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CRITICAL REVIEW: COVID-19 SCIENTIFIC COMMUNICATION

Low-Dose Whole Lung Irradiation for Treatment of COVID-19 Pneumonia: A Systematic Review and Meta-Analysis



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Purpose: Studies dating back to a century ago have reported using low-dose radiation therapy for the treatment of viral and bacterial pneumonia. In the modern era, since the COVID-19 pandemic began, several groups worldwide have researched the applicability of whole lung irradiation (WLI) for the treatment of COVID-19. We aimed to bring together the results of these experimental studies.

Methods and Materials: We performed a systematic review and meta-analysis searching PubMed and Scopus databases for clinical trials incorporating WLI for the treatment of patients with COVID-19. Required data were extracted from each study. Using the random-effects model, the overall pooled day 28 survival rate, survival hazard ratio, and intubation-free days within 15 days after WLI were calculated, and forest plots were produced.

Results: Ten studies were identified, and eventually, 5 were included for meta-analysis. The overall survival hazard ratio was calculated to be 0.85 (0.46–1.57). The pooled mean difference of intubation-free days within 15 days after WLI was 1.87, favoring the WLI group (95% confidence interval, –0.02 to 3.76). The overall day 28 survival rate of patients receiving WLI for the 9 studies with adequate follow-up data was 74% (95% confidence interval, 61–87). Except for 2 studies, the other 8 studies were assessed to have moderate to high risk of bias, and there were many differences among the designs of the studies, included patients, primary endpoints, outcome measurement methods, and reporting of the results.

Conclusions: Despite a mild improvement in intubation-free days, WLI had no significant effect on patients' overall survival. Currently, we cannot recommend routine use of WLI for the treatment of patients with moderate-to-severe COVID-19. © 2022 Elsevier Inc. All rights reserved.

Introduction

Coronavirus disease 2019 (COVID-19) caused by a large single-strand RNA virus from the beta coronavirus family was

recognized in December 2019 and rapidly became a global issue.¹ Acute respiratory distress syndrome (ARDS), caused by a hyperinflammatory state due to a cascade of cytokine release, is the leading cause of death in these patients.²

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Anti-inflammatory effects of low-dose radiation therapy have been established in preclinical models. Low dose radiation therapy reduces proinflammatory mediators such as tumor necrosis factor- α , selectins, and interleukin-beta 1, and at the same time increases the secretion of anti-inflammatory mediator transforming growth factor β 1 and apoptosis mediator nuclear factor kappa-beta.^{3,4}

In a recent review by Calabrese et al,⁵ the authors report that low doses of radiation (<1 Gy) can induce nuclear factor erythroid 2-related transcription factor-mediated cellular antioxidant states and also shift the balance of macrophages toward anti-inflammatory M2 phenotype from the M1 proinflammatory subtypes. This change of balance has been shown to result in an increase of IL-10 and decrease of Interferon γ and IL-6 production, thus resulting in attenuation of the cytokine storm caused by the SARS-CoV-2 virus.⁶

Low-dose radiation therapy was historically used for the treatment of viral and bacterial pneumonia,⁷ dating back to about a century ago, and also benign inflammatory diseases like arthritis.^{8,9} This use of radiation therapy for nonmalignant diseases was generally before the development of the vast inventory of modern antibiotics and anti-inflammatory agents. After the COVID-19 pandemic challenged our modern resources, many clinicians looked for the long-forgotten and readily available low dose whole lung irradiation as a possible means of preventing excessive morbidity and mortality of COVID-19. Although successful vaccination programs and recently approved therapeutics have decreased the enthusiasm for investigating the efficacy of WLI in COVID-19, multiple trials have been conducted on this topic, and some are still underway. To sum up these new findings so far, we intended to run a systematic review and meta-analysis of studies incorporating WLI for the treatment of COVID-19 pneumonia.

Methods and Materials

This study was registered in the international prospective register of systematic reviews (PROSPERO, ID: CRD42021277399) and was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist¹⁰ (Appendix E1).

Search methods

A systematic search was done on the English-language medical literature using electronic bibliographic databases, the Scopus and PubMed, until the end of January 2022 to identify relevant original peer-reviewed full-length articles. The following terms were used in each database according to their search strategy: (“radiation” OR radiotherapy) AND (“COVID*” OR “SARS-COV-2” OR coronavirus) AND (“pulmon*” OR lung) (Appendix E2). Further augmentation of the search was done by looking at the included articles’

references and forward citation searching for identifying updates of relevant studies. No time limit was considered for publications.

Study selection

The following criteria were considered necessary for included articles:

- Prospective phase 2 or 3 trials conducting whole lung radiation therapy in the treatment course of patients with COVID-19
- Following the patients for at least 28 days
- Provided adequate data to extract the hazard ratio (HR), overall survival (OS) rate, and their standard error (SE)

Abstracts without full articles, unpublished studies, notes, letters, comments, and conference articles were excluded from the study. Duplication removal was also done. Two researchers reviewed anonymized titles and abstracts to check the study's eligibility. Any study that had the agreement of both authors entered for full-text review. Both authors reviewed all full-texts, and if both agreed, the article was selected for meta-analysis. Discrepancies were solved by consensus or referred to a third senior researcher.

Data extraction

The investigating researchers independently extracted the following data: title, authors' name, journal title, year of publication, country of study, details of study design, included participant number, mean age, gender frequency, the severity of COVID-19, medical treatment received, duration of symptom onset, time of radiation therapy, dose, fraction, photon energy and radiation therapy technique, primary and secondary outcomes, ventilation free duration (VFD), time to clinical recovery, hospitalization duration, follow-up duration, level of C-reactive protein (CRP), O₂ saturation, PaO₂/FiO₂, SpO₂/FiO₂, chest x-ray or computed tomography (CT) severity, OS rate, and the number of event-positive/negative patients.

Two outcomes were selected for meta-analysis of studies with a control group: OS HR and intubation-free days in 15 days. Data for these 2 outcomes were extracted from the relevant studies for each participant (from either the main text or supplemental data).

As detailed individual participant data (IPD) was unavailable, we needed to extract raw survival data from the survival curves presented within the articles for which the *DigitizeIt* software was used,¹¹ and the exact date of death or censored data and the change of OS rate were recorded. In one case, due to discrepancies between the statistical method used, reported results, and the illustrated OS curve, we emailed the corresponding author of the study to provide IPD. However, our request was not responded to, and the

study was removed from the meta-analysis.¹² Data extraction was completed by February 2022 for all outcomes of interest, whether included for meta-analysis or not.

Assessment of methodological quality

Cochrane's risk-of-bias tool for randomized trials (RoB 2) and Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) were used for quality assessment of the randomized and nonrandomized interventional studies, respectively.^{13,14} Also, the Methodological Index for Non-Randomized Studies (MINORS) risk of bias assessment tool¹⁵ comprising of 8 domains was used for quality assessment of the single-arm noncomparative clinical trials, and a score of 0 to 2 was appointed for each domain. A total score of 15 to 16 was considered high quality, 9 to 14 was considered moderate quality, and 0 to 8 was considered low quality.

Statistical analysis

The extracted raw OS and follow-up data, including event and censor dates from each included study, were used to reproduce individual life tables using SPSS Statistics version 26 (IBM). Kaplan-Meier curves were reconstructed and overlapped with the published curves to ensure accuracy of extracted IPD. Cox proportional hazards regression analysis was used to extract OS HRs, standard errors, and confidence intervals from extracted IPDs. The Firth's penalized likelihood method was used for reduction of bias in Cox analysis when the number of events was zero in a subgroup. Also mean intubation-free days in 15 days and their standard errors were calculated for intervention and control groups. Using Review Manager (RevMan) version 5.3, a random-effects model was used to pool the OS HRs. Also, to calculate the pooled intubation-free days within 15 days after the intervention, the mean difference between intervention and control groups were pooled by the random-effects model. Heterogeneity assessment was performed by calculating Higgins' I^2 statistics and Cochran's Q test (with significance less than 0.1). Publication bias was assessed by funnel plot and Eggers's regression test. For calculation of aggregated day 28 OS rate in the intervention groups of all included studies, the "Metafor" package in R statistical analysis software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) was used.¹⁶

Results

Study characteristics

A total of 641 studies were found after database search. Duplicate results were removed (149 studies). Four-hundred-ninety-two studies were reviewed by title and abstract,

16 were selected for full-text review, and 10 were selected for the systematic review (qualitative analysis). A detailed process of screening is provided in Figure 1. One study was suspected of having provided incorrect results due to discrepancy between methodological analysis, reported results, and illustrated OS figures and was therefore removed from the meta-analysis¹²; however, the presented results are discussed separately. Finally, 9 studies (with a total of 151 WLI recipients) were considered eligible to enter the analysis of aggregated 28-day OS rate of patients receiving WLI¹⁷⁻²⁵ (quantitative analysis). Six studies had both intervention and control groups (115 participants in the intervention group and 98 participants as controls).^{12,17,20-23} One of these controlled studies was the excluded study due to erroneously reported results. Eventually, 4 studies were included for meta-analysis of intubation-free days within 15 days after WLI and 5 studies for meta-analysis of OS HR. Study design characteristics and outcomes of interest in each study are shown explicitly in Tables 1 to 3. Detailed information on quality and risk of bias assessment for included studies is provided in Figure 2 (RoB 2 and ROBINS-I tools) and Table E1 (MINORS tool).

Quantitative analysis

28-day OS rate

The pooled OS rate of the 9 included studies was calculated 74% (95% confidence interval [CI], 61%-87%) in the WLI group (Fig. 3). The heterogeneity between the studies was significant (Q: 26.62; df = 8; $P = .0008$; I^2 : 76.11%; tau²: 0.028).

Overall survival HR

The pooled HR of the 5 included studies was 0.85 (95% CI, 0.46-1.57; Fig. 4). There was no significant difference between the intervention and control groups considering the confidence interval. The confidence interval for Hess, 2021 study²⁰ was very wide due to a lack of terminal event in the control group which led to a large standard error. The heterogeneity of the studies was calculated as mild in this issue (Q: 1.61; df = 4; $P = .81$; I^2 : 0%). However, it should be mentioned that the low heterogeneity result could be due to the small number of studies.

Intubation-free days

The pooled mean difference of intubation-free days during 15 days after WLI between intervention and control groups was 1.87 days favoring the WLI group (95% CI, -0.02 to 3.76; Fig. 4). The results show that intubation-free days was relatively higher in the WLI group. The heterogeneity of the studies was also minimal (Q:1.33; df = 3; $P = .72$; I^2 : 0%; tau²: 0). Again, we should mention that the minimal heterogeneity could be related to the small number of studies.

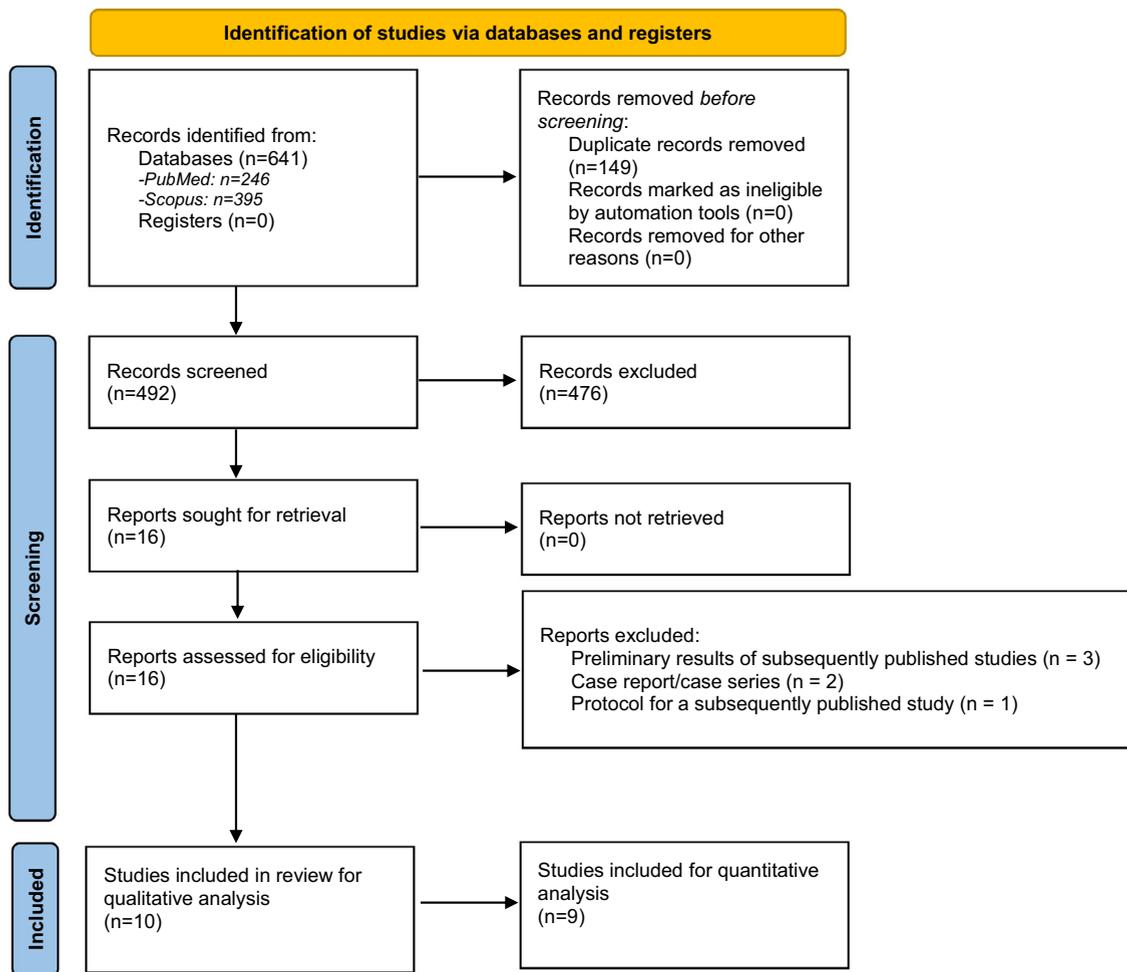


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Qualitative analysis

Overall survival

Ortiz et al¹² treated 30 patients with moderate-to-severe COVID-19 with 1 Gy WLI and compared the outcomes with a matched control group of 29 patients. They reported a crude OS rate of 72.5% in the intervention group versus 41.4% in the control group ($P = .05$). In an unplanned subgroup analysis based on the severity of ARDS, the crude OS rate in moderate and severe patients was 100% and 22% in the intervention group versus 40% and 0% in the control group, respectively ($P = .01$ and $.9$). The final 28-day OS rates varied significantly between studies, from 32% in Mousavi et al²² to 90% in Sharma et al²⁵ and Hess et al.²¹

Mechanical ventilation

Ortiz et al reported a 33% need for mechanical ventilation in the intervention group versus 58% in the control group ($P = .51$); however, in a subset analysis of moderate severity patients, none of the patients in the intervention group needed mechanical ventilation compared with 45% of the controls ($P < .001$). This difference was not statistically significant in

the severe ARDS subgroup of their patients (100% vs 89%, $P = .47$). Ganesan et al¹⁷ reported that 5 (15%) and 4 (23%) of their patients in the intervention and control groups respectively, required mechanical ventilation and later succumbed to the disease. Mousavi et al²² reported that 6 patients (54.5%) of the WLI group required intubation after WLI compared with 4 (36.4%) of the control group after allocation. In the study by Papachristofilou et al,²³ none of the 3 nonintubated patients needed intubation after WLI compared with 3 of the 6 nonintubated patients in the sham WLI group. The first cohort of Hess et al²¹ reported 28-day freedom from intubation of 90% in the WLI group, compared with 60% in the control group (HR, 4.9; 95% CI, 0.72-100; $P = .16$). However, their second cohort²⁰ reported a 28-day freedom-from-intubation rate of 86% for the WLI group versus 68% for the control group (HR, 0.27; 95% CI, 0.04-1.1; $P = .09$).

Clinical recovery and hospital discharge

Three studies with a control group reported time to clinical recovery (TTCR) defined as time to wean from supplemental oxygen and remain so for at least 12 hours. Hess et al in their first cohort²¹ reported TTCR to be 3 days (range,

Table 1 Studies included for systematic review and their design

Study	Accrual	Design	COVID-19 severity	Number of participants	Dose/fraction number	Planning/photon energy	Primary outcome	Secondary outcomes
Papachristofilou et al, ²³ Switzerland (February 2021)	November to December 2020	Randomized, double masked	Severe (ICU ad on MV or NIV)	22 (11 control, 11 intervention)	100 cGy/1	2D (AP)/10 MV	VFD at day 15	P/F, day 15/28 OS, inflammatory markers
Mousavi et al, ²² Iran (August 2021)	June to November 2020	Nonrandomized, prospectively controlled	Severe (ICU ad)	22 (11 control, 11 intervention)	100 cGy/1	2D (AP-PA)/18 MV	CXR severity score	SpO ₂ , day 28 OS
Hess et al, ²⁰ United States (October 2021)	June to December 2020	Nonrandomized, matched controls	Moderate to severe, oxygen dependent	40 (20 control, 20 intervention)	150 cGy/1	2D (AP-PA)/15 MV	Safety, TTCR, intubation rate	OS, hospital stay, CR, CRP response, freedom from intubation, intubation-free survival, intubation duration, cumulative oxygen supplementation, radiographic changes
Hess et al, ²¹ United States (December 2021)	April to May 2020	Nonrandomized, matched controls	Moderate to severe, oxygen dependent	20 (10 control, 10 intervention)	150 cGy/1	2D (AP-PA)/15 MV	TTCR	Hospital stay, intubation events, duration of intubation, oxygenation requirements, days febrile, and vital status, serologic course, radiographic changes
Ortiz et al, ¹² Mexico (November 2022)	April to August 2020	Nonrandomized, matched controls	Moderate to severe	59 (29 control, 30 intervention)	100 cGy/1	2D (AP-PA)/6 MV	Survival	Intubation, hospital stay, comorbidity effect on response to WLI
Sanmamed et al, ²⁴ Spain (November 2021)	April to June 2020	Single arm	Moderate to severe	9 intervention	100 cGy/1	3D (AP-PA)/6 MV	Radiologic response	N/A
Sharma et al, ²⁵ India (June 2021)	June to September 2020	Single arm	Moderate to severe	10 intervention	70 cGy/1	2D (AP-PA)/6 MV	ICU ad/death, NEWS score, hospital stay	N/A
Ganesan et al, ¹⁷ India (December 2021)	November 2020 to July 2021	Randomized, comparative	Moderate to severe, oxygen dependent	51 (17 control, 34 intervention)	50 cGy/1	2D (AP-PA)/6 MV	S/F improvement in 48/72 h, 7 d, 14 d	Radiologic improvement on day 14, day 28 mortality, lymphocyte count at day 1, 3, 7, and 14, inflammatory/immunologic response (CRP, Ferritin, IL-6), TTCR, hospital stay
Arenas et al, ¹⁹ Spain (July 2021)	June to November 2020	Single arm	Moderate to severe	36 intervention	50 cGy/1	3D (AP-PA)/NS	P/F or S/F improvement in 24 h	Radiologic improvement, day 15/30 OS, inflammatory markers
Ameri et al, ¹⁸ Iran (November 2021)	May to July 2020	Single arm	Moderate to severe, oxygen dependent	10 intervention	50-100cGy/1 or 2	2D (AP-PA)/NS	SpO ₂ improvement, CR	Hospital stay, ICU stay, intubation after WLI, day 28 OS, CRP, IL-6 changes

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; AP = anteroposterior; CR = clinical recovery; CRP = C-reactive protein; CXR = chest x-ray; ICU = intensive care unit; ICU ad = ICU admitted; IL-6 = interleukin 6; MV = mechanical ventilation/megavolt; N/A = not applicable; NEWS = National Early Warning Score; NIV = noninvasive ventilation; NS = not stated; OS = overall survival; PA = posteroanterior; P/F = PaO₂/FiO₂ ratio; S/F = SpO₂/FiO₂ ratio; TTCR = time to clinical recovery; VFD = ventilator-free days; WLI = whole lung irradiation.

Table 2 Study participants' clinical conditions and outcomes

Study	Age/male, %	Symptom onset	Comorbidity	Initial SpO ₂ , S/F, P/F	Initial CRP (mg/dL)	Radiologic involvement	COVID-19 medication	Admission to WLI(day)	WLI to discharge	Adverse events
Papachristofilou et al. ²³ Switzerland (February 2021)	75 [54-84]/77%	7 [0-16]	CCI: 5 [1-11] in WLI, 4 [3-7] in sham-WLI	P/F: 101 [69-238] in WLI, 108 [56-173] in sham-WLI	10.4 [1.3-32.9] WLI, 10.9 [0.4-18.5] sham-WLI		Dexamethasone 100%, remdesivir 50%, experimental 14%	2 [0-7]		Lymphopenia
Mousavi et al., ²² Iran (August 2021)	55.2 ± 14.2/86%	7.2 ± 3.8	63.6% WLI, 63.6% control		56.9 ± 20.0 WLI, 65.6 ± 9.9 control (P = .31)	CXR score: 10.9 ± 2.3	Corticosteroid 100%, remdesivir 100%, IVIG 22.7%, interferon 90.9%, atazanavir 68.2%	10 [4-15]	Median, 12 [6-33] in survivors	None
Hess et al., ²⁰ United States (October 2021)	63 [49-88]/62%	10 [1-15] WLI, 7 [2-14] control, 7 [1-15] all	CCI: 3 [1-10] in WLI, 3 [1-12] control	P/F: 169 [122-325] in WLI, 183 [94-314] in controls			Dexamethasone 72%, remdesivir 72%, HCQ 5%	3 [1-8]	Admission to discharge: 10.5 [5-33] WLI	None
Hess et al., ²¹ United States (December 2021)	76 [43-104]/45%	6.5 [0-30]	90% CCI: 6.5 [0-10] in WLI, 5.5 [0-8] in control	P/F: 138 [79-281] in WLI, 194 [100-452] in controls		60% of controls and 90% of WLI had bilateral CXR infiltrates	Remdesivir 20%, HCQ 10%, corticosteroids 20%, azithromycin 50%	4.5 [1-18]	12 [7-25]	Grade 1 nausea (1 patient; 10%)
Ortiz et al., ¹² Mexico (November 2022)	53 [27-87] WLI vs 57 [36-87] control/77.6%		HTN, diabetes, obesity in WLI vs control: 55.2% vs 51.7%, 41.4% vs 37.9%, 13.8% vs 51.7%, respectively			Very high per CO-RADS in 93.1% of intervention group vs 69% of controls	Remdesivir 0% of intervention vs 6.8% of controls			Not stated
Sanmamed et al., ²⁴ Spain (November 2021)	66 [55-77]/78%		89%	SpO ₂ : 90% [86-96] S/F: 7 patients <200, 2 patients <300			Corticosteroid and antibiotics 100%, HCQ 100%, lopinavir/ritonavir 44.4%, tocilizumab 33.3%, remdesivir 11.1%	52 [17-85]	Median, 13 [4-77]	Lymphopenia (2 grade 2, 1 grade 4)
Sharma et al., ²⁵ India (June 2021)	51 [38-63]/100%		30%					3 [1-9]	Average hospital stay was 15 d [10-24] for recovering patients	None
Ganesan et al., ¹⁷ India (December 2021)	Age >55 y in 53% of WLI and 71% of controls/65% WLI, 71% control	<14 d	85% WLI, 59% control	SpO ₂ <90 in 80% of WLI, 65% of controls	66 (IQR, 46-81) in WLI, 90 (IQR, 24-109) in controls	16 (IQR, 15-17) WLI, 15 (IQR, 14-17) controls	Corticosteroids and antibiotics 100%; remdesivir 47% of WLI, 59% of controls; tocilizumab 18% of WLI, 29% of controls	1 d (12 h to 72 h) in WLI, 2h (2h to 3h) in controls	Median, 7 d (IQR, 5.6-8.3)	Not stated
Arenas et al., ¹⁹ Spain (July 2021)	84 ± 8.1/53%	5.7 ± 1.5	100%	SpO ₂ : 94.3 ± 2.8 S/F: 255 ± 118 P/F: 251 ± 128	9 (1.14-24.7)	All had bilateral CXR infiltrates, 78% of patients >50% CT lung involvement	Dexamethasone 100%, remdesivir 5.6%, tocilizumab 5.6%			
Ameri et al., ¹⁸ Iran (November 2021)	75 [60-87]/80%	Not stated	80%	SpO ₂ : median (range): 80.5% (70%-89%)			No dexamethasone, remdesivir, HCQ, or macrolides	3 [2-4]	6 [2-14] in survivors	None

Data presented as x [a-b] are median [min, max] or mean ± standard deviation unless otherwise indicated.

Abbreviations: CCI = Charlson's comorbidity index; CI = 95% confidence interval; CO-RADS = COVID-19 reporting and data system; CRP = C-reactive protein; CXR = chest x-ray; HCQ = hydroxychloroquine; HR = hazard ratio; IQR = interquartile range; NIV = noninvasive ventilation; OS = overall survival; P/F = PaO₂/FiO₂ ratio; S/F = SpO₂/FiO₂ ratio; TTCR = time to clinical recovery; VFD = ventilator-free days; WLI = whole lung irradiation.

Table 3 Primary and secondary outcomes evaluated by the included trials

Study	Intubation	P/F or S/F	SpO ₂	CXR/CT	Recovery and/or discharge	CRP and inflammatory markers	Survival
Papachristofilou et al, ²³ Switzerland (February 2021)	VFD [†] at day 15 was 0 [0-9] in WLI, 0 [0-13] in control (<i>P</i> = 1)	Median P/F change in 24 h: +5 [−68 to +102] in WLI, +9 [−57 to +34] in control (<i>P</i> = .49)			14% discharged in the study period; 36% from each group were weaned off ventilation	Change was −60% [−90 to −6] day 0 to day 15 WLI vs −61% [−96 to −11] control (<i>P</i> = .85)	OS day 15: 72.7% (CI, 50.6%-100%) in WLI vs 63.6% (95% CI, 40.7%-99.5%) in control. OS day 28: 63.6% (CI, 40.7%-99.5%) in both groups (<i>P</i> = .69)
Mousavi et al, ²² Iran (August 2021)	54.5% got intubated WLI		Change in 24 h after WLI: 2.5 ± 4.1% <i>P</i> = .11	CXR score change in WLI: −2.2 ± 3.1, control: 0.7 ± 3.9 (<i>P</i> = .085). Final CXR score for WLI: 8.7 ± 2.5, control: 12.3 ± 3.3 (<i>P</i> = .016)	27.3% in each group recovered and discharged from hospital	Change was −14% [−67% to 43%] day 0 to day 4 in WLI vs 8% [−52% to 30%] in control (<i>P</i> = .83 ^α)	OS day 14: 32% (95% CI, 3%-61%) control vs 43% (95% CI, 12%-74%) WLI. OS day 28: 11% (95% CI, 9%-30%) control vs 32% (95% CI, 0%-61%) WLI (<i>P</i> = .48).
Hess et al, ²⁰ United States (October 2021)	Day-28 freedom from intubation: 86% for WLI, 68% for control (<i>P</i> = .09; HR, 0.27; CI, 0.04-1.1). Intubation-free survival day 28: 77% [42%-92%] WLI, 68% [42%-84%] control (<i>P</i> = .17). Intubation-free survival for WLI responders (100%) vs matched controls (66%) (HR, 0.27; CI, 0.04-1.1; <i>P</i> = .01).			Radiographic improvement not detected (<i>P</i> = .72)	TTTCR: 7.5 d [2-30] WLI vs 7 d [2-38] control (<i>P</i> = .37). From admission to recovery: 10 d [4-33] WLI vs 9 d [2-41] control (<i>P</i> = .37). Admission to discharge: 10.5 d [5-33] WLI vs 11.5 d [3-42] control (<i>P</i> = .61). Number clinically recovered: 80% WLI vs 85% control (<i>P</i> = 1). TTTCR: HR of 0.67 (CI, 0.31-1.4; <i>P</i> = .29) because WLI or first COVID-19 drug HR was 0.64 (CI, 0.28-1.4; <i>P</i> = .26) since admission (for WLI responders vs matched controls).	CRP decline in 3 d in 80% of WLI, 90% of control. Creatine kinase started higher in WLI patients but was also significantly reduced over controls (<i>P</i> < .01).	OS day 28: 85% in WLI (95% CI, 69.4%-100%), 100% in control (<i>P</i> = .23)
Hess et al, ²¹ United States (December 2021)	Freedom from intubation: 90% WLI vs 60% control (HR, 4.9; CI, 0.72-100; <i>P</i> = .16)			Radiographic improvement by day 21: 90% WLI, 57% control (<i>P</i> = .12)	TTTCR: 3 d [0-8.5] in WLI vs 12 d [1-32] in control (HR, 2.9; CI, 1.01-8.39; <i>P</i> = .048). Admission to recovery: 10 d WLI vs 13 d control (HR, 2.3; CI, 0.8-6.9; <i>P</i> = .13). Intervention to discharge: 12 d [7-25] WLI, 20 d [5-45] control (HR, 2.13; CI, 0.68-6.66; <i>P</i> = .19). Admission to discharge: 19 d [13-43] WLI vs 22.6 d [7-48] control (<i>P</i> = .53).	CRP declined 11% per day more rapidly in WLI than control (<i>P</i> = .01). LDH reduced significantly after WLI (<i>P</i> = .07).	OS day 28: 90% in WLI and control (95% CI, 71.4%-100%) (<i>P</i> = 1)
Ortiz et al, ¹² Mexico (November 2022)	33% in intervention group vs 58% in control group, <i>P</i> = .51 (in moderate cases: 0% vs 45%, <i>P</i> < .001)				Hospital stay: 11 d [3-43] in intervention, 10 d [1-36] in control		Mortality: 27.5% in intervention group vs 58.6% in control group (<i>P</i> = .024; in moderate patients survival was 100% in intervention group vs 40% in control group, <i>P</i> = .01)
Sanmamed et al, ²⁴ Spain (November 2021)		Significant improvement in S/F 3 and 7 d post-WLI (<i>P</i> = .01)		CT scores significantly improved between the first and third CT (day 7) (<i>P</i> = .03)	89% discharged	Inflammatory markers (ferritin, D-dimer, CRP) decreased 7 d post-WLI (only LDH decreased significantly [<i>P</i> = .04])	OS day 28: 89% (95% CI, 68.5%-100%)

(Continued)

Table 3 (Continued)

Study	Intubation	P/F or S/F	SpO2	CXR/CT	Recovery and/or discharge	CRP and inflammatory markers	Survival
Sharma et al, ²⁵ India (June 2021)	1 (10%) after WLI				Nine (90%) recovered and discharged. Average hospital stay: 15 d [10-24], 3 (30%) and 8 (80%) achieved NEWS score 0 on day 3 and day 7 post-WLI.		OS day 28: 90% (95% CI, 71.4%-100%)
Ganesan et al, ¹⁷ India (December 2021)	5 patients (of 34) in WLI and 4 patients (of 17) control arms (all eventually expired)	S/F difference from baseline to days 2, 3, and 7 statistically significant between WLI and control (favoring WLI)		CT severity score improvement in 14 d was significantly better for WLI (−4 [IQR, −5 to −2.75]) vs controls (−2 [IQR, −3 to −1]) (<i>P</i> = .011)	Median TTCR* was 4 d [2.1-5.8] for WLI and 11 d [10-12] for control arms (log-rank <i>P</i> < .001). Median time to discharge was 7 d [5.6-8.3] and 13 d [12-14] in the WLI and control arms (log-rank <i>P</i> < .001).	Baseline to day 14: −56 (IQR, −69 to 27) WLI vs −86 (−104 to −12) controls (<i>P</i> = .316; also insignificant for ferritin and IL-6)	OS day 28: 76% control vs 85% WLI. Day-28 survival log-rank test: $\chi^2 = 0.54$ (<i>P</i> = 0.46).
Arenas et al, ¹⁹ Spain (July 2021)	Not stated	S/F improvement (mean, 39%) in 50% of patients in 24 h (<i>P</i> = .002) and in 84% of patients (mean, 76%) at 1 wk (<i>P</i> < .001). P/F improvement significant at 1 wk (<i>P</i> < .001).	Significant increase in 1 day, 1 week, and 1 month after WLI (<i>P</i> ≤ .017)	CT scan at 1 wk after WLI showed a significant improvement (data not presented)		All patients had significant decrease in CRP 24 h after WLI (<i>P</i> < .05)	OS day 30: 64% (95% CI, 48.3%-79.7%)
Ameri et al, ¹⁸ Iran (November 2021)	10%		Improvement in 24 h of median (2.5% [1%-10%]) in 90% of patients. Response rate [§] : 63.5%		Clinical recovery [†] : 60%	30% had decreased CRP 1-2 d after WLI	OS day 28: 40% (95% CI, 9.6%-70.4%)
<p>Data presented as x [a-b] are median [min, max] or mean ± standard deviation unless otherwise indicated. α; unpublished data. Abbreviations: CI = confidence interval; CRP = C-reactive protein; CT = computed tomography; CXR = chest x-ray; HR = hazard ratio; IQR = interquartile ratio; OS = overall survival; P/F = PaO₂/FiO₂ ratio; S/F = SpO₂/FiO₂ ratio; VFD = ventilator-free days; WLI = whole lung irradiation. * Defined as time to wean from supplemental oxygen and remain off supplemental oxygen for at least 12 consecutive hours. † Number of days a patient was alive and free of mechanical ventilation. ‡ Defined as discharge from the hospital or weaning off the supplemental oxygen with SpO₂ ≥93% on room air. § Defined as improvement in SpO₂ on the first day after WLI, with an increasing or constant trend for the next 2 days.</p>							

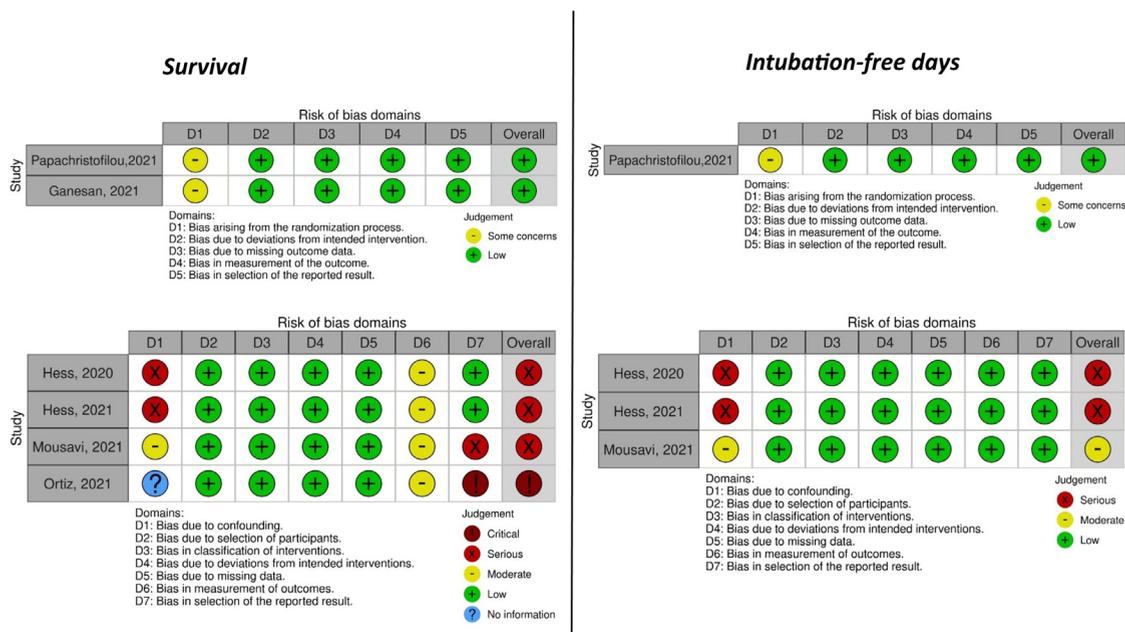


Fig. 2. Risk of bias assessment for overall survival and intubation-free days. The 5 domains of RoB 2 (Cochrane risk-of-bias tool for randomized trials) (top) and the 7 domains of the ROBINS-I (Risk of Bias in Non-randomized Studies - of Interventions) tool (bottom).

0-8.5) in the intervention group versus 12 days (range, 1-32) in the control group (HR, 2.9; 95% CI, 1.01-8.39; $P = .048$); however, in their second cohort²⁰ no significant difference was noted (7.5 days [range, 2-30] for WLI vs 7 days [range, 2-38] for controls, $P = .37$). Moreover, Ganesan et al¹⁷ reported a median TTCR of 4 (interquartile range [IQR], 2.1-5.8) and 11 (IQR, 10-12) days for their WLI and control arms, respectively (log-rank $P < .001$). Papachristofilou et al²³ reported that 36% of patients in each group were weaned off ventilation, and 14% in each group were

discharged from the hospital during the study period. Also, Mousavi et al²² reported that 27.3% of patients in each group were eventually discharged from the hospital. The median time from WLI to discharge was very different across the studies, reported to be between 6 to 15 days. Ganesan et al¹⁷ reported that time from intervention to discharge was 7 (5.6-8.3) days and 13 (12-14) days in the WLI and control arms, respectively (log-rank $P < .001$), whereas it was 12 days (7-25) in the WLI and 20 days (5-45) in the control group ($P = .19$) for the Hess et al trial.²¹

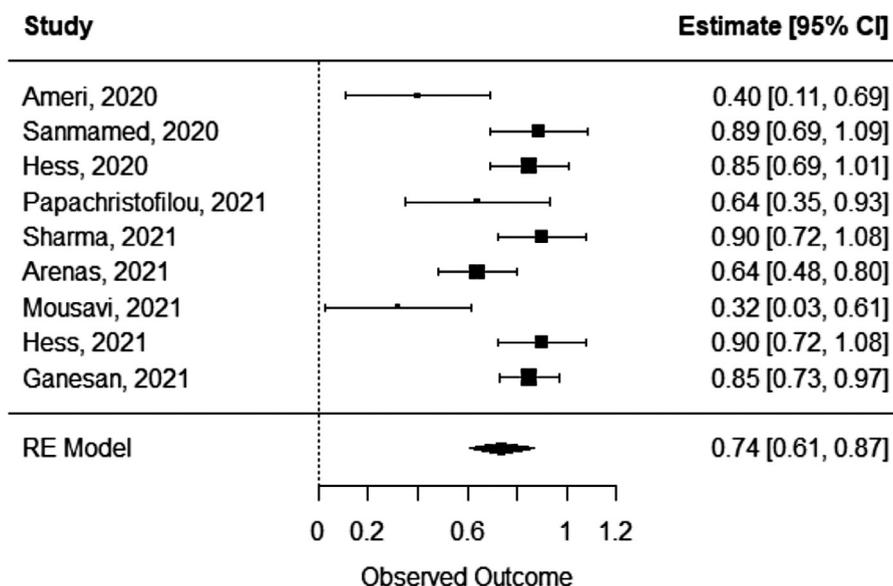


Fig. 3. Forest plot depicting pooled overall survival rate on day 28 after whole lung irradiation. Abbreviations: CI = confidence interval; RE = random effects.

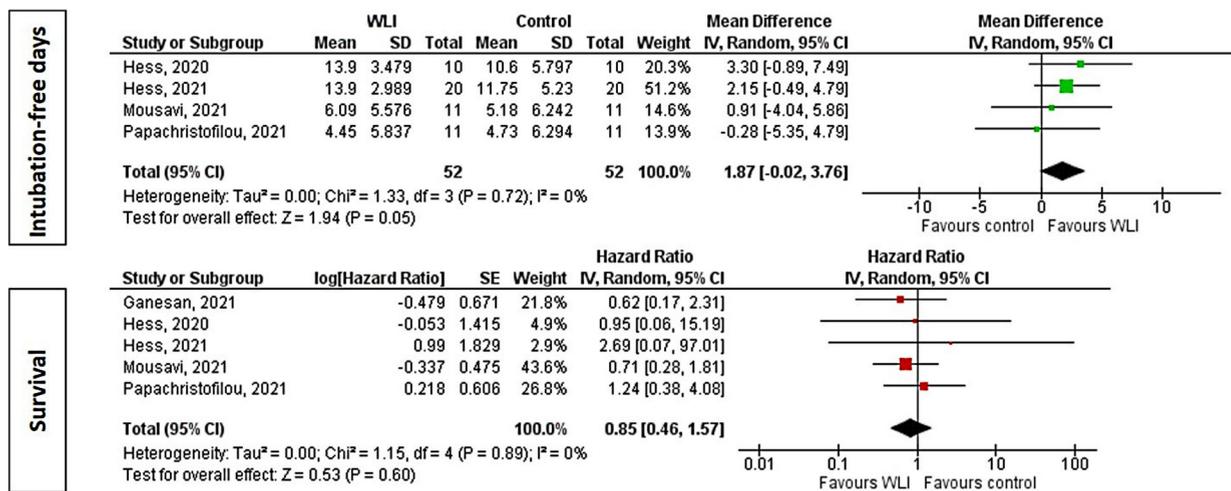


Fig. 4. Forest plots for intubation-free days (top) and overall survival hazard ratio (bottom). *Abbreviations:* CI = confidence interval; IV = weighted mean difference; SD = standard deviation; WLI = whole long irradiation.

Oxygenation

Six studies reported data on oxygenation status (ie, O2 saturation, PaO2/FiO2 [P/F ratio], and SaO2/FiO2 [S/F ratio]) of patients after receiving WLI. Papachristofilou et al²³ reported no significant difference in 24-hour change of P/F ratio between the WLI and control groups (median of +5 in WLI group vs +9 in the control group, P = .49), whereas Arenas et al¹⁹ reported a significant improvement in 1 week (P < .001). They also reported a significant increase in SpO2 in 1 day, 1 week, and 1 month after WLI (P ≤ .017). Mousavi et al²² reported an insignificant 2.5% rise of SpO2 24 hours after WLI. Ameri et al¹⁸ also reported a median 2.5% improvement of SpO2 in 90% of their patients within 24 hours. Sanmamed et al²⁴ reported a significant improvement of S/F ratio 3 and 7 days after WLI (P = .01). Also, Ganesan et al¹⁷ reported a significant improvement of the S/F ratio from baseline in 3, 7, and 14 days after WLI which was significantly higher than the control group on days 7 and 14 (P ≤ .001).

Radiologic improvement

Numerous studies have reported a significant correlation between radiologic findings and the clinical condition and prognosis of patients with COVID-19; therefore, a radiographic improvement could be a reliable indicator of clinical recovery.²⁶⁻²⁹

Of the 10 identified studies, 6 reported whether or not a radiologic difference was observed. Although their assessment methods and imaging modalities differed significantly and some presented subjective results rather than objectively measured findings, we will report the most important findings of these studies.

Mousavi et al²² reported a chest x-ray score change in the WLI group of -2.2 ± 3.1 versus 0.7 ± 3.9 in the control group (P = .085), which indicated a trend for improvement

of chest x-rays in patients receiving WLI. They reported that the final chest x-ray score in the WLI group was significantly lower (fewer infiltrations) than that of the control group (8.7 ± 2.5 vs 12.3 ± 3.3, P = .016). Sanmamed et al²⁴ reported that the objectively assigned CT scores significantly improved between the first and the third CT scans on day 7 after WLI (P = .03). Also, Ganesan et al¹⁷ reported that the pre-WLI CT score of 16 (IQR, 15-17) improved to 12 (IQR, 10-14) on day 14 after WLI (P < .001). This improvement of CT score from baseline to day 14 was significantly higher for the intervention group (P = .011). Arenas et al¹⁹ reported that in their single-arm cohort of 36 patients, the CT scan of surviving patients 1 week after WLI showed significant improvement; however, they did not present any subjective or objective data.

Despite these positive studies, Hess et al reported that through a subjective assessment of chest x-rays and ARDS scale scores, radiographic improvement was not observed in any of their cohorts (P = .17, .72 for cohorts 1²¹ and 2,²⁰ respectively). We did not enter these data into our meta-analysis because of the heterogeneity of imaging modalities and different methods of radiographic assessment incorporated by the studies.

C-reactive protein

Of the 10 included studies, 7 reported CRP changes after implementation of WLI. Unfortunately, each study had its unique time-points for evaluating CRP change, and we could not perform a meta-analysis on this relatively important inflammatory biomarker.

Papachristofilou et al²³ reported a median 60% decrease of CRP in the WLI group compared with a 61% decrease in controls (P = .85). Also, Ganesan et al¹⁷ despite noting a significant decline in CRP values from baseline in 7 and 14 days in both groups, reported that there was not a significant difference between the intervention and control groups

in this regard. Hess et al, in their first cohort,²¹ reported that CRP levels decreased 11% more rapidly in the intervention group relative to the control group 7 days after WLI ($P = .01$). In their second cohort,²⁰ this decline was again superior in the intervention group ($P = .02$). Mousavi et al observed a 14% decrease (range, -67% to 43%) in CRP within 4 days in WLI group compared with an 8% increase (range, -52% to 30%) in their controls. Three noncomparative studies also reported CRP changes after intervention in their participants. Sanmamed et al²⁴ reported that CRP decreased 7 days postintervention; however, nonsignificant. Arenas et al¹⁹ reported that CRP decreased significantly in all 36 patients receiving WLI within 24 hours ($P < .05$). Ameri et al¹⁸ reported that 30% of their participants had decreased CRP 1 to 2 days after WLI.

Adverse events

Acute adverse events were reported in 3 studies. Hess et al²¹ reported 1 (10%) grade 1 nausea. Papachristofilou et al²³ reported a 66% reduction in median lymphocyte count in the WLI group compared with a 10% reduction in the control group ($P < .01$). Also, Sanmamed et al²⁴ reported 2 grade 2 and 1 grade 4 lymphopenia in their cohort of 9 patients after WLI. The highest lifetime risk of WLI-induced risk of lung cancer and major coronary events is estimated to be 6% and 3%, respectively, in younger patients (50-60 years old) with risk factors.³⁰

Risk of bias assessment

Risk of bias assessment was done using Cochrane's RoB 2 tool for evaluation of the 2 randomized trials included (Fig. 2). Papachristofilou et al²³ used a sham-RT group as controls and masked patients and caregivers. This study was assessed to have a low risk of bias in all domains; however, some concerns remained in the domain related to the randomization process due to the observed differences in baseline characteristics between the intervention and control groups. The frequency of pulmonary diseases (36% vs 9%) and male sex (91% vs 64%) was higher in the intervention group, and the frequency of treatment with remdesivir (36% vs 64%) was higher in the control group (significance level not presented). All of these factors favored the control group. Ganesan et al¹⁷ also conducted a non-masked randomized 2:1 parallel group clinical trial after a successful phase 1 exploratory phase. This study was also assessed to have a low risk of bias despite some concerns remaining for the randomization process due to the observed differences between the intervention and control groups regarding participants' age and comorbidities.

Cochrane's ROBINS-I tool was used to evaluate the non-randomized comparative studies (4 studies; Fig. 2). Studies evaluated with this tool were assessed to have an overall serious (3 studies) and critical (1 study) risk of bias for OS outcome and overall serious (2 studies) and moderate (1 study)

risk of bias for intubation-free days outcome. Both cohorts reported by Hess et al^{20,21} were assessed to have a serious risk of bias because they permitted controls to be selected from other concurrent trials of COVID-directed therapies, and a significant difference was observed between the intervention and control groups on this regard ($P = .02$). Also, the domain of outcome assessment for OS was assessed to have a moderate risk of bias in their cohorts because the starting time-point for evaluation of the OS for the control groups was measured from the first day of anti-COVID-19 therapy (or the first day of hospitalization in patients not receiving any specific treatment) compared with the first day of WLI in the intervention group. Although the authors tried to justify this issue with a secondary analysis incorporating a similar starting time point (ie, day of hospital admission) and showed no significant lead-time bias, there remains an undeniable inherent bias due to the design of this study.

The study by Mousavi et al²² was also assessed to have a serious overall risk of bias for OS outcome. This study was assessed to have a serious risk of reporting bias because of deviations from their initially planned outcomes according to the registered protocol (IRCT20170211032494N3, irct.ir) and the different outcomes eventually reported. Moreover, the study by Mousavi et al was assessed to have a moderate risk of bias in the domain related to the confounding factors because they stated that patients clinically suitable for transportation to the treatment unit were allocated to the intervention group. In contrast, those not suitable for transportation were allocated to the control group. Despite similar baseline characteristics and disease severity of patients in their intervention and control groups, it is postulated that the WLI group could have comprised more favorable patients. The Ortiz et al¹² study was assessed to have an overall critical risk of bias due to reporting domain. Besides deviating substantially from their initially decided endpoints as per the registered protocol (NCT04534790, clinicaltrials.gov), their OS curves differed substantially from what they reported in their results.

MINORS risk of bias tool (Table E1) was used to assess the quality of all other included noncomparative clinical trials of WLI in patients with COVID-19. All these studies received a score of 13 to 14 (of 16) and were considered to have a moderate risk of bias.

Publication bias

There was a minor asymmetry in the funnel plot of publication bias (Fig. E1). The regression test also showed an almost significant publication bias among the studies ($P = .054$). Although there seems to be a significant publication bias in the first look, there are some critical considerations. First, the power of the test is low when the number of studies is less than 10.³¹ Second, the high level of heterogeneity could interfere with the test results.³² More attention to the plot shows that the asymmetry is on the areas of

higher significance (light and dark gray zones), which means that asymmetry is probably due to factors other than reporting bias.^{31,33} However, we believe that reporting bias could also exist even considering the mentioned issues. All studies have been performed rapidly during 2020 to 2021. Sampling error is also another essential issue considering small-size studies. On the other hand, there is no study from eastern Asia, Africa, or Oceania.

Discussion

Our meta-analysis did not demonstrate any OS benefit for WLI compared with usual anti-COVID-19 medications (HR, 0.85; 95% CI, 0.46-1.57). However, an almost significant reduction of about 2 days in postradiation requirement of endotracheal intubation was observed within 15 days after implementation of the WLI.

The included studies generally looked for answers to different questions, and the primary outcomes differed across the studies (Table 1). The primary outcomes consisted of clinical recovery (duration of hospital stay, need for intensive care unit [ICU] admission or mechanical ventilation, etc), clinical improvement of oxygenation status (SpO₂, P/F, or S/F ratio), radiologic improvement, and mortality rate.

Only 6 studies had a control group, enabling a comparative analysis of intended outcomes. Two of these studies were randomized,^{17,23} and 1 was double-masked, incorporating a sham-RT group as controls,²³ but the other 4 used a nonrandomized matched control group.^{12,20-22} Due to the heterogeneity of studies and their reported outcomes of interest, we could only use OS HRs and the number of intubation-free days within 15 days after intervention for the meta-analysis. Also, a noncomparative rate of day-28 OS was meta-analyzed for all included studies (9 studies). When pooled together, the 28-day OS rate translated into 74% (95% CI, 61-87) ranging from 32% to 90%. This difference in OS rate might be due to heterogeneity of the studies regarding patients' severity of ARDS, baseline comorbidities, different medications received by patients, and different timelines and settings for the treatment of patients.

Hess et al were the only researchers that used a radiation dose higher than 1 Gy. It has been previously noted that doses >1 Gy might shift the population of macrophages into the proinflammatory M1 phenotype³⁴ that might be the underlying reason for no significant resolution of radiographic infiltrations. Also, in a preclinical bleomycin-induced pneumonitis model, 1.5 Gy of WLI was shown to be incapable of reducing mice lung capacity deterioration as measured by CT scanning compared with 1 Gy dose.³⁵ Moreover, mice with moderate lung injury recovered significantly more than the severe pneumonitis cases. Also, in their second cohort, Hess et al²⁰ selected more favorable controls and excluded controls who experienced rapid clinical decline at admission, thus introducing an undeniable selection bias, which was probably the reason behind the lower mortality rate in this group.

Papachristofilou et al²³ were the only group incorporating sham WLI as the control group for their double-masked, randomized trial. Although the treatment methodology was superior to the other studies, they treated patients with 1 anteroposterior field, which raises doubts about appropriate dose distribution to the affected lung volume. Also, patients in the intervention group comprised of more males, had more frequent baseline pulmonary disease, and were treated with remdesivir less frequently. These differences, despite the randomized nature of the study, could have biased the observed results.

Mousavi et al²² and Sanmamed et al²⁴ treated their patients with WLI at a median of 10 and 52 days after hospital admission, which is exceptionally more prolonged than the other studies, and the patients treated in these 2 cohorts might have been at later stages of ARDS especially in the former study as stated by the authors and evident through their mortality rates.

We should keep in mind that OS was the primary endpoint in none of the analyzed studies. Also, 2 of the 5 meta-analyzed studies (for OS) included severe cases of ICU admitted patients under mechanical ventilation^{22,23} in which the observed fatal outcomes could be dictated by multiple major complications of SARS-CoV-2 that are irreversible by WLI after some point during the disease course. Uniform reporting of critical baseline characteristics such as objective scoring systems for disease severity and present comorbidities across all studies, would have presented valuable prognostic information.

We searched ClinicalTrials.gov for any relevant studies of WLI in patients with COVID-19. Thus far, 10 trials (5 of them with a matched control group), 1 case series,³⁶ and a case report³⁷ have been published, but when searching the registered trials, we found 9 more groups from the United States, Europe, and India that are still recruiting patients with COVID-19 for WLI (Table E2). The largest of these studies aim to recruit 100 and 150 participants (ClinicalTrials.gov identifiers: NCT04466683 and NCT04433949, respectively) and their results might provide more evidence on efficacy of WLI in patients with COVID-19. As previously stated, despite some benefits noted in different trials for WLI in oxygenation, radiologic, and clinical status, our meta-analysis does not establish a significant role of WLI on OS or length of intubation-free days; 2 seemingly critical clinical endpoints. In contrast to the era when every effort was considered welcome in the hope of finding a solution to diminish the high burden of the pandemic sufferings, major ethical issues remain regarding continuing patient enrollment in the ongoing complicated and laborious WLI trials. Given the currently available novel therapeutics, antivirals, and extensive vaccination programs with proven efficacy in COVID-19 prevention and treatment, the community should reassess the marginal gain versus risk of additional prospective studies of whole lung irradiation.

Limitations

The main limitation of this systematic review and meta-analysis was the heterogeneity of available studies researching the clinical applicability of WLI in COVID-19 pneumonia. The studies had different designs and generally included patients with different severity of disease, and each study included different endpoints and different methods for measuring them. The fact that HRs and associated confidence intervals were not reported was another limitation that compelled us to extract these data indirectly from the studies. Another important limitation of this study was the unavailability of individual participant data for each trial that, if accessible, could have reduced ambiguities that were confronted when assessing the studies, and probably more other outcomes of interest could be explored. Except for 1 study with a randomized, double-masked design with a sham-WLI group and another nonmasked randomized study that were assessed to have a low risk of bias, others were either nonrandomized comparative trials with matched controls or single-arm experimental trials that were assessed to have moderate to high risk of bias. Another important unmeasurable confounder is the different time ranges and geographic regions in which the studies were conducted (Table 1). These differences should be considered as available anti-COVID-19 medications, workforce pressures on health care systems, general ICU management quality, and pace of vaccination programs all differed extensively during periods of time and across countries.

Conclusions

Our study shows that despite some clinical benefit reported in different trials, WLI could not change the survival probability of patients with moderate-to-severe COVID-19. Whether there is a specific subgroup of patients with COVID-19 in which WLI would be more efficacious could not be answered yet. Nevertheless, we can speculate that very severe cases of COVID-19 may not benefit from WLI, and for mild cases, there is no justifiable rationale to pose patients to the risk of radiation-induced latent malignancy while the disease can be managed with available medical treatment.

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