

Brief Report

Low-dose Whole-lung Irradiation for COVID-19 Pneumonia: What is the Optimal Dose? Final Results of a Pilot Study

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Abstract

Purpose: Novel coronavirus disease (COVID-19) is the current global concern. Radiotherapy (RT), commonly employed in cancer management, has been considered one of the potential treatments for COVID-19 pneumonia. Here, we present the final report of the pilot trial evaluating the efficacy and safety of low-dose whole-lung irradiation (LD-WLI) in patients with COVID-19 pneumonia.

Methods and Materials: We enrolled patients with moderate COVID-19 pneumonia who were older than 60 years. Participants were treated with LD-WLI in a single fraction of 0.5 or 1.0 Gy along with the national protocol of COVID-19. The primary endpoints were improvement of SpO₂, the number of hospital/ICU stay days, and the number of intubations after RT, and the secondary endpoints were alterations of c-reactive peptide, interleukin-6, ferritin, procalcitonin, and D-dimer. The response rate (RR) was defined as a rise in SpO₂ upon RT with rising or constant trend in the next two days, and clinical recovery (CR) included patients who were discharged from the hospital or acquired SpO₂ ≥93% on room air.

Results: Between 21 May 2020 and 2 July 2020, ten patients were enrolled. The median age was 75 years, 80% were male, and 80% had comorbidities. The first five patients received a single 0.5 Gy-WLI, and others received 1.0 Gy. Patients were followed for 2-14 days (median 5.5 days). Following one day, nine patients experienced an improvement in SpO₂. Five patients were discharged (median 6th day, range 2nd-14th day), and four patients died (median 7th day, range 3rd-10th day). Overall, the RR and CR were 60.0% and 55.5%, respectively. The RR and CR rates of 0.5- and 1.0 Gy group were 80% vs 40% and 75% vs 40%, respectively. No acute radiation-induced toxicity was recorded.

Conclusions: LD-WLI with a single 0.5Gy fraction seems to be a more appropriate dose to warrant further evaluation in a large-scale, randomized trial.

Keywords: COVID-19; Pneumonia; Low-dose whole-lung irradiation; SpO₂

Introduction

Since December 2019, novel coronavirus disease (COVID-19) has become a major concern globally. It has led to 809,106 deaths worldwide as of August 24, 2020, with an average case fatality rate of 3-4%.^{1,2} COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may affect many systems.³ Lungs are the main targets of SARS-CoV-2 infection mainly due to uncontrolled inflammatory response, called the *cytokine storm*. Based on historical evidence using radiation therapy (RT) for viral pneumonia,⁴ some investigators have proposed the potential efficacy of lung irradiation for COVID-19 pneumonia.^{5,6} The preliminary results of low-dose whole-lung irradiation (LD-WLI) were encouraging in 5 patients.⁷ Herein, we report the clinical outcomes of 10 patients treated with two different applied RT doses.

Methods and Materials

Study population and eligibility

Patients aged > 60 years who had clinical manifestations of COVID-19 [based on positive real-time polymerase chain reaction (RT-PCR) of SARS-CoV-2 RNA, antibody tests, or radiographic pneumonic consolidations] with moderate pulmonary involvement [defined as blood oxygen saturation level (SpO₂) ≤93% on room air or respiratory rate >30/min] were eligible for the trial. Details of evaluating the eligibility criteria have been previously described.⁷ Briefly, peripheral blood SpO₂ was measured on room air within one hour before RT and in subsequent mornings using a pulse oximeter. The body temperature of patients was measured every morning using tympanic membrane thermometry. Likewise, c-reactive peptide (CRP), interleukin-6 (IL-6), ferritin, procalcitonin, and D-dimer were evaluated at baseline and daily following irradiation. Patients with hemodynamic instability or requiring mechanical ventilation, history of malignancy or heart failure, septic shock or end-organ failure, severe acute respiratory distress syndrome (defined as PaO₂/FiO₂ ≤ 100 mmHg), or those who had contraindication and those who did not declare informed consent for RT were excluded from the trial.

Study design and treatment

Eligible patients were enrolled in a single-arm clinical pilot trial of low-dose whole-lung irradiation (LD-WLI) (Clinical Trial Registration Number NCT04390412). The study design and details of the protocol for transportation of patients to the RT Department have been previously described.⁷ The protocol was approved by the Institutional Review Boards and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1399.073), and all patients declared written and verbal informed consent. Details of the LD-WLI have been described previously.⁷ Briefly, in conjunction with the national protocol for the management of patients with COVID-19 pneumonia,⁸ irradiation was delivered in a single fraction of 0.5 Gy to both lungs via two opposed anteroposterior (AP) and posteroanterior (PA) open portals. The irradiation was extended to another 0.5 Gy, with at least a three-day interval, based on the physician's discretion. Treatment with a single 1.0 Gy WLI was planned for 4 patients in the second phase of the pilot study to provide a small comparison with the single 0.5 Gy irradiation. This decision was based on the preliminary results of an ongoing study evaluating a single 1.5 Gy WLI.⁹ Incidentally, none of the patients in our trial received dexamethasone, remdesivir, (hydroxy)chloroquine, or macrolides.

Study endpoints and assessments

The primary objectives were improvement of SpO₂, the number of hospital/intensive care unit (ICU) stay days, and the number of intubations performed after RT, and the secondary objectives included changes in laboratory test results [including CRP, IL-6, ferritin, procalcitonin, and D-dimer] following RT. Of note, the applied ferritin test kit could not measure amounts higher than 1600 ng/mL. In this trial, the response rate (RR) was defined as improvement in SpO₂ on the first day after RT with increasing or constant trends for the next 2 days, and clinical recovery (CR) was defined as patients who were discharged from the hospital or weaned off supplemental oxygen with SpO₂ ≥93% on room air.

Results

Between 21 May 2020 and 2 July 2020, 10 patients with COVID-19 pneumonia received LD-WLI at the Clinical Oncology Department of Imam Hossein Hospital, Tehran, Iran. The patients' demographics and baseline disease characteristics are summarized in **Table 1**. Among the enrolled patients with a median age of 75 years (range 60-87 years), 80% were male. All except 2 patients had comorbidities, including hypertension in 6 patients, ischemic heart disease in 2 patients, diabetes mellitus in 1 patient, and congestive heart failure in 1 patient. At the time of admission, the median Glasgow Coma Scale (GCS) was 15 (range 10-15). Dyspnea was the predominant chief complaint (70%), followed by cough (30%) and fever (30%). All participants, except for 1 (patient #3), were positive for RT-PCR of SARS-CoV-2 RNA; patient #3 was enrolled for her typical computed tomography (CT) features of COVID-19 pneumonia and elevated CRP levels. Initial physical examination revealed stable vital signs for all patients, with a median SpO₂ of 80.5% (range 70-89%). All patients received O₂ supplementation mainly (60%) via facial masks with reservoir bags.

Patients were allocated to receive WLI in two radiation plans: (1) LD-WLI with a single 0.5 Gy fraction (patients #1-5), (2) LD-WLI with a single 1.0 Gy fraction (patients #7, 8, 9, and 10). Patient #6 received 2 fractions of 0.5 Gy with a 7-day interval. Within 24 hours following the initial fraction, his clinical status (SpO₂) improved significantly; however, in the following days, he developed clinical deterioration and received the second 0.5 Gy fraction based on the physician's discretion. Thereafter, his SpO₂ gradually declined, and he died on the 3rd day after the second irradiation. We did not include patient #6 in the analysis because of his exclusive treatment plan. Within 1 day after RT, 8 (88.9%) and 6 (66.7%) patients demonstrated initial improvement in their SpO₂ (median: 2.5%, range: 1 to 6%) and body temperature (median: -0.45 °C, range: -0.1 to -2.0 °C), respectively. Despite the clinical improvement, patient #3 opted out of the trial on the 3rd day after RT; therefore, he was entered into RR analysis and excluded from CR analysis. Overall, the RR and CR were 55.5% and 62.5%, respectively. The RR and CR rates of 0.5 Gy- and 1.0 Gy-single fraction WLI were 80% vs 25% and 75% vs 50%, respectively (patient #3 who opted out the trial and patient #6 who received two 0.5 Gy fractions were not included in CR). The clinical outcomes are presented in **Table 1**. The median time to discharge was 6 days (range 2-14 days) for 5 patients. The remaining 3 patients who died experienced a decline in SpO₂ on the median 2nd day (range 2nd-3rd day) after irradiation, which resulted in death on the median 3rd day (range 3rd-10th day) (**Figure 1-A**). Patient #5, 7, and 9 experienced SpO₂ ≥94% when administered O₂ supplement; however, 81% ≤SpO₂< 88% on room air. At the discretion of their physician and due to the limitation of ventilation facilities, they were discharged on the 6th, 2nd, and 14th day after irradiation with medical advice to receive O₂ supply at home. Patient #10 was the only patient who experienced intubation with mechanical ventilation performed on the 4th day after RT. The laboratory tests following irradiation had diverse patterns, which are demonstrated in **Figures 1 and 2**. The CRP and IL-6 graphs show different patterns in patients who recovered from COVID-19 in comparison to those who progressed to death. Three of 5 discharged patients had a drop in CRP over 1-2 days after RT, while all patients who had died experienced a rise in CRP over the same period (**Figure 1-C**). Following RT, IL-6 levels fell in all discharged patients after 1-3 days, while they rose within 2 days in 2 of 4 participants who died from COVID-19. (**Figure 1-D**). Ferritin, procalcitonin, and D-dimer tests were available in 5 patients, and their trends are demonstrated in **Figure 2**. During the observation, no acute skin, cardiac, pulmonary, or gastric toxicities were detected.

Table 1. Patient demographics, clinical characteristics, and clinical outcomes

Patients	Gender/Age	Comorbidity	Presenting symptom	Dx of COVID-19	Presenting V/S	O ₂ supply	Hospital stay after RT	Intubation after RT	Outcome
# 1	Male/60	CHF	Dyspnea	Clinical findings RT-PCR	PR/min: 75 RR/min: 12 SBP (mmHg): 110 T (°C): 37.5 SpO ₂ (%): 87	Facial mask	7 days	None	Discharged
# 2	Male/69	HTN-IHD	Fever-cough	Clinical findings RT-PCR	PR/min: 88 RR/min: 16 SBP (mmHg): 130 T (°C): 38.1 SpO ₂ (%): 86	Nasal cannula	5 days	None	Discharged
# 3	Female/82	IHD	LOC	Clinical findings Imaging	PR/min: 90 RR/min: 20 SBP (mmHg): 110 T (°C): 37.6 SpO ₂ (%): 75	Facial mask with reservoir bag	3 days	None	Opted out of trial
# 4	Male/84	HTN	Cough	Clinical findings RT-PCR	PR/min: 82 RR/min: 12 SBP (mmHg): 140 T (°C): 37.0 SpO ₂ (%): 89	Facial mask	3 days	None	Died
# 5	Male/64	HTN	Dyspnea-cough- Fever	Clinical findings Imaging RT-PCR	PR/min: 90 RR/min: 15 SBP (mmHg): 120 T (°C): 39.0 SpO ₂ (%): 74	Facial mask with reservoir bag	6 days	None	Discharged
# 6	Male/71	DM-HTN	Dyspnea	Clinical findings RT-PCR	PR/min: 80 RR/min: 20 SBP (mmHg): 110 T (°C): 37.0 SpO ₂ (%): 70	BiPAP	10 days	None	Died
# 7	Male/80	None	Dyspnea-fever	Clinical findings RT-PCR	PR/min: 90 RR/min: 18 SBP (mmHg): 130 T (°C): 37.0 SpO ₂ (%): 81	Facial mask with reservoir bag	2 days	None	Discharged
# 8	Male/87	HTN	Dyspnea	Clinical findings RT-PCR	PR/min: 60 RR/min: 18 SBP (mmHg): 110 T (°C): 37.1 SpO ₂ (%): 80	Facial mask with reservoir bag	4 days	None	Died
# 9	Male/68	None	Dyspnea	Clinical findings RT-PCR	PR/min: 100 RR/min: 16 SBP (mmHg): 130 T (°C): 37.4 SpO ₂ (%): 87	Facial mask with reservoir bag	14 days	None	Discharged
# 10	Female/79	HTN	Dyspnea	Clinical findings RT-PCR	PR/min: 86 RR/min: 16 SBP (mmHg): 120 T (°C): 37.0 SpO ₂ (%): 80	Facial mask with reservoir bag	10 days	For 7 days	Died

Abbreviations: BiPAP= bilevel positive airway pressure; CHF= congestive heart failure; COVID-19= coronavirus disease-2019; DM= diabetes mellitus; Dx= diagnosis; HTN= hypertension; IHD= ischemic heart disease; LOC= loss of consciousness; PR= pulse rate; RR= respiratory rate; RT= radiotherapy; RT-PCR= real-time polymerase chain reaction; SBP= systolic blood pressure; SpO₂= blood oxygenation; T= temperature; V/S= vital signs.

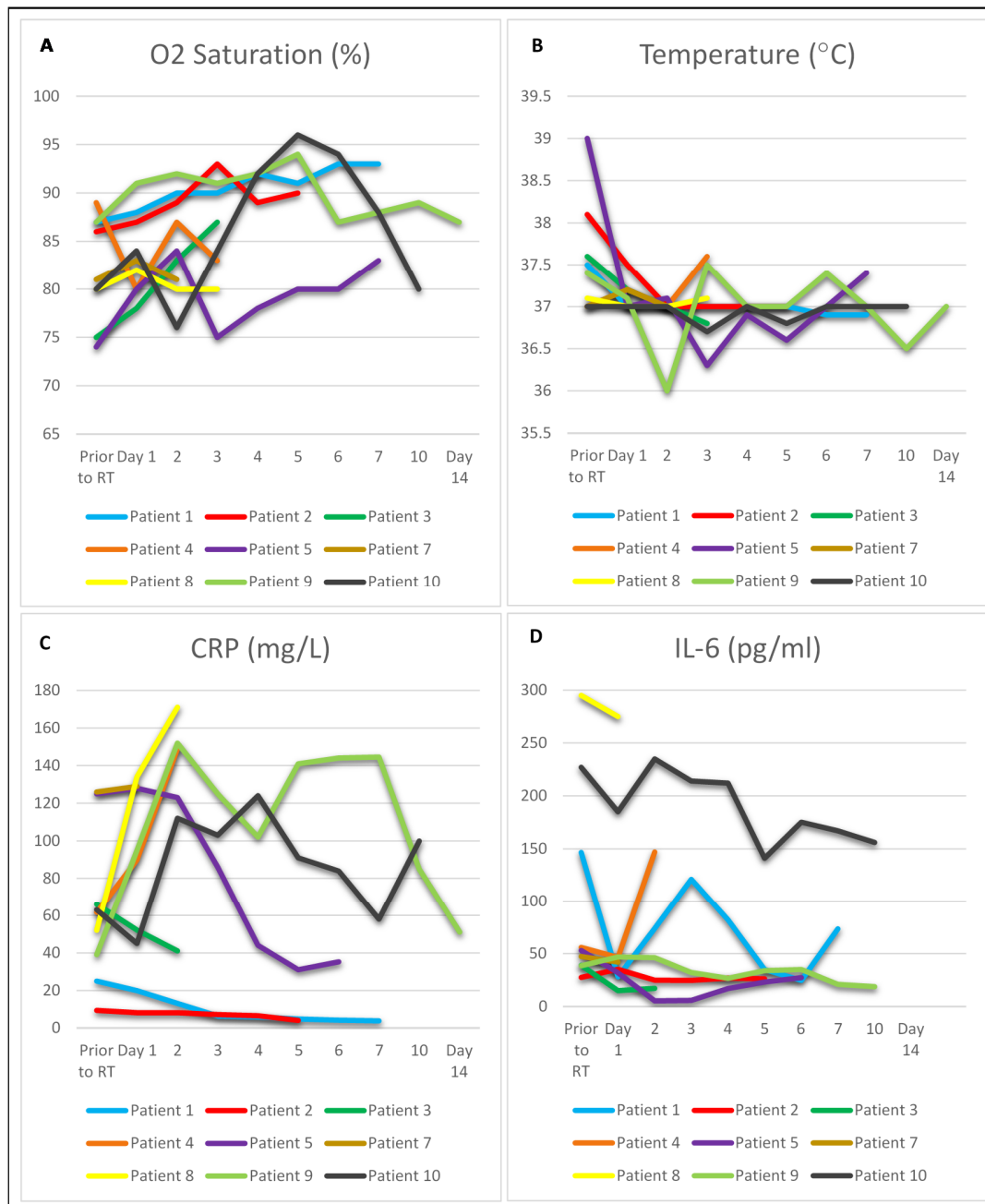


Figure 1. Evolution in time of (A) O₂ saturation, (B) body temperature, (C) c-reactive peptide, and (D) IL-6 in patients with COVID-19 pneumonia following whole-lung irradiation.

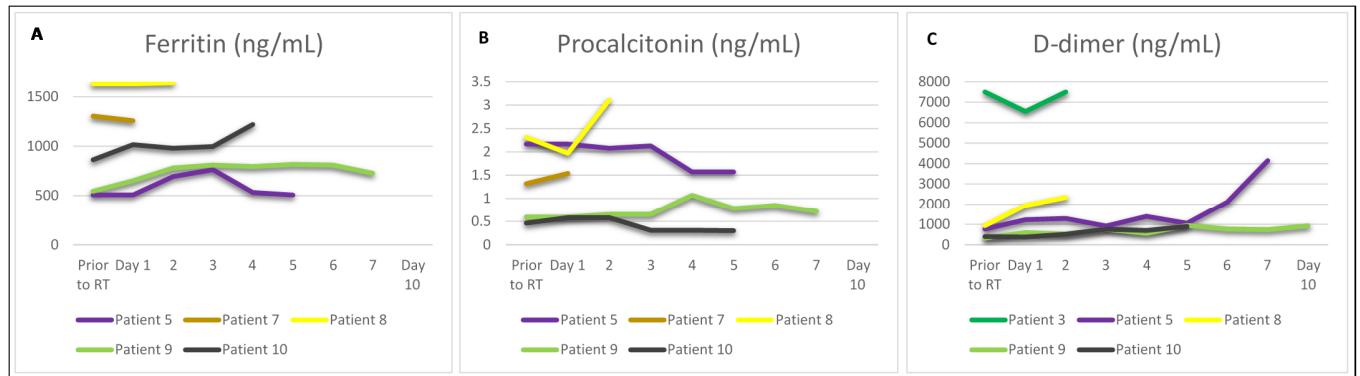


Figure 2. Evolution in time of (A) ferritin, (B) procalcitonin, and (C) D-dimer in patients with COVID-19 pneumonia following whole-lung irradiation.

Discussion

The initial results of this pilot trial addressed the potential efficacy of 0.5 Gy-WLI in 5 patients with moderate COVID-19 pneumonia.⁷ Herein, we investigated the clinical outcomes of 5 more patients with moderate COVID-19 pneumonia after exposure to 1.0 Gy-WLI and compared them with the 0.5 Gy group. Within 1 day after 0.5 Gy-WLI, the SpO₂ of 4 (80%) and 4 (100%) patients rose, respectively; however, it decreased later in 1 (20%) and 2 (50%) patients who eventually died. In 1.0 Gy group, both patients who were discharged had no underlying medical condition, whereas others who died had at least one of the comorbidities that are considered risk factors for COVID-19 mortality.¹⁰

Considering a RR of 80% and CR of 75%, WLI with a single dose of 0.5 Gy demonstrated encouraging results.⁷ In this updated report, however, the RR and CR of 1.0 Gy-WLI were 25 and 50%, respectively. This may reflect the concept that doses less than 1.0 Gy have an anti-inflammatory effect, while higher doses may exacerbate the pro-inflammatory response.¹¹ In an *ex vivo* analysis by Wunderlich et al., the inflammatory response to a single fraction of radiation between 0.1-2.0 Gy was evaluated. They found that the transmigration of activated macrophages significantly decreased between 0.1-0.5 Gy, secretion of IL-1 β (a pro-inflammatory cytokine) decreased between 0.5-2.0 Gy, TGF- β release (an anti-inflammatory cytokine) increased between 0.1-0.5 Gy, and the expression of NF-kB p65 (a pro-inflammatory mediator) decreased between 0.5-2.0 Gy. They concluded that a maximal anti-inflammatory effect of irradiation is at a single dose of 0.5 Gy.¹² However, we should consider several factors that may interfere with our results. First, the mean age of patients in the 1.0 Gy group was approximately 9 years older (71.8 vs 81.0 years), which may influence the RR and CR. The effect of age on radiosensitivity and inflammation has been demonstrated.^{13,14} Moreover, the distribution of patients between the two treatment groups was uneven by age; all three patients who were discharged in 0.5 Gy group were 60-70 years, while only one patient in the 1.0 Gy group was in this age range and recovered from COVID-19. Second, data on body mass index and smoking were not evaluated. The effect of these two factors on the prognosis of COVID-19, inflammation, and radiosensitivity has been demonstrated.¹⁵⁻¹⁷ Third, according to the national protocol for the management of patients with COVID-19 pneumonia, patients who had

SpO₂ <90% under noninvasive ventilation with FiO₂ >50% were indicated for ICU admission, intubation, and mechanical ventilation.⁸ Given these criteria, 7 patients were indicated for intubation and ICU admission. However, due to the limited ventilation facilities, only 1 patient was intubated, and we had to apply basic ventilation supports using a facial mask ± reservoir bag for the remaining 6 patients. This limitation may affect the clinical results of patients #4 and #8. Fourth, patients with 1.0 Gy group were recruited on average 22 days later in the study. This may have faced them with SARS-CoV-2 with more genetic mutations, which possibly make the overall prognosis worse.¹⁸

Overall, patients above 70 years old who received LD-WLI progressed to death, except for one who had no underlying medical condition. This finding signals the efficacy of LD-WLI in patients <70 years, and further trials are needed to reveal this notion. However, the concern of radiation-induced malignancy impedes clinical trials, including young patients.

CRP and IL-6 demonstrated relatively consistent changes with the patients' outcomes; however, other biomarkers did not. The prognostic significance of CRP and IL-6 in patients with COVID-19 pneumonia has been demonstrated.^{19,20} Considering the plasma half-life of CRP (19 hours) and IL-6 (10 minutes), they declined in 100% and 77.8% of available patients after 2 days and on the day of RT, respectively.^{21,22} This highlights the anti-inflammatory effect of LD-WLI in patients with COVID-19 pneumonia. We have also previously identified a potential association between paraclinical parameters (CRP and IL-6) and SpO₂.⁷ These updated results support this notion. We found that 1-2 days after RT, CRP and IL-6 changes were in agreement with clinical improvement (i.e. SpO₂) in 66.7 and 77.8% of cases.

Currently, three other ongoing clinical trials are evaluating LD-WLI in patients with COVID-19 pneumonia using a radiation dose between 0.7-1.5 Gy.⁷ The only available results are from the RESCUE 1-19 trial that was published in a non-peer-reviewed journal.⁹ In this pilot study by Hess et al., 5 patients with COVID-19 pneumonia received WLI with a single dose of 1.5 Gy. After 35 hours on average, 4 patients (80%) recovered rapidly and were able to breathe in room air. No acute toxicity was detected. The results were consistent with our findings for 0.5 Gy-WLI. However, we found inferior results with 1.0 Gy irradiation. Higher CR rates in the preliminary results of the RESCUE 1-19 trial may pertain to better hospital care or a higher female ratio (80.0 vs 22.2%) with potentially better prognosis.

Although the aforementioned limitations (noted in the second paragraph of discussion) are important, this study is the first to apply two radiation doses in WLI of patients with COVID-19 pneumonia. Moreover, we went beyond the RESCUE 1-19 trial by examining the body temperature and inflammatory biomarkers of patients following irradiation. Given the importance of a massive inflammatory response (so-called cytokine storm) in the mortality of patients with COVID-19 and the anti-inflammatory effect of low-dose irradiation, this trial may pave a new way for better management of patients with COVID-19.

Conclusion

Regardless of the age distribution and comorbidities, the results signal the superiority of 0.5 Gy-WLI in terms of RR and CR, possibly due to its anti-inflammatory effect. This finding may serve as a new benchmark for randomized trials of LD-WLI in patients with moderate COVID-19 pneumonia.

Conflicts of interest: The authors have no relevant relationships to disclose.

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Clinical trial registration number: NCT04390412

Data sharing: Research data are stored in an institutional repository and will be shared upon request to the corresponding author

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