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ORIGINAL ARTICLE

Low-dose whole-lung irradiation in severe COVID-19 pneumonia: a controlled clinical trial

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Abstract

Introduction: The COVID-19 pandemic has caused significant morbidity and mortality thus far. Considering the historical uses of high-voltage X-ray beams for unresolvable pneumonia, we aimed to assess whether low-dose whole-lung irradiation (WLI) could provide any benefits for patients with refractory COVID-19 pneumonia. **Methods:** Eleven patients with refractory COVID-19 pneumonia were treated with WLI to a total dose of 1 Gy and compared to 11 patients in a matched control group from June to November 2020. The study's primary endpoint was improvement of chest X-ray severity score (CXRS), followed by changes in mean oxygen (O2) saturation and 28-day mortality as secondary endpoints. **Results:** The final CXRS was significantly lower in the WLI group (8.7 ± 2.5) compared to the control group (12.3 ± 3.3) (P: 0.016). Change of CXRS from the first to the last chest X-ray was −2.2 ± 3.1 for the WLI group and 0.7 ± 3.9 for the control group, which showed a trend for lower CXRS in the WLI group (U = 30, p: 0.085). Mean O2 saturation showed insignificant improvement in the first 24 hours after radiotherapy (mean difference: 2.5 ± 4.1, Z=−1.6, *P* value: 0.11). Overall survival after 28 days was 32% in the WLI group and 11% in the control group (*P*: 0.48). The reason for death in many patients was not merely respiratory failure, but also other adverse situations like pneumothorax, cardiogenic shock and pulmonary thromboembolism. **Conclusions:** Low-dose WLI could improve the CXR severity score and O2 saturation in severely ill COVID-19 patients, but larger studies are required to determine its impact on mortality.

Introduction

The single-stranded RNA virus known as SARS-CoV-2 has caused an extensive pandemic rapidly since 2020. SARS-CoV-2 infection can cause various symptoms, from asymptomatic carrier state to life-threatening acute respiratory distress syndrome (ARDS) and respiratory failure.[1] Different medication has been used in the severe form of the disease with limited success.[2] The high fatality rate of the severe form of the disease, besides the lack of effective medications, deserves investigating different treatment approaches.

Low-dose irradiation of the lung has been suggested to have a therapeutic effect on refractory pneumonia. There

are several historical reports of successful treatment of viral and bacterial pneumonia in the pre-antibiotic era in the first half of the 20th century.[3–8] In these reports, low-dose irradiation of the lung with kilo-voltage X-rays was presumed to decrease the mortality rate by 20%.[9] This observation and also the proposed anti-inflammatory effect of low-dose radiotherapy (LDR) in vitro and in vivo models[10, 11] lead the investigators to propose low-dose whole-lung irradiation (WLI) as a treatment option in COVID-19 as well.[12, 13] This study aimed to assess the efficacy of low-dose WLI in COVID-19 refractory pneumonia.

Methods

Study Design

This non-randomised controlled clinical trial was conducted in the radiation oncology department of a tertiary referral university hospital in Tehran, Iran, between June and November 2020. The study was registered in the Iranian Registry of Clinical Trials (IRCT20170211032494N3) after being approved by the institutional review board and ethics committee (IR.TUMS.VCR.REC.1399.362).

Patients

The eligibility criteria for study participation were as follows: 1- age >18 years old, 2- diagnosis of COVID-19 confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR), 3- severe pneumonia due to COVID-19 with poor or no response to multiple lines of medical treatment (including antivirals and anti-inflammatory agents) and 4- critical disease state with PaO2/FiO2 less than 250 mmHg despite continuous oxygen (O2) supplementation. The exclusion criteria were a history of previous irradiation to the lung and pregnancy. The trigger point for enrolling patients was the time that the treating physician came to the conclusion of progressive clinical deterioration and unresponsiveness to the multiple lines of therapy for an eligible patient and consulted the radiation oncology team for allocation. This time of enrolment was taken as time zero for subsequent follow-up of survival outcomes.

The eligible patients who provided written informed consent by themselves or their valid proxies in case of unconsciousness were non-randomly assigned to two groups: the WLI group or the control group. Allocation was done based on appropriateness of all required conditions (i.e. safety of patient transfer to the radiation oncology ward, availability of the required equipment and personnel and decision being made on the last working days of the week when non-COVID cancer patients were not treated in the ward). The WLI group received one Gy dose to both lungs and usual care at the intensive care unit.

Treatment Protocol

Since the patients were critically ill, a 2-D technique was used to irradiate the lungs, omitting the excessive risk of transferring patients to perform simulation CT scan for 3-D conformal radiation therapy. The goal was to deliver 1 Gy dose to both lungs. Field borders were marked using patient's chest X-ray. Anterior–posterior parallel opposed fields with 18 MV photons were used. The mid centre of the lung was defined as the reference point for dose prescription. Monitor unit was calculated based on traditional methods. After the last working shift, the procedure was done while the radiation oncology ward was closed to anyone other than the study investigators. The overall treatment was performed as quickly as possible (maximum of 5 min as total treatment duration for 2-D set-up and radiation delivery and about 8 min for transportation from and back to the ICU). All the closed spaces within the transportation route and the treatment room were disinfected according to the standard guidelines after each patient's arrival, and adequate room air ventilation was ascertained.

Almost all of the patients were treated with the same volunteer team, including two radiation oncologists, an infectious disease specialist, a pulmonologist, an anaesthesiologist, a radiation therapist and a nurse. The anaesthesiologist observed patients during the whole procedure for any emergent situation (i.e. need for intubation or cardiopulmonary resuscitation).

Outcome assessment

The primary endpoint was improvement of chest X-ray severity score (CXRS) of the subjects. This scoring system was used as a parameter for assessment of radiological improvement. It was first developed by Borghesi and Maroldi[14] and was reported to be significantly higher in COVID-19 patients who died than those discharged from the hospital (P value < 0.002). This scoring system divides each lung into three distinct regions separated by two horizontal lines drawn on the standard chest X-ray: one through the inferior wall of the aortic arch and the other through the inferior wall of the right inferior pulmonary vein. In this method, each region is appointed a score of 0 to 3 based on the severity and pattern of lung involvement (0 for no abnormalities, 1 for interstitial infiltrates, 2 for interstitial and alveolar infiltrates with interstitial predominance, and 3 for

interstitial and alveolar infiltrates with alveolar predominance). Thus, the final CXRS can range from 0 to 18 for each patient. The chest X-rays were independently scored by two pulmonologists blinded to the study groups. The specialists reviewed any images with different scores simultaneously, and a final agreed score was substituted. Chest X-ray severity score improvement was defined as ΔCXRS (CXRS final – CXRS initial) <0. The secondary endpoints were change in daily O2 saturation and 28-day mortality. Using cardiac monitoring device, O2 saturation was assessed and documented once every hour on daily ICU vital sign sheets and the daily mean O2 saturation was recorded by dividing the sum of hourly measures by 24 for the WLI group since 24 h before radiotherapy (RT) until 120 h after RT. Mortality status 28 days after allocation to either study group was recorded.

Statistical analysis

Descriptive analysis was done to determine the baseline parameters of the study participants for each group. The binominal parameters in the two groups were compared by Pearson's chi-squared test. The quantitative variables were compared between the control and intervention groups using Mann–Whitney U-test. To compare the O2 saturation change in the intervention group, we conducted Wilcoxon signed-rank test. For all statistical tests, we defined 0.05 as the significance level. To estimate the overall survival, we calculated the time from allocation of the patients to the study groups (WLI or control) until the last follow-up or death. Then, we performed a time-event analysis with the Kaplan–Meier method. All analyses were done using SPSS software version 26.

Results

Patient characteristics and treatment

Forty-three critically ill COVID-19 patients with refractory pneumonia were screened for eligibility for this study between June and November 2020, and 23 patients were finally enrolled. Eleven patients were allocated to the WLI group and 12 patients were allocated to the control group. One patient withdrew consent from the control group and exited the study. Eventually, 11 patients were assigned to each group (Figure 1). All patients were ICU-admitted except two in the control group who were kept in non-ICU wards because of overcrowding. Nine patients in the WLI group needed mechanical ventilation during their stay, 3 of whom were intubated before RT. Also, 8 patients from the control group needed mechanical ventilation during their stay, 4 of them since before allocation to the control group. Two patients from the WLI group and 3 patients from the control group did not require mechanical ventilation during their course of hospital stay and used masks with reservoir bag for oxygen supplementation. The demographic, clinical, laboratory and imaging characteristics of the patients are presented in Table 1. Three patients were female (2 in the WLI group and 1 in the control group). The patients' mean age was 55.2 and 51.4 years in the WLI group and control group, respectively. A history of diabetes was present in 31.8% of patients, ischaemic heart disease in 22.7%, hypertension in 36.4% and smoking in 18.2% of patients.

There were no significant differences regarding the patients' baseline characteristics. Initial room air O2 saturation was 82.7% and 77.2% in the WLI and control groups, respectively (*P*: 0.06). Initial chest X-ray severity score was 10.9 out of 18 overall with no significant difference between the two groups (10.4 in the WLI group and 11.5 in the control group, *P* value: 0.24).

Chest X-ray severity score

The final chest X-ray severity score (before death or discharge) was significantly lower in the WLI group (8.7 ± 2.5) compared to the control group (12.3 ± 3.3) (*P*: 0.016). ΔCXRS (CXRS final – CXRS initial) was -2.2 ± 3.1 for the WLI group and 0.7 ± 3.9 for the control group, which showed a trend for lower CXR score in favour of the WLI group; (U = 30, p: 0.085). ΔCXRS was <0 in 7 (63.6%) patients from the WLI group compared to 4 (36.4%) patients in the control group (Chi^2=2.9, *P* value: 0.09). The pattern of changes in CXR score after WLI is shown in Figure 2. Figure 3 demonstrates the sequence of chest X-ray patterns in one of the sample-treated patients.

O2 saturation

In the WLI group, time from symptoms onset to RT was 18.8 ± 6.0 (mean ± SD) days and the median time from hospital admission to RT was 10 days [range: 4–15]. Mean O2 saturation in 8 out of 11 patients in the WLI group showed improvement in the first 24 h after RT; however, this difference did not reach statistical significance based on a Wilcoxon signed-rank test (mean difference: 2.5 ± 4.1, Z=−1.6, p value: 0.11). Mean O2 saturation at the time of radiation, 12, 24, 48 and 72 h after radiation was 89.3%, 89.7%, 91.8%, 89.5% and 89.6% respectively. Also, mean O2 saturation in the control group patients at the same time points after allocation was 86.8%, 86.3%, 87.5%, 87.1% and 86.8%, respectively.

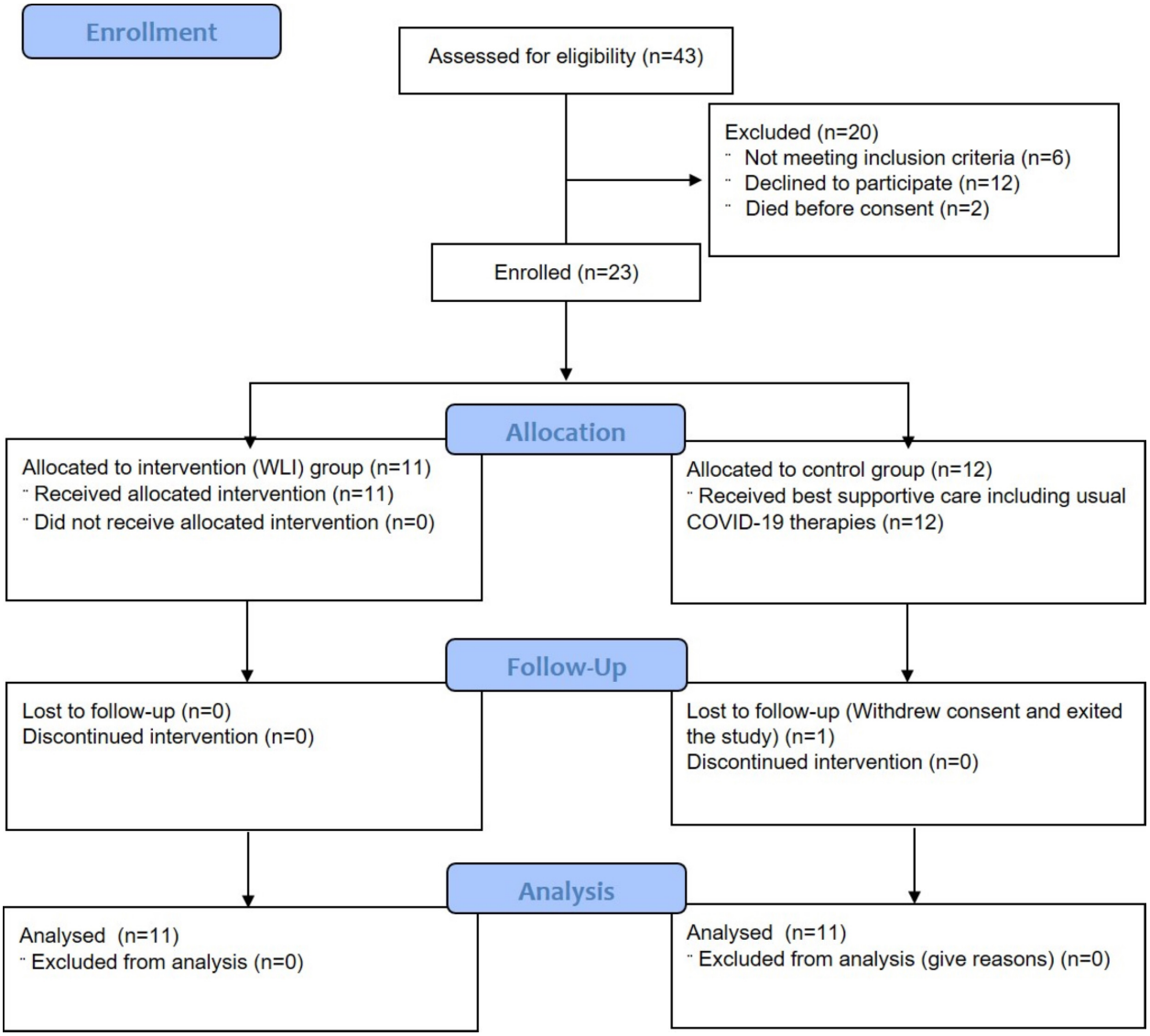

Figure 1. Consort flow diagram for the study participants

Survival

The patients were followed up for a median of 20 [range: 7-104] and 8 [range: 2-96] days after hospital admission and allocation to the treatment arms, respectively. Overall survival 7 days after allocation to the groups was 91% in the WLI group and 64% in the control group, after 14 days since allocation was 43% in the WLI group and 34% in the control group, and after 28 days was 32% in the WLI group and 11% in the control group. The median survival time of the WLI group was 11 days [95% CI: 4.9-17.1] compared with 10 days [95% CI: 4.2-15.8] in the control group (log-rank P value: 0.48) (Fig. 4). One patient died 47 days after WLI at home. Only 2 patients from each group were alive in the follow-up period. Pulmonary thromboembolism and cardiopulmonary arrest in the WLI group and renal failure in the control group were the most common critical conditions contributing to the participants' death (Table 2). Timelines for hospital admission and treatment allocation for both groups are depicted in Figure 5.

Discussion

Our study results show that low-dose WLI could improve the CXR severity score and also early O2 saturation in severely ill COVID-19 patients. Although the 28-day mortality rate was lower in the WLI group compared to the control group, this

Table 1. Baseline characteristics, hospitalization, radiographic and laboratory data across study participants

	All patients (n = 22)	WLI group (n = 11)	Control group (N = 11)	P value*
Sex				
Male	19 (86.4%)	9 (81.8%)	10 (90.9%)	0.53
Female	3 (13.6%)	2 (18.2%)	1 (9.1%)	
Age	55.2 ± 14.2	59 ± 16.0	51.4 ± 11.8	0.22
Symptom onset	7.2 ± 3.8	8.8 ± 3.8	5.2 ± 2.9	0.05
Medical and habitual history				
DM	7 (31.8%)	3 (27.3%)	4 (36.4%)	0.65
HTN	8 (36.4%)	4 (36.4%)	4 (36.4%)	0.99
IHD	5 (22.7%)	4 (36.4%)	1 (9.1%)	0.13
CKD	1 (4.5%)	0 (0%)	1 (9.1%)	0.31
Active smoker	4 (18.2%)	2 (18.1%)	2 (18.1%)	0.99
Obesity (BMI > 30)	1 (4.5%)	0 (0%)	1 (9.1%)	0.31
Presenting vital signs				
SBP	130 ± 18	126 ± 15	133 ± 20	0.99
DBP	80 ± 11	81 ± 9	80 ± 13	0.28
RR	22.6 ± 2.9	23.9 ± 3.6	21.4 ± 1.4	0.13
PR	92 ± 12	98 ± 13	87 ± 10	0.04
Body temperature	37.5 ± 0.7	37.4 ± 0.8	37.6 ± 0.7	0.55
Room air SO_2 (%)	80.1 ± 11.8	82.7 ± 13.4	77.4 ± 9.9	0.06
Hospitalization				
Mechanical ventilation (day)	5 [0–38]	5.5 [0–38]	4 [0–21]	0.83
ICU admission (day)	13 [0–42]	16 [5–42]	8 [0–37]	0.09
Hospital stay (day)	20.5 ± 11.6	22.2 ± 11.7	18.9 ± 11.9	0.52
Chest X-ray score				
Initial	10.9 ± 2.3	10.4 ± 2.3	11.5 ± 2.3	0.24
Laboratory data				
WBC (*10^3/μL)	10.4 ± 6.5	8.9 ± 5.4	11.9 ± 7.4	0.36
Lymph (/μL)	884 ± 486	825 ± 397	944 ± 575	0.95
Hb (g/dL)	13.9 ± 1.3	13.9 ± 1.3	14.0 ± 1.3	0.99
PLT (*10^3/μL)	209 ± 82	200 ± 89	218 ± 79	0.56
Cr	1.31 ± 0.38	1.16 ± 0.25	1.46 ± 0.44	0.08
AST	44.9 ± 18.0	43.3 ± 16.7	46.6 ± 20.0	0.97
ALT	36.3 ± 17.9	39.9 ± 22.8	32.7 ± 11.3	0.91
ALP	161.1 ± 57.4	155.3 ± 59.8	166.9 ± 57.5	0.63
ESR	67.8 ± 25.3	60.6 ± 31.0	74.4 ± 17.8	0.35
CRP	61.5 ± 15.8	56.9 ± 20.0	65.6 ± 9.9	0.31
Procalcitonin	0.3 [0.06–3.72]	0.23 [0.06–0.46]	0.59 [0.11–3.72]	0.31
LDH	1013 ± 642	908 ± 345	1127 ± 870	0.99
Medication before allocation				
Dexamethasone	12 (54.5%)	7 (63.6%)	5 (45.5%)	0.39
Methylprednisolone	22 (100%)	11	11	0.99
Remdesivir	22 (100%)	11	11	0.99
Atazanavir	15 (68.2%)	9 (81.8%)	6 (54.5%)	0.17
Interferon beta 1-a	20 (90.9%)	10 (90.9%)	10 (90.9%)	0.99
IVIG	5 (22.7%)	3 (27.3%)	2 (18.2%)	0.61

*The binominal parameters in the two groups were compared by Pearson's chi-squared test. The quantitative variables were compared using Mann–Whitney U-test. Abbreviations: ALP: alkaline phosphatase, ALT: alanine transferase, AST: aspartate transferase, CKD: chronic kidney disease, CRP: C-reactive protein, DBP: diastolic blood pressure, DM: diabetes mellitus, ESR: erythrocyte sedimentation rate, HTN: hypertension, IL-6: interleukin 6, LDH: lactate dehydrogenase, MS: multiple sclerosis, N/A: not applicable, PLT: platelet count, PR: pulse rate, RR: respiratory rate, SBP: systolic blood pressure, WBC: white blood cells, WLI: whole-lung irradiation

difference did not translate into a statistically significant finding and the results provide no particular evidence for a survival advantage with WLI in the study participants. However, the impact on mortality might have been attenuated due to the small sample size and multiple confounding factors for death in COVID-19 patients.

In 2013, Calabrese and Dhawan[9] published a comprehensive review of historical reports on low-dose

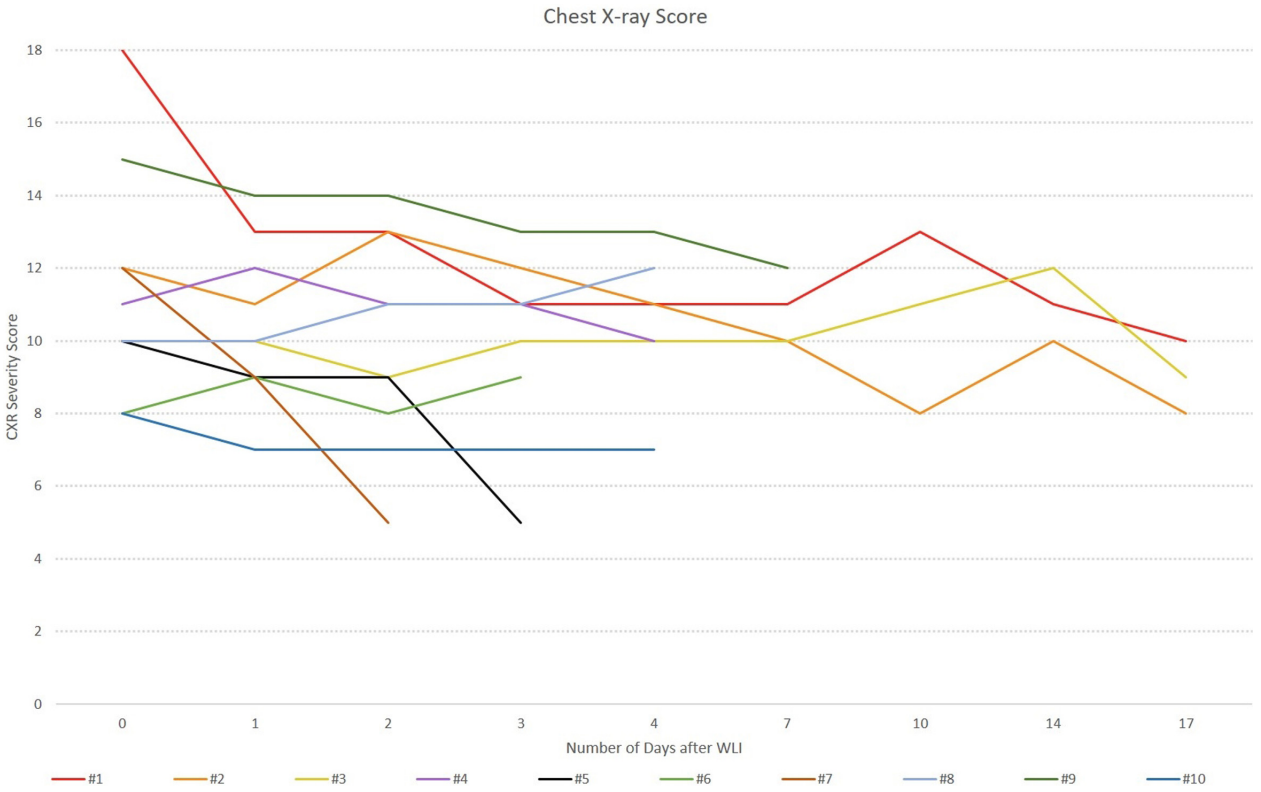

Figure 2. Chest X-ray severity score in the patients treated with low-dose whole-lung irradiation

radiotherapy efficacy in refractory pneumonia. They suggested that a clinical research programme to assess the use of X-ray therapy for high-risk pneumonia is a reasonable next step. This suggestion was not taken seriously until the COVID-19 pandemic.

The mechanism of efficacy of low-dose radiation therapy is mainly attributed to its anti-inflammatory effect. This effect is mentioned to be the result of the polarisation of macrophages to an M-2 anti-inflammatory phenotype.[15]

Two trials are published on efficacy of WLI in COVID-19 patients: one is a non-randomised controlled trial and the other is a single-arm study.[16, 17] Both studies claimed that WLI would improve clinical condition in oxygen-dependent COVID-19 patients. In the first trial (RESCUE 1-19), 10 patients with COVID-19 received 1.5 Gy radiation to both lungs and were compared to a matched control group. Time to clinical recovery defined as the time required for patients to remain for 12 hours off supplemental oxygen was significantly lower in the WLI group (3 vs 12 days). Time to hospital discharge, time from admission to recovery, intubation rates and number of days on supplemental oxygen were not significantly different between the two groups but a significant reduction of several inflammatory markers and also significant improvement in radiographic score was seen in the WLI group.[17] In the second study, 10 patients with COVID-19 were treated with 0.5 to 1 Gy radiation to both lungs and the clinical recovery was reported to be 55.5%, and the 28-day mortality rate was reported to be 60%.[16] Both studies showed that the efficacy of RT begins on the first day after treatment.

The present study's results in terms of clinical response measured as radiologic response and O2 saturation are in accordance with the previous studies, but these objective responses could not improve the patients' survival. This might be due to two issues. The first one is the severity of the disease. Although in the RESCUE 1-19 trial,[17] the patients' median age was 78, and they were reported to have multiple comorbidities, it should be noted that clinically deteriorating patients in the prior days of RT were excluded. The only patient, whose oxygen demand was rapidly rising before RT, did not respond to RT and was intubated and expired later. On the other hand, the patients' condition was not severe in this trial, since the median oxygen requirement at the time of irradiation was 3 L/min (the patients with more than 6 L/min oxygen demand were excluded) and the 28-day mortality was reported to be only 10%. In the present study, initial room air O2 saturation in the WLI group was 82.7%, and

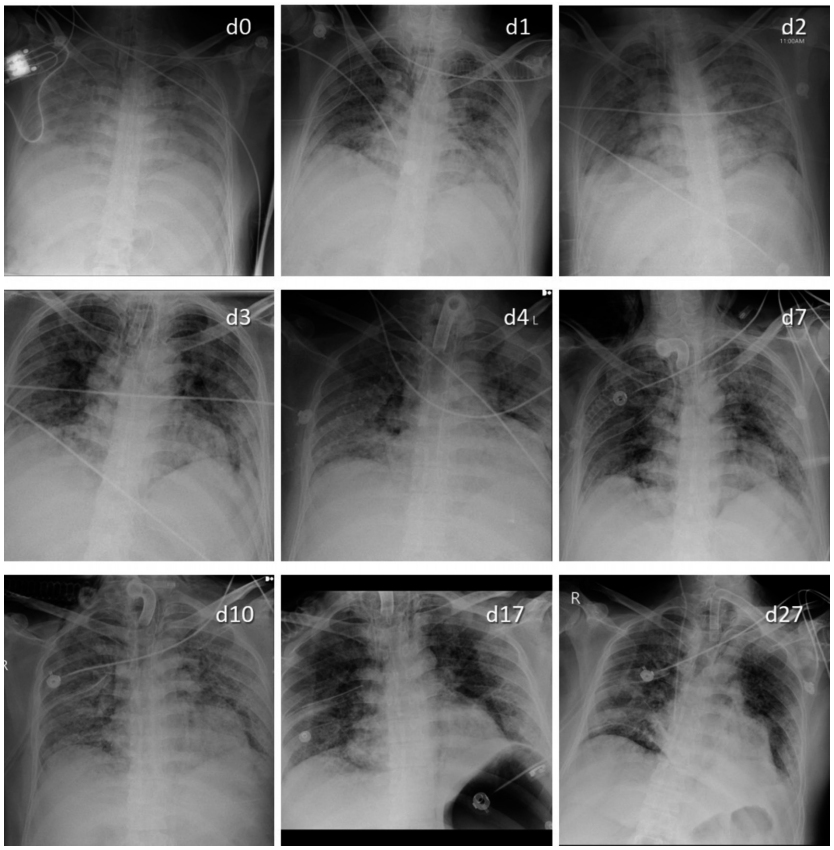

Figure 3. Chest X-rays of a 40-year-old male patient from the WLI group on days 0, 1, 2, 3, 4, 7, 10, 17 and 27 after 1 Gy radiation to both lungs. The chest X-ray scores were calculated to be 18, 13, 13, 11, 11, 11, 13, 10 and 9, respectively

all of the patients in the WLI group were ICU-admitted with at least 10 L/min supplemental oxygen requirement, and three patients were intubated at the time of irradiation. Also, all patients had a PaO2 to FiO2 ratio of less than 250 mmHg at the time of allocation to treatment groups. The patients' mortality rate in this study is much higher than the overall mortality rate in ICU-admitted COVID-19 patients in the same centre (81.8% vs. 50%), which further reflects the severity of the disease in the selected patients.

The second issue is the timing of RT. In our study, the mean time from symptoms onset to RT was 18.8 ± 6.0 days and the median time from admission to RT was 10 days. In the RESCUE 1-19 trial,[17] the median time from symptoms to hospitalisation and time from hospitalisation to RT were 7.5 and 4.5 days, respectively. The importance of treatment in the early phases of the disease has been described in historical studies.[18] For example, in one study that used low-dose radiotherapy in 56 patients with interstitial pneumonia, patients treated within a few days after symptom onset had a better recovery than those treated with delay.[19] It is suggested that the anti-inflammatory effect of most medications is more effective in the early phases of the disease.[20] In a recent case report, a 65-year-old man was successfully treated with 1 Gy of WLI. The time from hospitalisation to RT was 3 days, and O2 saturation at baseline and one day before RT was 89% in the room air and 92.7% with a high-flow nasal cannula.[21]

Compared to the previously mentioned reports, in our study, patients were generally selected for RT very late as they were clinically deteriorating in the course of their hospitalisation after prescription of multiple lines of antivirals (e.g. remdesivir) and anti-inflammatory agents (e.g. corticosteroids). The main reason for death in many patients was not merely respiratory failure due to the severe pneumonia, but other adverse and life-threatening situations like pneumothorax, cardiogenic shock probably due to myopericarditis and most prominently pulmonary thromboembolism were involved as well. All of these conditions are considered as major complications of SARS-CoV-2.[22] In the RESCUE 1-19 trial,[17] a temporary stabilisation of oxygen demands was reported in the non-responding patient which was followed by systemic

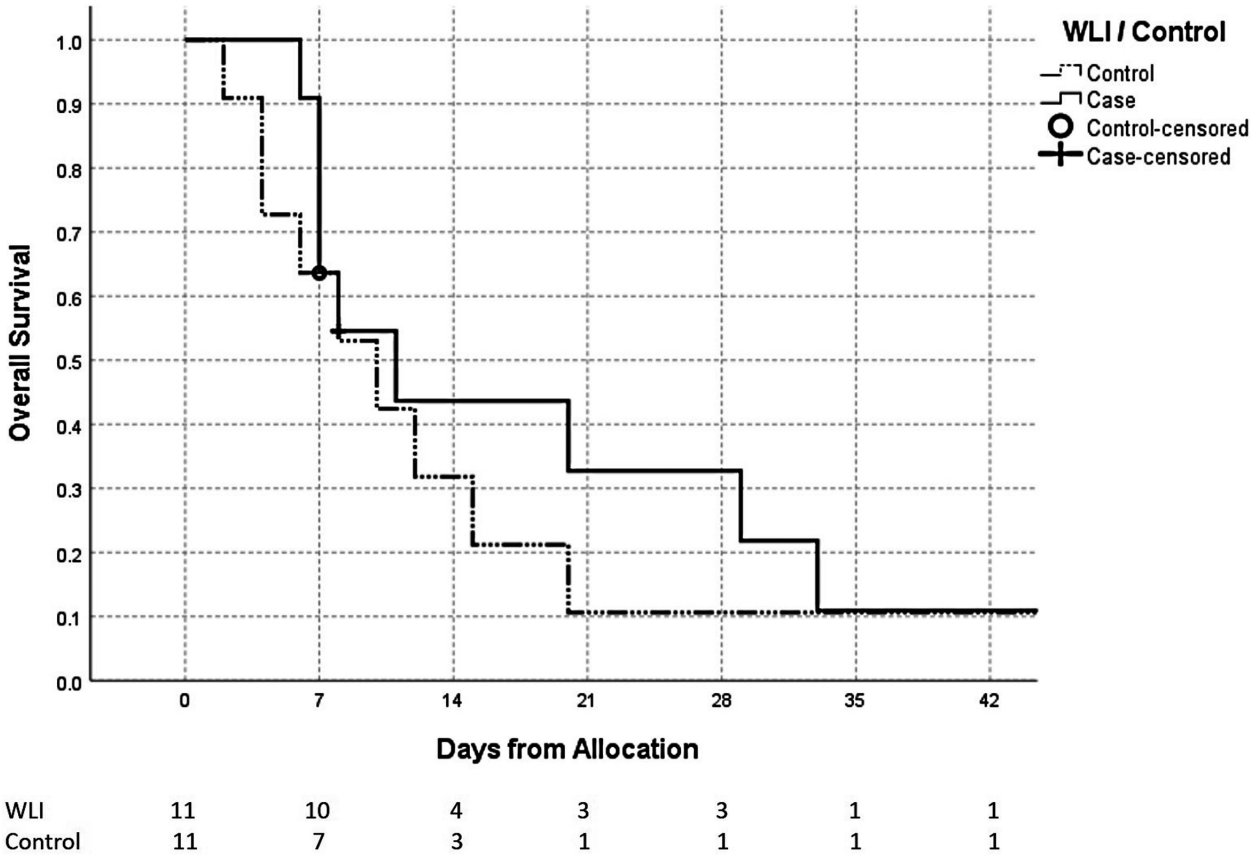

Figure 4. Comparison of overall survival in COVID-19 patients undergoing whole-lung irradiation and the control group since eligibility for RT. Log-rank: 0.50, *P* value: 0.48

Table 2. Critical conditions contributing to death of study participants.

	WLI group	Control group
Pulmonary thromboembolism	4 (36.4%)	1 (9.1%)
Cardiopulmonary arrest	4 (36.4%)	2 (18.2%)
Renal failure	1 (9.1%)	6 (54.5%)
Pneumothorax/pneumomediastinum	2 (18.2%)	2 (18.2%)
Sepsis	1 (9.1%)	3 (27.3%)
Multi-organ failure	2 (18.2%)	3 (27.3%)
Severe thrombocytopenia	2 (18.2%)	2 (18.2%)
Iatrogenic*	1 (9.1%)	0 (0%)

*One patient died due to severe vasovagal spasm during NG tube replacement.

clotting, a cardiac event and intubation after 5 days and the authors admitted that the study's result is not generalisable to patients who experience rapid clinical decline.

The primary endpoint of this study was improvement in chest X-ray severity score defined as a lower score on the last CXR compared to the initial CXR; 7(63.6%) patients from the WLI group compared to 4(36.4%) patients from the control group achieved this outcome ($Chi^2 = 2.9$, p value = 0.09) which shows a trend for improvement in chest X-ray severity in patients who underwent WLI. The significance of this finding is that radiation might have played a role by decreasing the inflammatory phase of the cytokine storm, thus improving CXRS and oxygenation; however, this did not result in a significant survival benefit in our patients.

We might be able to say that WLI could be efficacious in selected COVID-19 patients, but in the severe cases with refractory pneumonia, it cannot change the fatal outcome of the patients, which is dictated by other major complications of SARS-CoV-2. Low doses of radiation used in this trial did not cause any acute radiation-induced complications, which is in accord with the previous trials.

While considering WLI for COVID-19 patients, there are many technical challenges for the healthcare system. Patients, especially those with a significant oscillating O2 saturation, must be ascertained to be hemodynamically

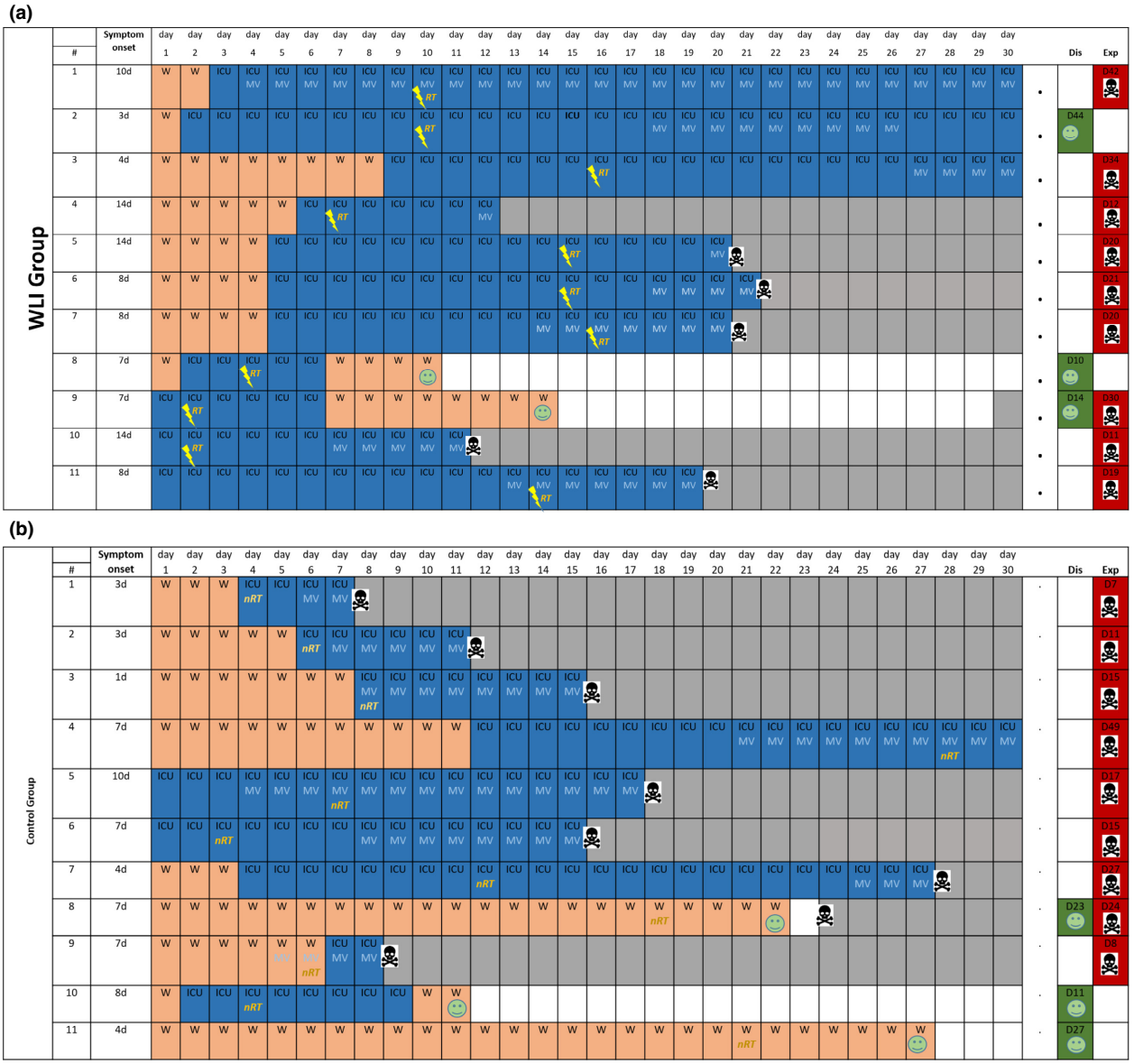

Figure 5. Timelines depicting hospital admission (ward or ICU), need for mechanical ventilation and allocation to treatment groups (A: WLI group and B: Control group). Abbreviations: ICU: intensive care unit, W: ward, MV: mechanical ventilation, dis: discharged, exp: expired, RT: allocated to receive RT, nRT: allocated to not receive RT

stable before planning transportation. An anaesthesiologist or pulmonologist should be in charge of transfer to and from the radiotherapy ward accompanied by a nurse and transfer personnel. Oxygen supplies should be secured for the treatment time and transportation pathway, especially for patients under mechanical ventilation who require extensive amounts of oxygen. Cardiopulmonary resuscitation might be required during the process, so necessary devices should be available. Also, these patients should be adequately isolated from the cancer patients who routinely refer to the radiation oncology ward. Treatment planning has to be done as fast as possible by the radiation oncologist on the radiotherapy device, and the time the patient stays out of ICU has to be minimal. After WLI, the radiotherapy unit and the transportation route at risk of contamination by the virus particles have to be disinfected appropriately. Moreover, the added risk of acquiring COVID-19 by the physicians and personnel is another issue that has to be considered. Finally, the financial cost pertaining to the utilisation of radiotherapy device on a separate day from cancer patients' treatment,

or dedicating an exclusive radiotherapy device to COVID-19 patients, is another important matter in this regard. Considering all the above-mentioned issues, the practicality of WLI in COVID-19 patients should be appraised with special attention.

Limitations

The main limitation of this study was its non-randomised design. Due to technical issues (i.e. difficult and high risk of patient transportation to the radiotherapy device, need for constant monitoring of the patients under an anaesthesiologist's supervision, need for constant oxygen supplies on the way to the radiotherapy department, treatment limited to the weekends for the safety of non-COVID cancer patients, safe decontamination of the treatment area and transportation routes), only those patients fulfilling all these conditions could be selected for WLI. Although allocation decisions were not made on the basis of patient-level prognostic factors, our results inevitably contain some selection bias. Despite the mentioned limitations of this study, thus far, this is the first clinical trial of WLI conducted in the COVID-19 era with a control group, which warrants further evaluation of RT effectiveness in refractory COVID-19 patients.

Conclusion

Low-dose WLI could improve the CXR severity score and early O2 saturation in severely ill COVID-19 patients. Impact on mortality might not be conclusive due to the small sample size and multiple confounding factors for death in these patients. We recommend evaluation of possible effects of WLI in COVID-19 patients in early stages of the disease, before emergence of other devastating major complications.

Ethics approval

This study was approved by the institutional review board and ethics committee of Imam Khomeini Hospital Complex of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.362).

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ClinicalTrials.gov:

Registered in Iranian Registry of Clinical Trials: WWW.irct.ir

Trial registration number: IRCT20170211032494N3.

Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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