with moderate to severe COVID-19. It was conducted in 2 phases:

1. An initial exploratory phase enrolling 10 patients, which assessed the feasibility and efficacy of low-dose whole lung irradiation, evaluated according to an increase in the SpO<sub>2</sub>/FiO<sub>2</sub> ratio of at least 20% at 48 hours with respect to the pre-irradiation value. Only upon achieving this minimum pre-defined improvement in at least 30% of patients treated, did the study proceed to the next phase
2. Randomized comparative phase in two groups:
  - a. a control group, which received pharmacological treatment only, and
  - b. an experimental LDRT arm with pharmacological treatment and LDRT. It included 51 patients, the allocation was 2:1, that is, 34 in the LDRT arm and 17 in the control arm. Computer based random sequences were generated and no blinding was done.

The flowchart of study design is shown in [Fig. 1.Fig 2](#).

### Patient selection

All patients with moderate to severe COVID-19 pneumonia were evaluated by a multidisciplinary board (including specialties such as Radiation Oncology, Internal Medicine, Pulmonology, Critical Care and Anesthesia) to determine the benefits and risks of their inclusion in the study.

### Inclusion criteria

1. Adult patients above the age of 40 with RT-PCR proven COVID-19 with fewer than 14 days of symptom onset, that warranted hospitalization and currently receiving pharmacological therapy for COVID-19 at appropriate doses as per national standard COVID-19 management recommendations

And

2. Patients with moderate to severe dyspnea requiring oxygen support (Nasal Cannula/Simple face mask/Venturi mask/non-rebreathermask/High flow nasal cannula/CPAP) with respiratory frequency  $\geq 24$ /min, oxygen saturation on room air SpO<sub>2</sub> <94% and SpO<sub>2</sub>/FiO<sub>2</sub> ratio >89 and <357.

And/or

3. Laboratory abnormalities such as C-reactive protein >100 mg/L or D-dimer >1000 ng/ml or IL-6 >50 IU or suspected cytokine release syndrome

(Criteria 1 and 2 were mandatory and 3 was optional)

### Exclusion criteria

1. Actual or planned Pregnancy

2. Prior lobectomy or pneumonectomy
3. Prior thoracic radiotherapy resulting in a maximum lung dose of 100 cGy or higher within 14 days of enrollment
4. Prior chemotherapy or other systemic therapy with potential for pulmonary toxicity or radio sensitization within 14 days or 5 half-lives, whichever is greater, of enrollment, e.g., bleomycin, gemcitabine
5. Prior cancer immunotherapy with an immune checkpoint inhibitor within 60 days of enrollment
6. Severe pre-existing heart disease, e.g., New York Heart Association (NYHA) functional class  $\geq 3$  congestive heart failure
7. History of bone marrow or solid organ transplantation
8. Known history of autoimmune collagen vascular disease, e.g., scleroderma
9. Known hereditary syndrome with increased sensitivity to ionizing radiation, e.g., Ataxia-telangiectasia or Fanconi anemia

### End points:

#### Primary endpoint:

- Comparison of efficacy of LDRT based on an improvement in SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio, defined as the ratio of Oxygen saturation by pulse oximetry to that of fraction of inspired oxygen, measured at 48 h, 72 h, 7 days and 14 days from the time of intervention (LDRT in LDRT group and first steroid dose in control group) compared to the baseline measurement in LDRT group and controls.

#### Secondary endpoints:

- Assessment and comparison of radiological response with the help of CT scan done at baseline and 14 days post intervention in LDRT group and controls
- Assessment and comparison of mortality rate at day 28 post intervention in LDRT group and controls
- Assessment and comparison of Absolute Lymphocyte counts (ALC) at baseline, day 1, day 3, day 7 and day 14 post intervention in LDRT group and controls
- Assessment and comparison of inflammatory response with the help of CRP, Serum Ferritin and immunological response with the help of IL-6 done at baseline and on Day 3, Day 7 and day 14 post intervention in LDRT group and controls

#### Tertiary endpoints

- Time to clinical recovery, defined as time to wean from supplemental oxygen and remain off supplemental oxygen for at least 12 consecutive hours
- Time to hospital discharge

### Statistical analysis

The data was analyzed using SPSS Software version 23. Descriptive statistics were performed for demographic and clinical characteristics independently for intervention and control groups. Frequency was reported for categorical variables and mean ( $\pm$ SD) or median (Interquartile range) for continuous variables as appropriate. Boxplots were used to visualize the distribution of clinical parameters and assess the presence of outliers. Normality was assessed by use of the Shapiro-Wilk test. Upon violation of the assumption of normality, Friedman tests and Wilcoxon-signed rank tests were run where applicable to determine significant difference in clinical parameters over time separately for the intervention and control groups. Post hoc analysis was performed with a Bonferroni correction applied for multiple comparisons.

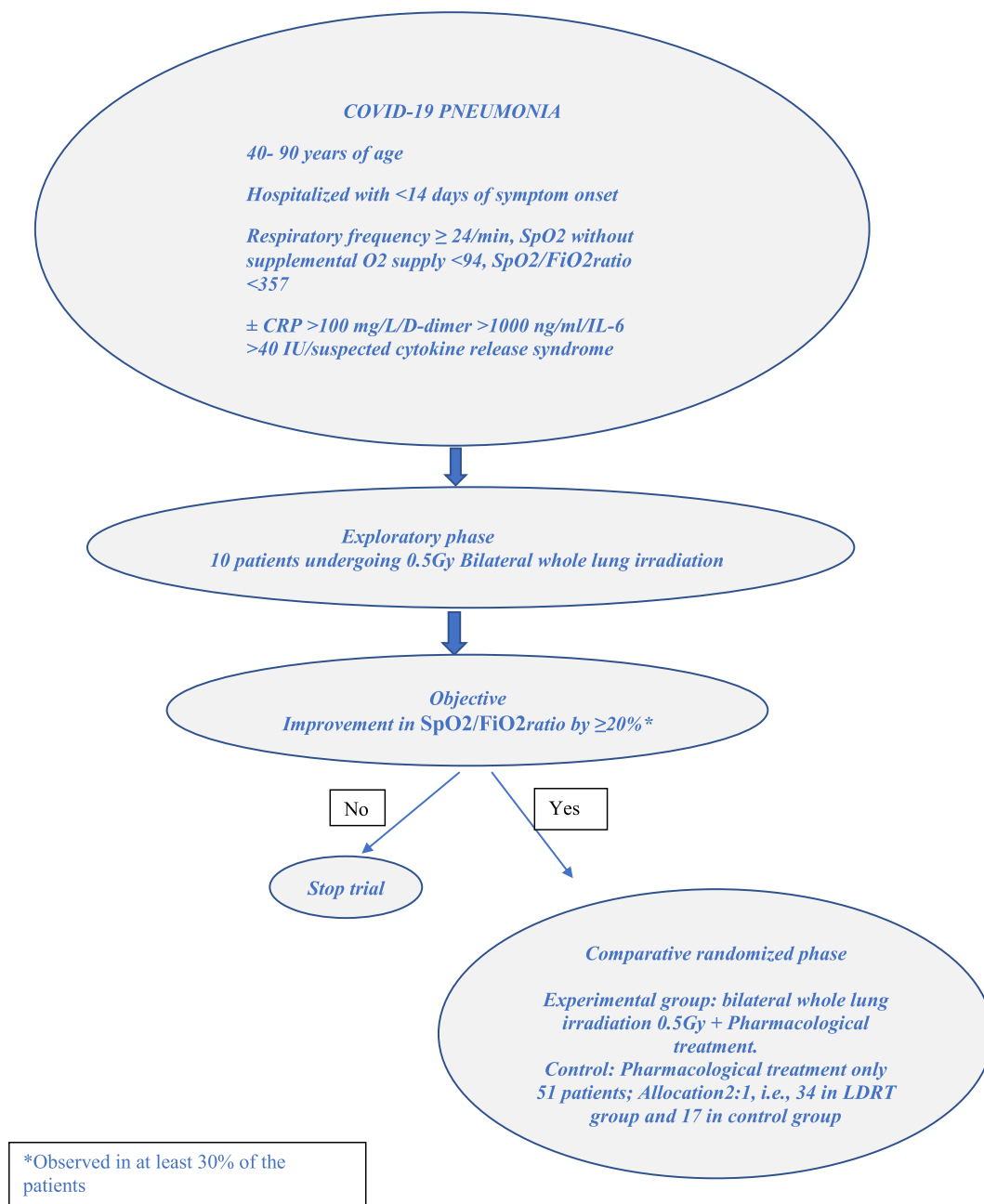


Fig. 1. Flowchart of study design.

Change in clinical and laboratory parameters at each time point compared to the baseline, were assessed for statistically significant difference between the two arms using a Mann Whitney U test. Kaplan Meier curves for time to clinical recovery, hospital discharge and death in the two arms were assessed using the Log Rank test. A two-sided p value less than 0.05 was considered to be statistically significant.

**Pharmacological treatment**

General measures for all patients included Awake prone positioning and Protein rich diet (1 g/kg/day). All patients received corticosteroids (Methylprednisolone/Dexamethasone), anti-coagulants (Enoxaparin sodium), Antibiotics, Pirfenidone, Vitamin C and Zinc supplementation. Dose of corticosteroids were 1 mg/kg/day of methylprednisolone in two divided doses (or an equivalent

dose of dexamethasone) for moderate cases (SF ratio >213 but <357) and 1.5 mg/kg/day of methylprednisolone in two divided doses (or an equivalent dose of dexamethasone) for severe cases (SF ratio >89 but <214). For both the groups, corticosteroids were given for a median of 7 days (Range 5–10days). 16/34 (47%) patients in the LDRT group and 10/17 (58.8%) patients in the control group received Remdesivir. Six (17.6%) patients in the LDRT group and five (29.4%) patients in the control group received Tocilizumab.

**Results**

Upon conclusion of the initial exploratory phase in 10 patients at 1 month follow-up, we found that LDRT was well tolerated. Clinical profile and baseline parameters of these 10 patients are tabulated in Tables 1 and 2 respectively. The pre-defined efficacy

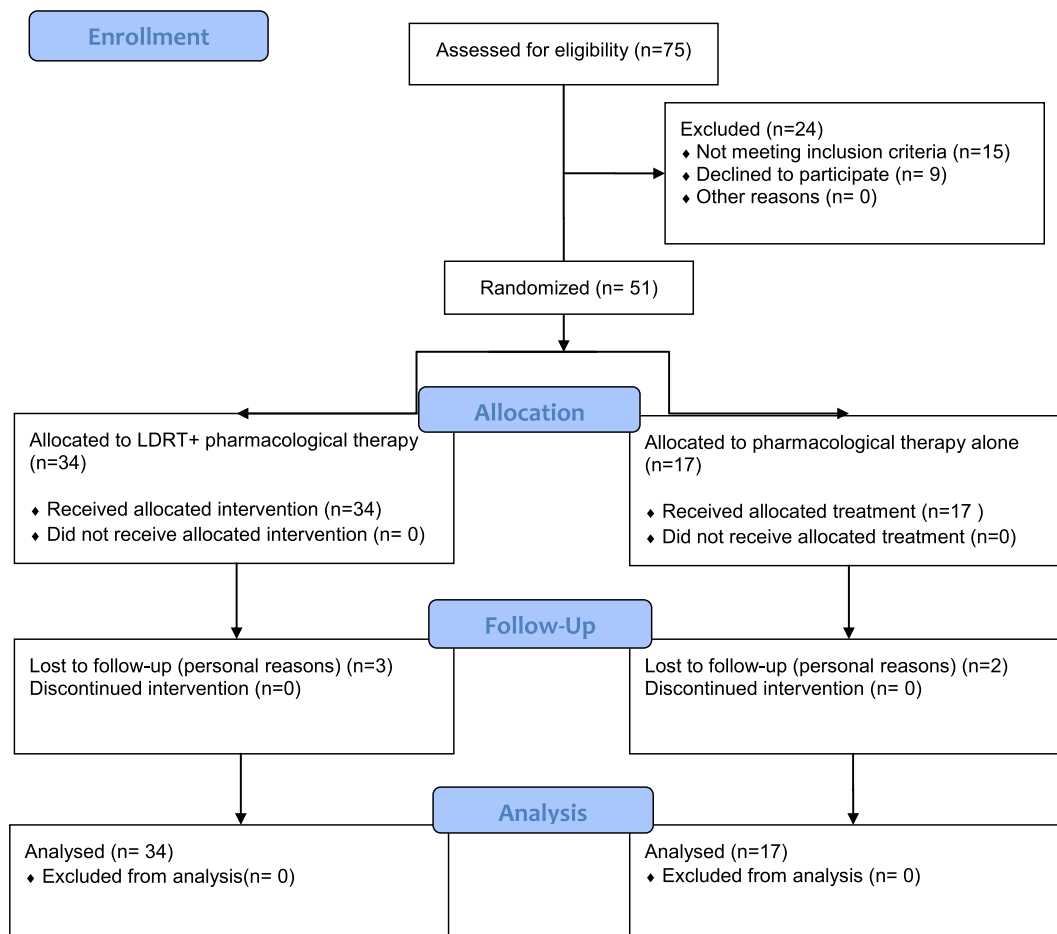


Fig. 2. Flow diagram of “Randomized comparative phase” study participants.

criteria of “minimum 20% improvement in SF ratio in at least 30% of the patients at 48 h” was achieved, as 50% of treated patients fulfilled this (Table 3). SF ratio distribution of these 10 patients is depicted using a boxplot in Fig. 3.

The randomized phase of the study comprised of 34 cases and 17 controls. The characteristics of the participants and baseline

Table 1 Profile of patients in exploratory phase (n = 10).

Characteristic	Number of study participants, n (%)
Age in years	
40–59	4 (40)
60–69	5 (50)
≥70	1 (4.0)
Sex	
Male	5 (50)
Female	5 (50)
Presence of comorbidity	
Co-morbid	6 (60)
Diabetes	6(60)
Hypertension	5(50)
Non-comorbid	4 (40)
Baseline SpO <sub>2</sub> in room air, %	
70–79	2 (20)
80–89	8 (80)
≥90	0
CT severity score	
12–19	5 (50)
≥20	5 (50)

Table 2 Baseline parameters of study participants (n = 10).

Test name	Laboratory values		
	Minimum	Maximum	Median (IQR)
CRP	18	316	138 (98–215)
Ferritin	155	567	360 (234–468)
IL-6	2.4	588	84 (24–170)
D-dimer	100	6000	150 (100–2325)
NLR	1.2	10.3	6 (4.4–6.7)
CT Severity Score	16	23	20 (17–23)

Table 3 Relative difference in SF ratio between baseline and Day 2 (n = 10).

SF ratio percentage difference (%)	Number of study participants, n (%)
<20	5 (50)
≥20	5 (50)

lab parameters are outlined in Table 4 and 5. Median time to intervention was 24 h (12–72 h) in the LDRT group and 2 h (2–3 h) in the control group (first steroid dose). Median time to first steroid dose in the LDRT group was 2 h (2–3 h).

For the primary endpoint of SF ratio assessment, comparison was done both within and between the two groups. Key time points defined for comparison were baseline, day 2, day 3, day 7 and day 14.

Within the LDRT group, there was a statistically significant increase in SF ratio with time,  $\chi^2(4) = 94.20, p < 0.001$ . Post hoc

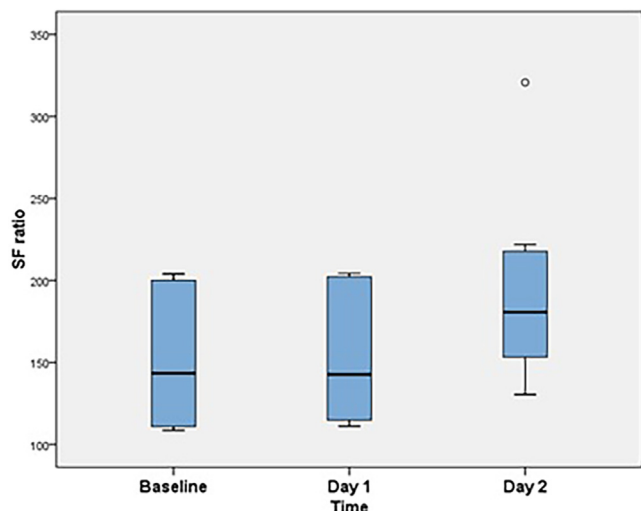


Fig. 3. Boxplot showing distribution of SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio in “Initial Exploratory phase” patients (n = 10).

Table 4  
Baseline characteristics of ‘Randomized phase’ study participants.

Characteristic	Intervention arm	Control arm
	Frequency, n (%)	
<b>Age in years</b>		
41–55	16 (47)	5 (29)
56–70	12 (35)	11 (65)
71–85	6 (18)	1 (6)
<b>Sex</b>		
Male	22 (65)	12 (71)
Female	12 (35)	5 (29)
<b>Comorbidity</b>		
Comorbid	29 (85)	10 (59)
Diabetes	25 (74)	10 (59)
Hypertension	13 (38)	5 (29)
Asthma	1(2.9)	–
Liver Disease	4 (12)	–
Non-comorbid	5 (15)	7 (41)
<b>SpO<sub>2</sub> in room air, %</b>		
60–69	2(5.8)	–
70–79	3 (9.0)	3 (18)
80–89	22(65)	8 (47)
≥90	7 (20)	6 (35)
<b>CT Severity score</b>		
12–19	29 (85)	15 (88)
≥20	5 (15)	2 (12)

Table 5  
Baseline Laboratory Parameters of the study participants.

Laboratory parameter	Intervention arm	Control arm
	Median (IQR)	
CRP	66 (46–81)	90(24–109)
D-dimer	650 (357–1335)	970 (393–3421)
Ferritin	520 (286–855)	463 (381–1188)
IL-6	64 (36–94)	48 (36–87)
NLR	7.9 (6–16)	7.2 (5.5–17)
Lymphocyte count	782 (621–1195)	1092 (711–1375)
TLC	9450(6942–11637)	8000 (4950–11770)

analysis revealed that LDRT elicited a statistically significant reduction in SF ratio beyond Day 3 of the intervention.

Within the Control group, a statistically significant reduction in oxygen requirement was observed with time,  $\chi^2(4) = 41.88$ ,

$p < 0.001$ . Post hoc analysis revealed a significant increase in SF ratio only beyond Day 7 of the intervention.

Between the two groups, there was a significant difference in increase of SF-ratio in LDRT group compared to the control group on Days 2, 3 and 7 of radiotherapy ( $p < 0.001$ ).

Within and between group comparisons are tabulated in Tables 6 and 7 respectively and depicted using a boxplot in Fig. 4.

Incidence of lymphopenia was compared between the groups by monitoring serial absolute lymphocyte counts at baseline, day 1, day 3, day 7 and day 14 and no statistically significant reduction was found at the measured time points (Table 8). Inflammatory and immunological response biomarkers such as CRP, Serum ferritin and IL-6 were compared based on their baseline, day 3, day 7 and day 14 values between the groups. There was no statistically significant difference with respect to any of the biomarkers (Tables 9–11).

All patients in the LDRT and control group had undergone a baseline CT scan. The radiological response in terms of reduction of CT severity score (CTSS) was observed in the LDRT group as compared to the control group showing statistically significant difference ( $p = 0.011$ ). This is given in Table 12. The median (IQR) baseline CTSS for LDRT group was 16 (15–17) which reduced to 12(10–14) on day 14 post intervention ( $p < 0.001$ ). For the control group, the median (IQR) baseline CTSS was 15 (14–17) which reduced to 13 (12–17) on day 14 post intervention ( $p = 0.094$ ).

Five patients in LDRT group and four patients in control group progressed to critical stage and required mechanical ventilation. All of these patients succumbed to the disease eventually. Mortality rate at 28 days post-admission was 0.59 per 100 person-days and 1.02 per 100 person-days in the intervention and control group respectively. A log rank test was run to determine if there were differences in the survival distributions among the two arms and it showed no statistically significant difference,  $\chi^2(1) = 0.545$ ,  $p = 0.460$ . Kaplan Meier curves were drawn to represent the survival data, depicted in Fig. 5.

The median time to clinical recovery was 4 (2.1–5.8) days and 11 (10–12) days in the intervention and control groups respectively. A log rank test noted a statistically significant difference in the distributions,  $\chi^2(1) = 19.510$ ,  $p < 0.001$ . This is represented using a Kaplan Meier curve in Fig. 6.

The median time to discharge was 7 (5.6–8.3) days and 13 (12–14) days in the intervention and control arms respectively. A log rank test noted a statistically significant difference in the distributions,  $\chi^2(1) = 20.013$ ,  $p < 0.001$ . The corresponding Kaplan Meier curve is represented in Fig. 7.

## Discussion

Several hematological, coagulation, immunological and inflammatory biomarkers have been associated with severity and progression of COVID-19 [3]. A meta-analysis commented that most of these biomarkers could not be ranked in terms of correlation with severity of COVID-19 [4]. In this study, we assessed response of selected biomarkers to LDRT in terms of inflammatory (CRP, Serum ferritin) and immunological (IL-6) aspects and compared it with controls. A significant reduction from the baseline values was noted for both the groups individually, for CRP, Serum ferritin and IL-6 at day 7 and day 14. However, we did not observe a significant difference in terms of response of these biomarkers between the two groups at any of the measured timepoints. Amongst the patients who died, except for one LDRT group patient’s baseline serum ferritin, all other patients in both the groups had a higher baseline CRP, serum ferritin and IL-6 when compared to their respective median baseline values. While these are very useful prognostic markers, they may not be the ideal response assessment



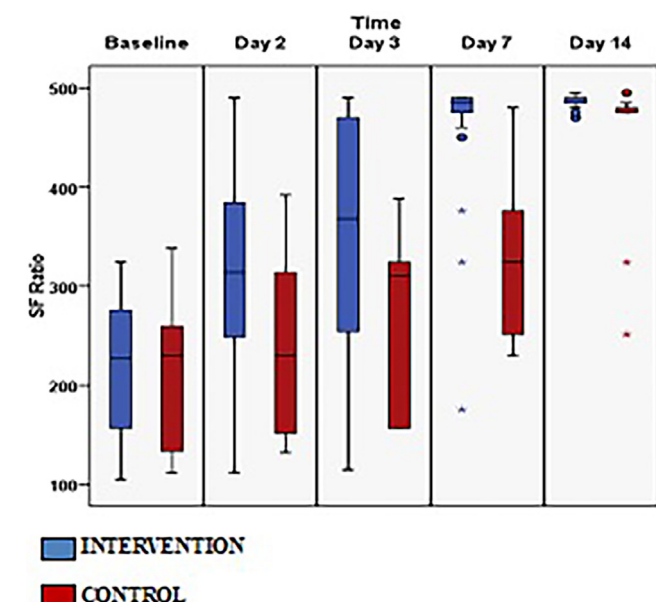
**Table 6**  
Within-group temporal difference in SF ratio in Intervention and Control Arms.

Time	Intervention group		Control group	
	SF ratio, Median (IQR)	p value	SF ratio, Median (IQR)	p value
Baseline	208 (147–276)	Reference	174 (141–260)	Reference
Day 2	285 (188–378)	0.70	155 (152–312)	1.000
Day 3	319 (204–470)	0.000	204 (157–324)	0.545
Day 7	485 (475–490)	0.000	303 (229–376)	0.001
Day 14	485 (482–490)	0.000	475 (475–480)	0.000

**Table 7**  
Between-group comparison of Temporal change in SF ratio.

Time	Difference in SF ratio, Median (IQR)		p value
	Intervention arm	Control arm	
Baseline to Day 2	71 (4–153)	18 (–19–48)	0.008
Baseline to Day 3	123 (4.3–214)	26 (–11–76)	0.007
Baseline to Day 7	231 (205–318)	108 (13–160)	0.000*
Baseline to Day 14	258 (212–340)	225 (151–322)	0.176

\*Statistically significant at  $p < 0.05$ .



**Fig. 4.** Boxplot showing SF ratio: Within and Between group comparison.

**Table 8**  
Between-group comparison of Temporal change in Lymphocyte count.

Time Point difference	Median (IQR)		p value
	Intervention arm	Control arm	
Baseline to Day 1	–19 (–154, –147.25)	–80 (–31, –158)	0.510
Baseline to Day 3	–105 (–397, –26.25)	–59 (–465, –157)	0.984
Baseline to Day 7	–231 (–600, –118)	–280 (–546, –83)	0.770
Baseline to Day 14	101 (–72.95, –354)	–71 (–203, –116)	0.087

\* Statistically significant at  $p < 0.05$ .

markers as these are prone to fluctuations in presence of factors like co-existing bacterial infections.

LDRT group had a significant improvement in SF ratio on day 2, day 3 and 7 compared to the control group. Also, LDRT group patients had much earlier improvement in median SF ratio compared to control group (Day 3 for LDRT vs Day 7 for controls) while compared within the group. A wide range of SF ratio has been con-

**Table 9**  
Between-group comparison of Temporal change in CRP.

Time Point difference	Median (IQR)		p value
	Intervention arm	Control arm	
Baseline to Day 3	–24 (–31, –12.8)	–23 (–38, –2.8)	0.952
Baseline to Day 7	–49 (–62.9, –30.3)	–80 (–110, –8.8)	0.246
Baseline to Day 14	–56 (–69, 27)	–86 (–104, –12)	0.316

\*Statistically significant at  $p < 0.05$ ,  $\chi^2(3) = 31.03$ .

**Table 10**  
Between-group comparison of Temporal change in Serum Ferritin.

Time Point difference	Median (IQR)		p value
	Intervention arm	Control arm	
Baseline to Day 3	–38 (–76, –0.37)	–53 (–133, –14)	0.569
Baseline to Day 7	–90 (–162, –35)	–85 (–99, –40)	0.453
Baseline to Day 14	–163 (–257, –71)	–170 (–279, –73)	0.939

\*Statistically significant at  $p < 0.05$ .

**Table 11**  
Between-group comparison of Temporal change in IL-6 value.

Time Point difference	Median (IQR)		p value
	Intervention arm	Control arm	
Baseline to Day 3	–42 (–64, –23)	–34 (–62, –26)	0.780
Baseline to Day 7	–53 (–84, –28)	–43 (–67, –31)	0.542
Baseline to Day 14	–56 (–89, –29)	–42 (–56, –33)	0.366

\*Statistically significant at  $p < 0.05$ .

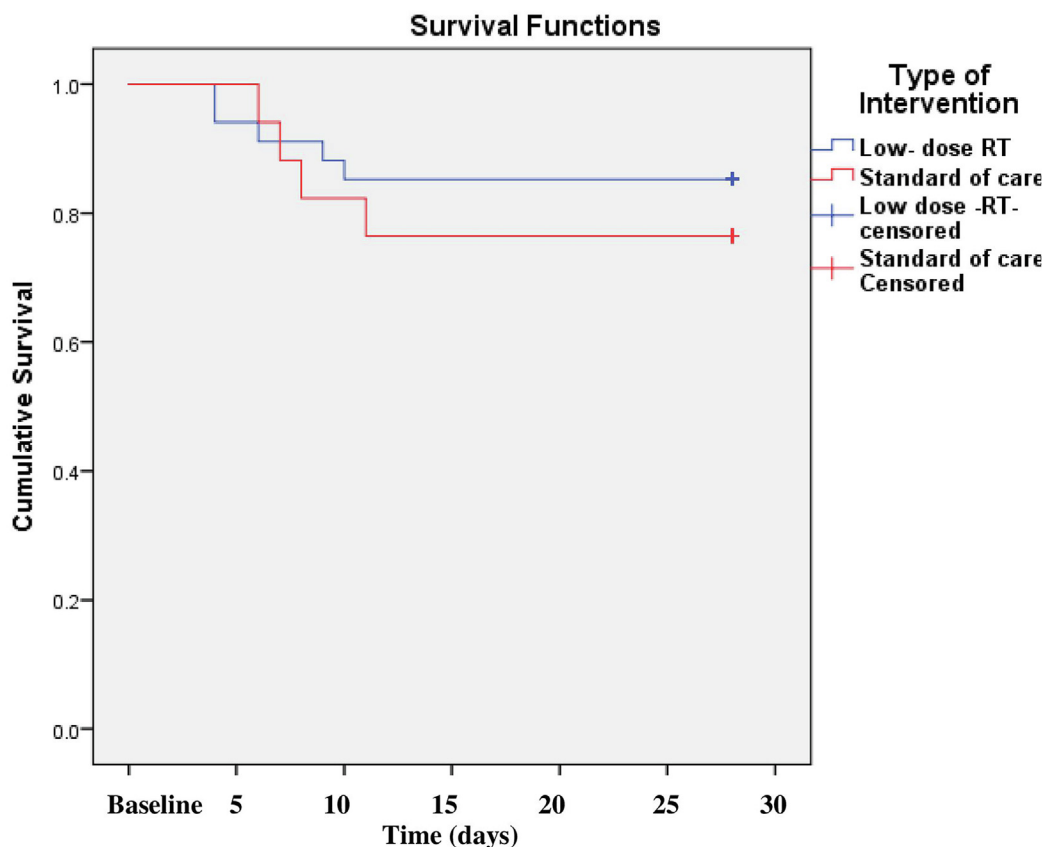
**Table 12**  
Between-group comparison of temporal change in CT severity score.

Time Point	Median (IQR)		p value
	Intervention arm	Control arm	
Baseline to Day 14	–4 (–5, –2.75)	–2 (–3, –1)	0.011

\* Statistically significant at  $p < 0.05$ .

sidered for inclusion (90–356) causing a notable difference in the median baseline SF ratio values between the two groups (208 for LDRT group vs 174 for controls). However, the median values fall within the definition of severe respiratory distress (SF ratio >89 and <214) defined earlier [2]. In one of the largest series of LDRT for moderate to severe COVID-19, Arenas et al noted a considerable improvement in SF ratio by a median of 76% at day 7 in majority of the patients treated after a single fraction of 0.5 Gy [5]. Our LDRT and control groups had a median SF ratio improvement of 128.77% and 74.1% at day 7 post intervention respectively.

We observed speedy clinical recovery and an earlier hospital discharge for patients who underwent LDRT compared to the control group. This meant better availability of beds for other needy patients and conservation of oxygen supplies for the hospital. Notably, a major part of patient recruitment happened during the times of acute oxygen crisis in our country.



	Number at risk (Number censored)						
	Baseline	5	10	15	20	25	30
LDRT Group	34(0)	32(0)	29(0)	29(0)	29(0)	29(0)	0(29)
Control Group	17(0)	17(0)	14(0)	13(0)	13(0)	29(0)	0(29)

Fig. 5. Kaplan Meier Curves for survival at 28 days post-admission in LDRT (n = 34) and control groups (n = 17).

Radiological assessment was done using the scoring criteria proposed by Li et al. [6]. Three out of five patients in the LDRT group who died, had a baseline CT severity score of  $\geq 20$ . LDRT may be of limited use in these patients and upcoming clinical trials could consider the same while devising selection criteria.

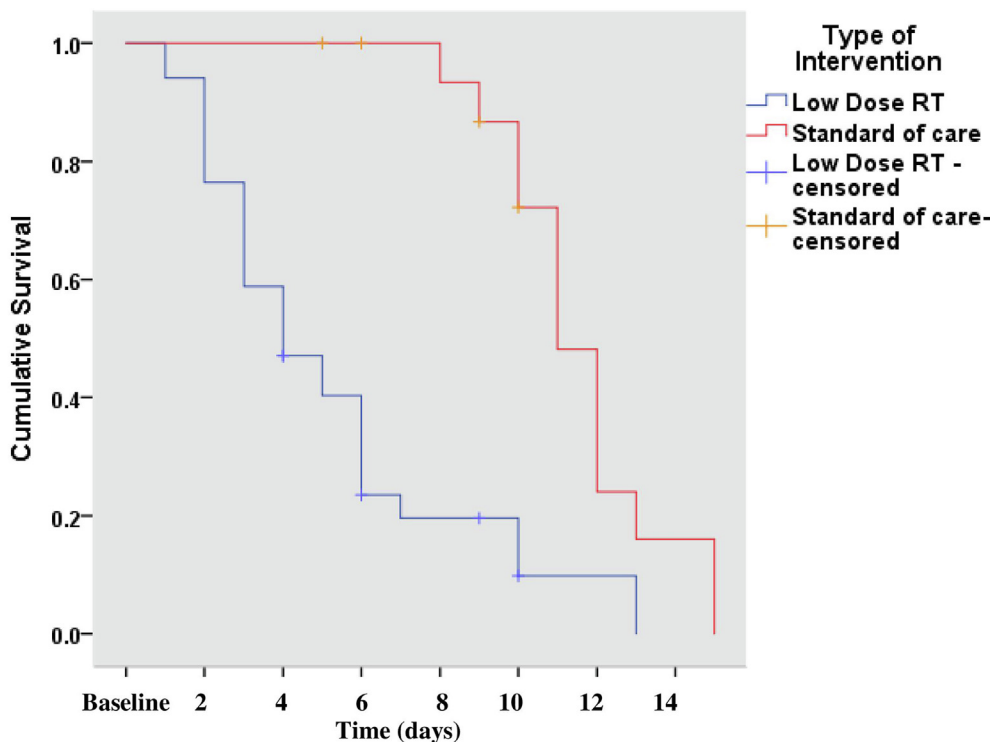
At 28 days of follow-up, the all-cause mortality rate was 14.7% in the LDRT group and 23.5% in the control group. The clinical characteristics of the patients who died is represented in Table 13. It is noteworthy that the percentage of co-morbid patients in LDRT group (85%) was markedly higher compared to the control group (59%). Also, the overall median baseline CT severity score was worse for the LDRT group compared to the control group (16 vs 15). Amongst the non-survivors, the median baseline CT severity score was 20 for LDRT group vs 18 for control group. These factors might have adversely impacted the mortality outcome of LDRT group. Given the remarkable improvement in SF ratio and early clinical recovery observed in the LDRT group, a possible reduction in mortality rate cannot be disregarded, although the difference could not be perceived in statistically significant terms in this study.

Arruda et al assessed the risk of radiation-induced cancer (RIC) and cardiovascular risk of radiation exposure induced death (REID) following LDRT for COVID-19 on a virtual case. They concluded that an acceptable lifetime attributable risk of  $\leq 1\%$  for RIC and REID was observed with a dose  $\leq 0.5$  Gy irrespective of sex and age [7]. This is further supported by Shuryak et al. who estimated the excess absolute risk (EAR) of lung cancer and heart disease in patients receiving 0.5 Gy dose of LDRT for COVID-19 to be in the  $\leq 1\%$  range across age groups 50–85 for both men and women belonging to the non-smoking group with no or few cardiac risk factors [8].

Risk-benefit balance needs to be assessed and discussed with the patient before irradiating relatively younger female patients with smoking history and in those with several cardiac risk factors as the EAR % may be higher for this sub-group. In our study, neither female smokers nor pre-existing cardiac co-morbidity cases were part of the patient population.

Several published preliminary results have shown favorable outcomes with the use of LDRT for COVID-19 with negligible side effects [2,5,9–11]. But some clinicians in the radiation oncology





	Baseline	2	4	6	8	10	12	14
LDRT group	34 (0)	26(0)	14(2)	6(3)	5(3)	1(5)	1(5)	0(5)
Control group	17(0)	17(0)	17(0)	15(2)	14(2)	9(4)	3(4)	3(4)

Fig. 6. Kaplan Meier Curves for Time to Clinical Recovery in LDRT (n = 34) and control groups (n = 17).

community continue to be hesitant on usage of this approach, quoting lack of robust data, feasibility and logistic issues [12]. These barriers need to be overcome for LDRT to be studied under a large scale multi-institutional research setting worldwide.

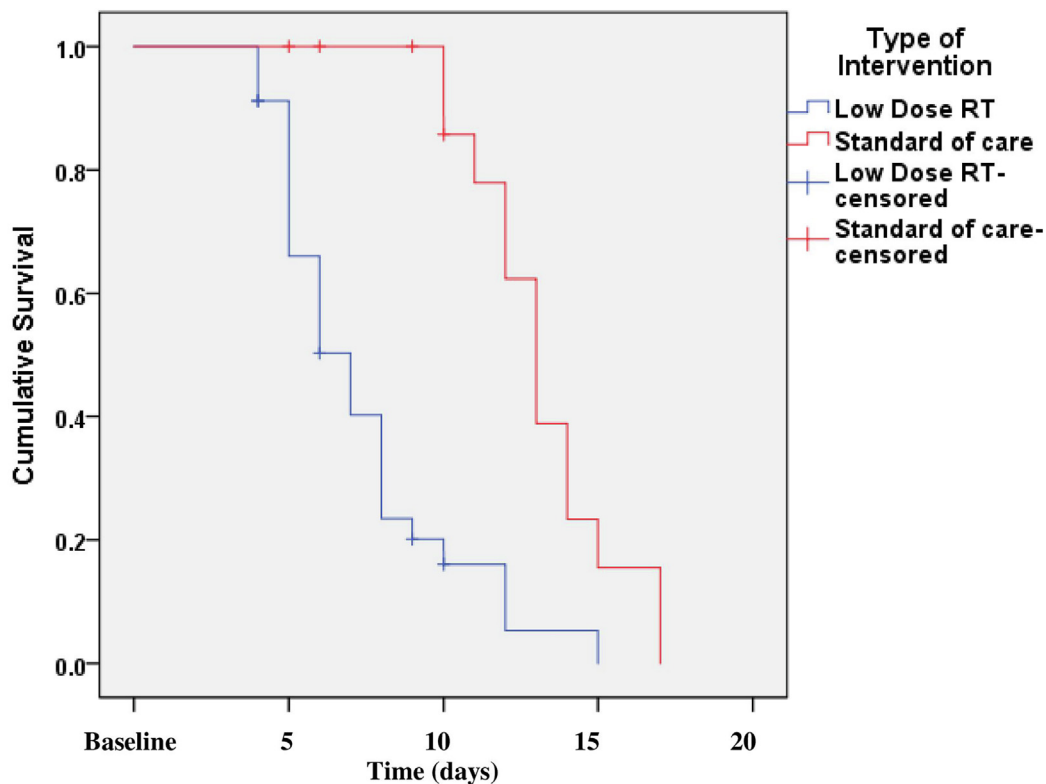
This prospective, randomized study is not without its limitations. It utilized a 2:1 allocation ratio for statistical comparison between the intervention and control group. Although this is scientifically not validated, this allocation has been selected for better patient recruitment and gathering additional safety profile of LDRT. Remdesivir, tocilizumab, Pirfenidone, Vitamin C and zinc were used for patients in both groups in addition to 'standard pharmacologic treatment' according to physician's discretion. Notably, there were several revisions to guidelines about the best use of these pharmacological drugs throughout the duration in which this trial was conducted. This had resulted in varying number of patients receiving these drugs between the two groups and some patients not receiving the drugs, which may have influenced the outcome.

**Conclusion**

This prospective, randomized trial shows that addition of LDRT to pharmacological treatment hastens clinical recovery and time to hospital discharge compared to pharmacological treatment alone in selected moderate to severe COVID-19 patients. This was achieved by improvement in oxygenation and is backed by radiological resolution of pneumonia in majority of patients treated, in the absence of limiting side effects. The all-cause mortality rate was lower in the LDRT group compared to the control group, although this was not statistically significant. These findings need to be further validated by larger samples and long-term follow-up.

**Conflicts of interest**

None.



Number at risk (Number censored)

LDRT Group	34(0)	21(2)	3(5)	0(5)	0(5)
Control Group	17(0)	16(1)	11(4)	2(4)	0(4)

Fig. 7. Kaplan Meier Curves for Time to hospital discharge in LDRT (n = 34) and control groups (n = 17).

Table 13  
Clinical Characteristics of patients who died.

Group	Age	Co morbidities	Baseline SF ratio	Baseline CRP	Baseline IL6	Baseline Ferritin	Baseline CTSS	Remdesivir	Tocilizumab
LDRT	75/M	Diabetic	150.0	78.3	88	1676	21	NO	NO
LDRT	70/F	Nil	182.0	86.8	81	2387	22	NO	NO
LDRT	43/M	Diabetic & Hypertensive	200.0	80.2	76	1590	20	NO	NO
LDRT	59/F	Diabetic	112.3	67.5	110	788	19	YES	NO
LDRT	42/M	Diabetic	182.0	96	161	475.6	17	YES	NO
CONTROL	48/F	Nil	153	104	124	1406	18	YES	NO
CONTROL	59/F	Nil	174	125	110	1350	17	YES	YES
CONTROL	54	Diabetic	150	110	91	1145	18	YES	YES
CONTROL	60	Diabetic	161	74	82	2160	19	YES	YES

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