

Response to Review Comments

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Dear Editor

Thank you for sharing the comments of the reviewers/editor of our manuscript entitled **"Impact of X-radiation in the management of COVID-19 disease"** submitted to the World Journal of Radiology. We have addressed the issues raised by the reviewers in the rebuttal letter and suitably modified in the revised manuscript and the changes are highlighted. We shall be thankful if the revised manuscript can be considered for publication.

Comments from the Reviewers

Reviewer: 1

Specific Comments to Authors

Comment: This is an interesting topic, and I think this is helpful for medical workers. However, I worried about the ethical concern about the X-ray used for the treatment of the 2019 COVID-19 disease. Could you highlight the ethics and mechanism concerns in your article? After all, radiation could induce inflammation and injury of lung, even tumor in long time.

Response: The authors would like to bring to the kind attention of the reviewer that the focus of this review was on the consolidation of potentials of X-ray-based imaging modalities (CXR and Chest CT) and Low-Dose Radiation Therapy (LDRT) for screening and management of COVID-19 infection/disease. We did not claim that an X-ray was used for the treatment of COVID-19. A major apprehension on the use of radiation in LDRT might be owing to the concerns on the risk of developing stochastic effect from the low dose radiation exposure based on the "Linear-no-Threshold" model adopted for radiation protection viewpoint. When it comes to the therapeutic application of X-rays in medicine, it is considered a double-edged sword; therefore, its medical use is always justified in terms of risk and benefit ratio. The speculated risk/benefit considerations for LDRT were the possibility of short-term worsening of the disease course and long-term population-based radiation risks: that is should a large number of patients live many years/decades vs the potential

benefit of reduced mortality and morbidity in the most severely ill patients in the immediate term (days/weeks). Its potential benefit that would have derived from the utilization of LDRT to save many lives during the pandemic was debated (Rachna Kapoor et al., 2021). Well-established guidelines are stringently followed to maximize the benefit of routine cancer radiation therapy. Based on the existing knowledge on various aspects, (biological knowledge and clinical experience to date with the pandemic and LDRT) a guideline for the delivery of LDRT for COVID-19 has been discussed and recommended (Prasanna et al., 2020). We also believe that the principle is adopted stringently by the clinicians, who attempted LDRT towards the management of COVID-19. Since the use of LDRT is in the trial phase and also the authors did not conduct any trial and or practice LDRT, not in a position to comment on the ethics aspect in further detail.

A suitable sentence on the ethics aspect was incorporated in the revised manuscript and reads as follows *“Despite the beneficial effects, the ethical concerns to using LDRT in the management of COVID-19 were the risk of spread of infection, time frame for a patient, and inconvenience in treating an intubated patient.”* (Page Number 12).

The possible mechanisms proposed in the literature are that the LDRT could inhibit the cytokine storm, activation of immune and endothelial cells, and inhibition of subsequent virus-induced pulmonary dysfunction contributing to the development of acute respiratory distress syndrome in COVID-19 patients (Prasanna et al., 2020).

A suitable sentence on the possible mechanisms was incorporated in the revised manuscript and reads as follows *“The mechanisms proposed in these recent studies are that the LDRT could inhibit the cytokine storm, activation of immune and endothelial cells, and inhibition of subsequent virus-induced pulmonary dysfunction in COVID-19 patients.”* (Page Number: 9; Paragraph: 2).

Comment: Besides, I think some errors need to be revised. such as, evaluated as %recovery and less severity?

Response: As pointed out by the reviewer, the typographical error in the sentence has been corrected in the revised manuscript and reads as follows *“The therapeutic benefits of LDRT for pneumonitis were evaluated based on the percentage of recovery and the extent of severity”* (Page Number: 9; Paragraph: 1).

Reviewer: 2

Specific Comments to Authors

This is a good study, but I hope the author can add the following:

Comment: Prognosis of COVID-19 treated with LDRT.

Response: Despite many clinical trials being ongoing throughout the world, three studies published their prognosis outcome as 80 to 90% for COVID-19 from the use of LDRT (Ameri et al., 2020; Hess et al., 2021; Sharma, D.N. et al., 2021). These studies also highlighted that the severity of the disease, and the associated co-morbid conditions are the major factors that can impact the outcome of the treatment.

A suitable sentence has been incorporated in the revised manuscript and reads as follows *"Despite many clinical trials being ongoing, three studies reported the prognosis of COVID-19 patients treated with LDRT as 80 to 90%."* (Page Number: 9; Paragraph: 2).

Comment: Brief guidelines for clinical application of LDRT in the treatment of COVID-19.

Response: Delivery of 0.5–1.5 Gy as a single fraction (lower than doses used in clinical radiotherapy and higher than the 50 mSv/year occupational exposure limit and 1 mSv/year limit to the general public) is considered as LDRT. Exposure of 1.5 Gy to whole-lung-irradiation to patients on supplemental oxygen and all other radiotherapy guidelines routinely practiced for the patients have been applied for COVID-19 by LDRT (Prasanna, P.G. et al., 2020).

A suitable sentence has been incorporated in the revised manuscript and reads as follows *"The guidelines routinely used for whole-lung-irradiation of patients undergoing radiotherapy have been applied for COVID-19 patients treated using LDRT."* (Page Number: 9; Paragraph: 2).

Comment: Inclusion and exclusion criteria for LDRT in the treatment of COVID-19.

Response: The inclusion/eligibility criteria adopted in most of the recent studies that used LDRT is COVID-19 positive patients were, adult (>18 years) of both genders, National Early Warning Score (NEWS) of ≥ 5 , and provided consent. The

exclusion criteria were patients on mechanical ventilatory support, and hemodynamically unstable patients (Sharma, D.N. et al., 2021).

An appropriate sentence has been incorporated in the revised manuscript and reads as follows *"The inclusion criteria for LDRT adopted in recent studies were COVID-19 +ve patients, age >18 years, both genders, and national early warning score of ≥ 5 , and the exclusion criteria were healthy volunteers, patients on mechanical ventilatory support, and hemodynamically unstable patients."* (Page Number: 9; Paragraph: 2).

Reviewer: 3

Major Comments

Comment: In the Introduction, the authors quite fully describe the COVID-19 disease, but write almost nothing about the subject of the paper, i.e., X-ray methods. In addition, there is absolutely no information about earlier reviews on this topic, which were written by other researchers. Such reviews already exist. For example, in my opinion, one cannot help but refer to the excellent review by A. Pal et al., published in the World Journal of Radiology (A. Pal et al., World J Radiol 2021; 13: 258), or to the special issue "Medical Imaging of COVID-19" (M. Giger, J Med Imaging 2021; 8: 010101). I recommend the authors give appropriate additions to the Introduction.

Response: We wish to bring to the reviewer's kind attention that we have provided very limited information in the introduction because we have discussed the recent studies in the later sections of the manuscript. However, as suggested by the reviewer, we have provided additional information in the introduction section of the revised manuscript for better understanding and reads as follows:

"CXR examination after two days of RT PCR tests revealed that the yield of improved heatmaps of influential regions contributed to deep learning prediction scores via machine learning. CT a routine imaging modality is being performed for immediate diagnosis which is even effective in asymptomatic patients whose RT-PCR test results reveal to be negative as the CT scores give better disease findings and long-term follow-up with 29% increased sensitivity in comparison with chest radiography." (Page Number: 5; Paragraph: 2).

"In addition to CXR and CT, Infrared thermography has been useful in the identification of asymptomatic carriers via the detection of true core body temperature but its thermal cameras

are insufficient for screening the disease. The single-photon emission computerized tomography, and in vivo molecular imaging allows the observation of patient-specific and disease-specific characteristics for physiological models of COVID-19 patients.” (Page Number: 5; Paragraph: 2).

“Absence of knowledge on the COVID-19 disease, screening, and specific treatment regimes, multiple approaches were tried to contain the spread of infection in the early time of the pandemic. Thus, the X-radiation technology was used in the early diagnosis, management, and containment of COVID-19 disease.” (Page Number: 6; Paragraph: 1).

Comment: The authors do not provide any example of an image obtained with CXR and CT. It seems a little strange for a review, where, among other things, imaging methods are considered. I think a few examples of images would be quite appropriate and could make the paper more representative.

Response: We agree with the reviewer's view on the representation of the images of CXR and CT in the manuscript. Since it is a mini-review and we also don't have access or consent to obtain the images of CXR and CT, we did not provide them in the present manuscript. Regardless, such information is available to the readers in recent original articles (Aman Pal et al., 2021).

Comment: To my surprise, I did not find the section "Conclusion" in the manuscript. In my opinion, this is a shortcoming, and it should be eliminated. Standardly, the Conclusion section should first review, analyze and systematize all results the authors obtained and only then, based on these results, formulate the conclusion and, possibly, announce future research.

Response: The authors provided the conclusion at the end of the discussion, However, as pointed out by the reviewer, the conclusion section has been included in the revised manuscript and reads as follows *“Overall the review of the literature suggests that the chest CT has high sensitivity (98%) and less specificity for COVID-19 disease diagnosis compared to RT-PCR method. The LDRT therapy for COVID-19 patients compliments the drug therapy in the early recovery stage by maintaining the physiological parameters better than the drug therapy alone. All the recent studies results demonstrated that the X-ray-based technology continues to evolve and play a significant role even during the COVID-19 pandemic.” (Page Number: 13).*

Minor Comments

Comment: Abstract. In my opinion, the first sentence "... that infect many different animals including humans" is not quite successful.

Response: As it is pointed out by the reviewer, the sentence has been modified for better clarity in the revised manuscript and reads as follows "Coronaviruses are a diverse group of viruses that infect both animals and humans."

Comment: Abstract. The abbreviation "LDRT" must be disclosed.

Response: LDRT has been abbreviated in the first use in the abstract and the text of the revised manuscript and reads as follows "This review focuses on the consolidation of potentials of X-ray-based imaging modality (CXR and Chest CT) and Low-Dose Radiation Therapy (LDRT) for screening, severity, and management of COVID-19 disease."

Comment: Abstract, line 8. "focus" should be "focuses".

Response: The typo error has been corrected in the revised manuscript and reads as follows "This review focuses on the consolidation of potentials of X-ray-based imaging modality (CXR and Chest CT) and Low-Dose Radiation Therapy (LDRT) for screening, severity, and management of COVID-19 disease."

Comment: Page 2, line 2 from the bottom: "is been widely used" should be "are been widely used".

Response: "Therefore, X-rays on a whole are been widely used for both diagnostic and therapeutic management of COVID-19 disease."

Comment: Page 6, the last sentence: It can be assumed that there should be a comma after "moderate (8-17)".

Response: In general, the CT features and scores ranging between, mild (0-7), moderate (8-17), and severe (18 or more) are usually associated with clinical manifestation and COVID-19 disease prognosis.

Comment: Page 10, line 4 from the bottom: "which is been reliably used" should be "which are been reliably used".

Response: Although, exposure to radiation from these X-ray imaging is a concern, due to its wide application in delivering intense structures of the organs which are been reliably used for the diagnosis of COVID-19 disease.

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