



## Impact of X-radiation in the management of COVID-19 disease

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### Abstract

Coronaviruses are a diverse group of viruses that infect both animals and humans. Even though the existence of coronavirus and its infection to humans is not new, the 2019-novel coronavirus (nCoV) caused a major burden to individuals and society *i.e.*, anxiety, fear of infection, extreme competition for hospitalization, and more importantly financial liability. The nCoV infection/disease diagnosis was based on non-specific signs and symptoms, biochemical parameters, detection of the virus using reverse-transcription polymerase chain reaction (RT-PCR), and X-ray-based imaging. This review focuses on the consolidation of potentials of X-ray-based imaging modality [chest-X radiography (CXR) and chest computed tomography (CT)] and low-dose radiation therapy (LDRT) for screening, severity, and management of COVID-19 disease. Reported studies suggest that CXR contributed significantly toward initial rapid screening/diagnosis and CT- imaging to monitor the disease severity. The chest CT has high sensitivity up to 98% and low specificity for diagnosis and severity of COVID-19 disease compared to RT-PCR. Similarly, LDRT compliments drug therapy in the early recovery/Less hospital stays by maintaining the physiological parameters better than the drug therapy alone. All the results undoubtedly demonstrated the evidence that X-ray-based technology continues to evolve and play a significant role in human health care even during the pandemic.

**Key Words:** Corona virus; COVID-19 infection; COVID-19 disease; X-rays; Computed tomography; Low dose radiotherapy

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**Core Tip:** Majority of asymptomatic individuals with coronavirus disease 2019 (COVID-19) disease, an early diagnosis was a challenge despite the gold standard reverse-transcription polymerase chain reaction measures the viral nucleic acid with a turnaround period of reporting for 5-6 h. This ultimately led to the usage of chest-X radiography with sensitivity up to 80%, which served as a screening tool for COVID-19. X-radiation-based computed tomography imaging served as another modality to monitor the severity of COVID-19 disease with sensitivity up to 98%. Low-dose radiation therapy with a limited setting showed that it can complement drug therapies in the management of COVID-19. Therefore, X-rays on a whole are been widely used for both diagnostic and therapeutic management of COVID-19 disease.

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## INTRODUCTION

Coronaviruses are a diverse group of viruses that infect both animals and humans. The existence of coronavirus and its infection to humans is not new; since the beginning of this century, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus are infecting humans and are of concern to public health[1]. The coronavirus infection is majorly associated with an array of clinical symptoms, which range from upper respiratory tract infection of moderate clinical concern to lower respiratory tract including bronchiolitis and pneumonia leading to fatality, especially in the elderly, and individuals with compromised immunity. The 2019-novel coronavirus (nCoV) outbreak leads to a lower respiratory tract disease called novel coronavirus pneumonia and renamed this beta-corona virus SARS-CoV-2, the established etiology for COVID-19 disease.

### COVID-19 disease

The World Health Organization (WHO) has declared 2019-nCoV infection as a global health emergency, because, within a few months not only did several thousand individuals test positive for the virus infection but also resulted in a significant number of deaths worldwide. That was because of the disease burden, the WHO officially characterized the global COVID-19 flare-up as a pandemic on 11 March 2020. Important clinical features of COVID-19 spread documented were: (1) An infection rate of 83% within the family; (2) Mild to moderate with more systematic symptoms and severe radiological abnormalities as clinical manifestations seen in older patients; and (3) Transmission of SARS-CoV-2 from asymptomatic carriers to others[2]. Given the rapid spread of the disease and asymptomatic carriers, it remains a major health problem throughout the world. Although genetic evidence suggests that SARS-CoV-2 is a natural virus that likely originated in animals, there is no conclusion yet about when and where the virus first entered humans. However, these viruses are known to constantly change through mutation and result in a new variant of the virus; such a new variant is known to affect the virus properties, such as infection rate, the severity of disease, the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures. Of late many variants form of the virus has been reported with a higher infection rate (Omicron) despite the severity of the disease and the need for hospitalization is less when compared to that of earlier variants (beta and delta coronavirus as SARS-CoV-2) and COVID 19 disease[3]. Even the variant reported causing less severe disease, in general, an increase in the total number of cases could lead to an upsurge in hospitalizations, laying more strain on healthcare resources.

### Symptoms and Pathogenesis of the disease

The most common symptoms after COVID-19 infection are fever, fatigue, and dry cough. Less common symptoms include sputum production, headache, hemoptysis, diarrhea, anorexia, sore throat, chest pain, chills, nausea, and vomiting[2,4-7] olfactory and taste disorders[8]. The majority of infected people showed signs of disease for about fourteen days (frequently around five days), and dyspnea and pneumonia developed within a median time of eight days from illness onset[9,10]. The pathogenesis of SARS-CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure. Upon entry of the virus in the nasal route, the virus binds to epithelial cells in the respiratory tract, starts replicating and migrating down to the airways, and goes into alveolar epithelial cells in the lungs. Owing to the hasty replication of SARS-CoV-2 in the lungs, activate a strong immune response, and cascade into a cytokine storm, resulting in acute respiratory distress syndrome and then respiratory failure, which is considered the notable cause of death in patients with COVID-19 infection[2,5]. Even multiple organ failure has also been reported in some COVID-19 cases. Despite the range and severity of the disease, clinical manifestations differ with age; men >60 years with co-morbidities are more

prospective to develop a severe respiratory disease that required hospitalization or even death, whereas most young people and children had only mild diseases and/or are asymptomatic[7,11]. Moreover, regardless of evidence of trans-placental transmission of SARS-CoV-2 from an infected mother to a neonate, the risk of disease was not higher for pregnant women[4,12]. Thus, the disease caused a major burden on the individual and society i.e., anxiety, fear of infection, struggle and extreme competition for hospitalization, and more importantly financial liability.

### Diagnosis of COVID-19

Given the rapid spread of infection, early diagnosis is crucial for controlling the spread of COVID-19. Choice of diagnosis options is: (1) detection of SARS-CoV-2 nucleic acid; (2) detecting antibodies to N or S protein; and (3) imaging by simple chest X-ray and high-resolution computed tomography (CT) with X-rays. The detection time ranges from several minutes to hours depending on the technology used for the diagnosis[13-18]. Among those tools, a quantitative reverse-transcription polymerase chain reaction (RT-PCR) test is the current standard of test and remains the “gold standard” to confirm the COVID-19 infection. RT-PCR has also its challenges such as delays in result turnaround time and interpretation of the results. Another major hurdle is the dynamic conversion of RT-PCR results from either negative to positive or vice-versa. Serology tests detecting antibodies to N or S protein could complement molecular diagnosis, particularly in late phases after disease onset or for retrospective studies[19-21].

In alternate, imaging using X-rays such as conventional chest X-rays (CXR) and high-resolution CT was used to quickly identify a patient when the capacity of molecular detection was overloaded as well as to identify the disease severity. 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[22]. 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[23]. CT scanning combined with repeated swab tests was used for individuals with high clinical suspicion of COVID-19. Thus, combining RT-PCR with CT of the chest in an appropriate clinical setting is considered the best modality to investigate any patient. Ai *et al*[24], 2020 suggested a higher sensitivity of CT chest (98%) than RT-PCR (71%) in diagnosing COVID-19. 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[25]. 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[26,27].

### Therapy and management of COVID-19 infection

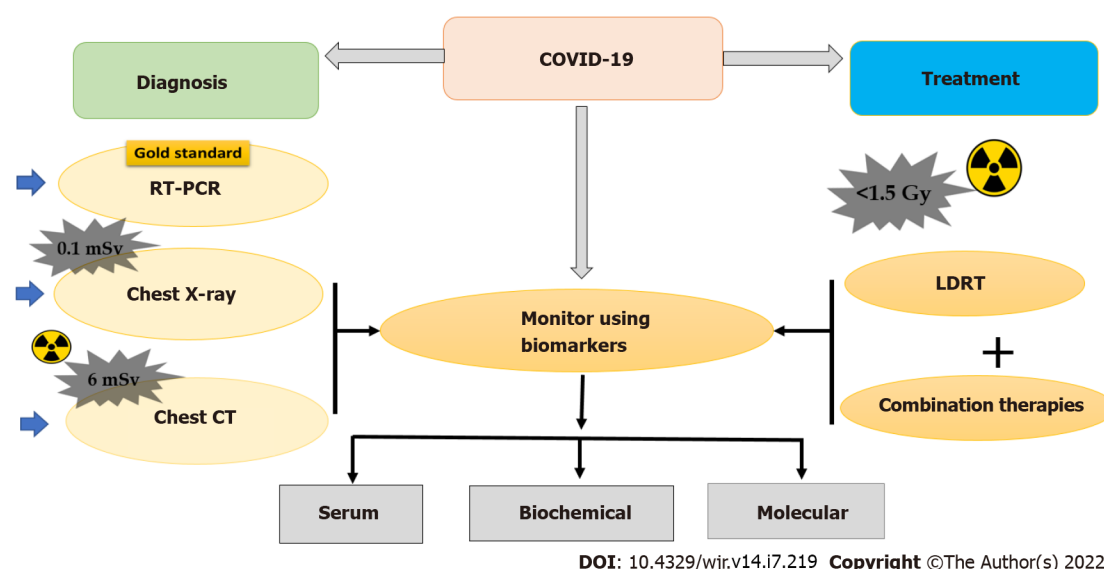
Until the introduction of vaccines, test-positive subjects were isolated/ quarantined and provided with medication and supplements to boost their immune mechanism to overcome the disease. Initially, in the absence of proven effective therapies for COVID-19 or antivirals against SARS-CoV-2, researchers and manufacturers are conducting large-scale clinical trials to evaluate various therapies for COVID-19. Some of the existing options are to prevent viral entry, inhibition of virus replication, immunomodulatory agents, immunoglobulin therapy, vaccines, and potential control measures using ultraviolet radiation, and low-dose ionizing radiation[28]. The illustration of the use of X-rays in the diagnosis and therapy for COVID-19 has been provided in Figure 1. 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. The present review focused on consolidating the role of X-radiation in various stages of COVID-19 infection and disease manifestations: Screening, diagnosis, and management. Also, concerns associated with the use of X-rays in those phases of disease management were discussed.

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## CXR AND CT IMAGING OF COVID-19 PATIENTS

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X-ray-based imaging is being used for the diagnosis of numerous health conditions for several decades. In the sudden outbreak of COVID-19, X-ray-based imaging was considered a relevant and rapid modality in the diagnosis of patients with COVID-19 disease, especially if the availability of other diagnostic methods like RT-PCR becomes limited due to a large number of infected patients and the time required for the reporting. CXR and high-resolution chest CT are the two important non-invasive examinations for the diagnosis of lung damage caused by COVID-19 infection[29]. Because of its intense resolution capacity and also clarity of organizational structures, these two X-ray imaging modalities have been used for the diagnosis of COVID infection and severity of disease in several countries. The prominent chest CT imaging findings of COVID-19 patients were found to be bilateral lung involvement and Ground Glass Opacities (GGO). Since then, many hospitals from different countries used both chest X-ray and chest CT imaging for the initial diagnosis of lung damage and published at a rapid pace. An



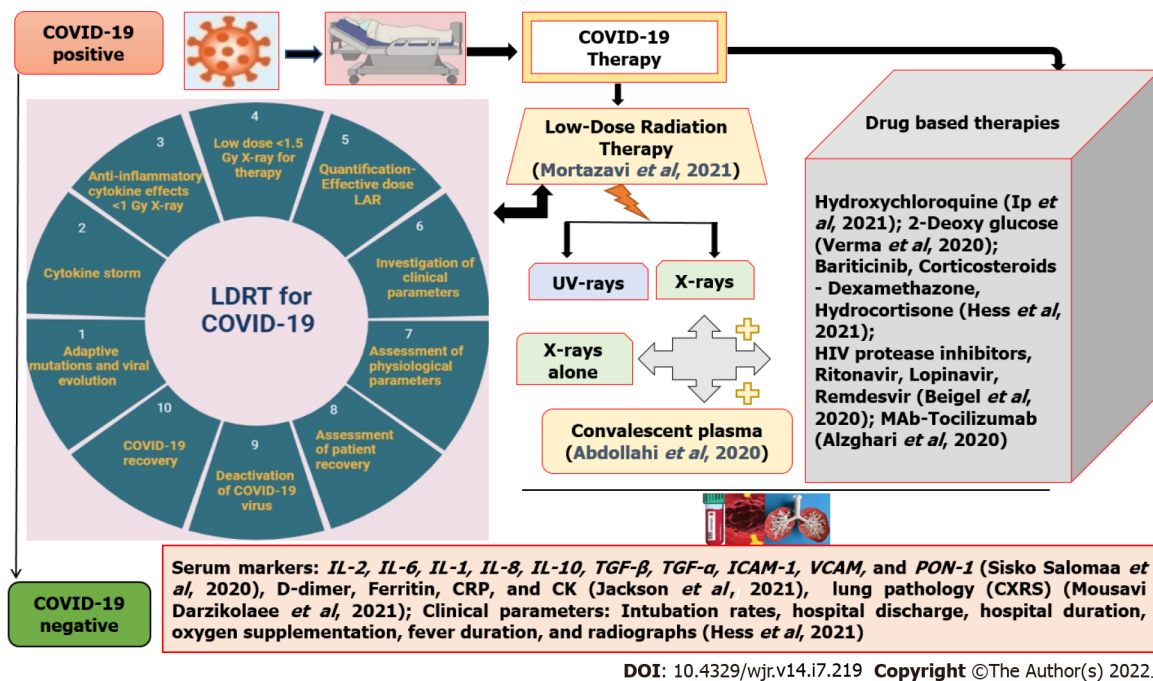
**Figure 1** The use of X-rays in the diagnosis and therapy for coronavirus disease 2019 disease. COVID-19: Coronavirus disease 2019; CT: Computed tomography; LDRT: Low-dose radiation therapy; RT-PCR: Reverse-transcription polymerase chain reaction.

overview of the published articles on the diagnosis of COVID-19 infection using chest X-ray and chest CT imaging were shown in [Supplementary Table 1](#). The finding from all those studies suggests that the radiographic findings seem to be good predictors for assessing the progress of COVID-19 disease. It was found that the chest CT has high sensitivity and lower specificity for diagnosis and severity of COVID-19 disease. CXR was used as a primary imaging technique for the initial screening of COVID-19 in many hospitals[30,31]. However, few studies sounded controversial that chest CT detected a combination of lung abnormalities that were not observed in CXR[32]. The enhanced use of CT substantially improved diagnostic performance over CXR in COVID-19 infections and diseases. Age-dependent variations on CT features were associated with clinical manifestation and also with patient prognosis[33]. Therefore, CT was considered for the initial assessment of suspected COVID-19 infections compared to CXR. 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[34]. CT imaging had good diagnostic value in symptomatic infections and was insufficient to justify its use as a first-line screening approach in asymptomatic infections[35]. CXR severity was correlated with known laboratory markers of disease such as higher lactate dehydrogenase (LDH), higher C-reactive protein (CRP), and lower lymphocyte count[36]. In a similar study, CT findings showed characteristics of GGO, which were correlated with biochemical markers such as CRP, erythrocyte sedimentation rate, and LDH to the severity of COVID-19 infection[37]. Although the gold standard RT-PCR has been the primary source of diagnosis of COVID-19 infection, chest CT imaging has a high sensitivity for diagnosis and finding the severity of COVID-19 disease when compared to RT-PCR[24]. Both RT-PCR and X-ray-based imaging has been used extensively throughout the world to contain the spread of COVID-19 infection and disease severity in COVID-19 patients.

## LOW DOSE X-RADIATION THERAPY (LDRT) FOR THE MANAGEMENT OF COVID-19 PATIENTS

The sudden outbreak of SARS-CoV-2 infections results in COVID-19 disease, which is associated with compromised immunological defense and lung damage[38]. Therefore, the COVID-19 patients were isolated/quarantined and provided with medication and supplements to boost their immune mechanism to overcome the disease[39]. In addition to the boosters to immune mechanisms, several therapy strategies were tested to prevent viral entry, inhibition of virus replication, immunomodulatory agents, immunoglobulin therapy, vaccines, and potential control measures[28]. The schematic representation of the possible therapy has been provided in [Figure 2](#). One of those therapy strategies is the use of LDRT for COVID-19-infected patients because it has been proven to cure pneumonia in the early 20<sup>th</sup> century[40]. The treatment with low-dose X-rays complements other treatment modalities and has a profound role in minimizing COVID-19 infection severity[39]. Low dose comprises doses below 100 mGy as defined by UNSCEAR and has the characteristics such as accelerated immune senescence, altered immune fitness, a shift in peripheral lymphocyte, balance in favor of B-cells, and pro-inflammatory responses[39]. The first attempt on the use of LDRT for COVID-19-related pneumonia was made





**Figure 2 Overview of the therapy strategies to treat coronavirus disease 2019 disease.** COVID-19: Coronavirus disease 2019; CT: Computed tomography; LDRT: Low-dose radiation therapy; RT-PCR: Reverse-transcription polymerase chain reaction.

by Italian and American scientists for which the patients received a single dose of either 0.10, 0.18 or 0.25 Gy[38]. Since then, many studies have attempted to exploit the potential of radiation in the management of COVID-19 disease. The list of major studies (animal models, isolated studies, and multi-centric clinical trials) related to LDRT and their salient findings are presented in [Supplementary Table 2](#).

The range of doses employed in the LDRT among the published literature varies between 0.5-1.5 Gy of X-rays[39]. Whole lung LDRT may serve as a better option as it presents a low-risk treatment for COVID-19 pneumonia patients[38]. The LDRT is possible by using LINAC equipment that can deliver an appropriately low dose[39]. A recent study with nine clinical trials used the dose range between 0.5-1 Gy in a single fraction to investigate the effect of whole-lung irradiation of COVID-19 patients by analyzing the parameters such as CRP, IL-6, D- dimer, and ferritin as it can affect the lung macrophages at these doses[39]. The therapeutic benefits of LDRT for pneumonitis were evaluated based on the percentage of recovery and the extent of severity[41]. The most commonly evaluated outcome parameters were ventilator-free numerous hematologic, cardiac, hepatic, and inflammatory markers. Few parameters such as the probability of intubation rates, hospital discharge, hospital duration, oxygen supplementation, fever duration, radiographs, clinical recovery, SatO<sub>2</sub>/FiO<sub>2</sub> index, and lung inflammation [42,43]. The radiation toxicity effects had also been studied apart from other parameters [44]. Physiological parameters such as blood oxygen level, clinical recovery rate, mean oxygen saturation, improvement in oxygenation SF ratio, and demand for supplemental oxygen in post-radiotherapy[45]. Clinical parameters such as overall survival, response rate, and X-ray severity score were mainly considered[46]. The level of serum biomarkers such as CRP, CK, and inflammatory cytokines such as IL-2, IL-6, IL-1, IL-8, IL-10, TGF-beta, TGF-alpha, ICAM-1, VCAM, and oxidative marker (PON-1) had been evaluated in previous studies[42]. LDRT can increase interferon- $\gamma$  production, activates natural killer cells, stimulates antigen processing and antigen presentation to T- cells and activates natural killer T-cells (NKT),  $\gamma\delta$  T cells, and  $\alpha\beta$  CD8+ T-cells[47]. The results of these initial studies highlight that the LDRT can be used as one of the treatment options to treat pneumonia in COVID-19 patients.

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  $\geq 5$ , and the exclusion criteria were healthy volunteers, patients on mechanical ventilatory support, and hemodynamically unstable patients[48]. 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[49]. Despite many clinical trials being ongoing, three studies reported the prognosis of COVID-19 patients treated with LDRT as 80% to 90% [45,46,48]. The guidelines routinely used for whole-lung-irradiation of patients undergoing radiotherapy have been applied for COVID-19 patients treated using LDRT[49].

COVID-19 patients are associated with mucormycosis, shortly referred to as CAM, being one notifiable disease in India with a 50% fatality rate for which administering anti-fungal drugs (amphotericin-B) is the treatment[50]. This CAM condition had been observed in 79% of males, either

with 59% active COVID-19 or with 41% COVID-19 recovered status[44]. Further CAM studies were inquisitive for COVID-19 variants with mucor-immunity-associated disturbances, population-associated genetic susceptibilities, and the presence of virulent strains or influence of environmental factors. In such cases, LDRT is a hope in reducing CAM as it can increase CD3, CD4, and CD8 cells thereby transforming them to CD8 cells that can destroy acute respiratory syndrome-infected cells. An example of this LDRT was its implementation in treating tinea capitis till the discovery of griseofulvin[44].

### **Radiation as the choice of COVID-19 infection containment**

LDRT also regulates lymphocyte counts, and bacterial co-infections in COVID-19 patients by modulating excess inflammatory responses[5]. The use of UV or  $\gamma$ -rays for sanitization will effectively kill viral particles[51]. Thus, deactivating COVID-19 viral cells and not allowing the infection to recur by implicating minimal dose radiation therapy by assessing the patient's condition can cure COVID-19[52]. The LDRT was also tested by combining with 2-deoxy glucose (2-DG), which has a potential adjuvant to enhance the efficacy of LDRT in the treatment of COVID-19 pneumonia[53]. Anti-inflammatory effects in LDRT are found to be associated with anti-viral or anti-bacterial effects[53]. Targeting the glycolytic pathway by 2-DG has been well established for its radio- and chemo-sensitizing effects in both *in vitro* and *in vivo* conditions. The 2-DG has been suggested as a therapeutic for the management of COVID-19 patients[53]. The 2-DG in combination with LDRT may also protect other virus-sensitive tissues and organs leading to a reduction in mortality and morbidity[53]. Azido-2-DG will produce the electron-mediated formation of oxidizing aminyl radicals, thus an adjuvant to LDRT[53].

## **BIOMARKERS FOR DIAGNOSIS OF COVID-19 INFECTION AND DISEASE**

The biomarkers for the diagnosis of COVID-19 disease have been categorized into hematological [lymphocyte count, neutrophil count, and neutrophil-lymphocyte ratio (NLR)], inflammatory (CRP, Erythrocyte Sedimentation Rate, and procalcitonin), immunological (cytokines), and biochemical (D-dimer, troponin, creatine kinase, and aspartate aminotransferase), coagulation cascades in disseminated intravascular coagulation in most of the studies[54]. Retrospective studies conducted in COVID-19 patients admitted in intensive care unit (ICU) and post-recovery had been assessed for levels of several biomarkers wherein interleukins (IL)-2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF $\alpha$  were higher in ICU patients than non-ICU patients[2]. Elevation of glomerular filtration function markers such as serum urea, CREA, and Cys C had been observed in severe COVID-19 patients more than in mild COVID-19 patients[55]. In comparison with the recovered group, the deceased group had an elevation in levels of leukocytes, neutrophils, high-sensitivity C-reactive protein (hsCRP), prothrombin, D-dimer, serum ferritin, IL-2, and IL-6[56]. Elevated levels of LDH, CRP, ferritin, and D-dimer had been found in most of the cases. IL-6 significantly increased in severe type, also IL-6, CRP, LDH, and ferritin were the most commonly elevated biomarkers and were associated with the severity of COVID-19[57]. On the other hand, a decrease in the density of natural killer cells and CD3+ T cells, including all T cell subsets had been observed in patients. Multiplex gene expression analysis showed an up-regulation of genes involved in type-I IFN signaling (*IFNAR1*, *JAK1*, and *TYK2*) contrasting with a striking down-regulation of IFN-stimulated genes (*MX1*, *IFITM1*, and *IFIT2*) in critical SARS-CoV-2 patients[58]. Lymphocytopenia was found to be the most common marker of infection in most critically ill COVID-19 patients[59]. These biomarkers are thus significant in the early identification of COVID-19 disease; hence disease prognosis can be improved and also helpful to monitor the LDRT.

## **LIMITATIONS/ FUTURE IMPROVEMENTS ON USING X-RAYS FOR THE DIAGNOSIS AND THERAPY OF COVID-19 DISEASE**

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. However, the use of this X-ray-based imaging should be done with the most precaution since it might result in stochastic effects later in the life span of the exposed individual. Also, the concerns associated with the use of radiation in terms of risk for carcinogenesis were evaluated using phantom models[60]. The stochastic effects are seen with low doses in LDRT and thus quantifying the effective dose and Lifetime Attributable Risk will help in the effective treatment of COVID-19 pneumonia[41]. Delivering radiotherapy by giving quality assurance is impossible as the system conditions of portable X-ray machines delivering low-dose radiation therapy are not compatible. The concept of being as low as reasonably achievable is the basis of the radiation protection approach[61]. Targeting the whole lung requires vast knowledge about the biological mechanisms and hence deliverance of a low dose for an appropriate target volume is highly challenging. Examining LDRT in a trial setting in the case of COVID-19 treatment can be beneficial for patients and can be taken to the next level for scientific scrutiny. Shortening overall therapy time by giving multiple fractions/weeks may enhance COVID-19

management[62]. Based on the previous clinical trials, the effectiveness of LDRT in treating COVID-19 was up to 80%; therefore, the Food and Drug Administration recommended LDRT (by irradiating 0.5 Gy) as a treatment for COVID-19[63]. Thus, the contribution of X-ray-based imaging is enormous and its use is inevitable in modern-day health care including the COVID-19 pandemic. Despite the beneficial effects, the ethical concerns to use 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[64]. Even though medical imaging is widely used, divergent thoughts existed on the health effects of low-dose IR in scientific communities/stakeholders[65,66]. An “enhanced risk of stochastic effects due to radiation dose received by the patients during CT imaging” and “clarifications” from professional associations and regulatory authorities during this COVID-19 pandemic raised the anxiety among the public at the national level[67,68]. Any technology is not devoid of risk/side effects. Nevertheless, the improvements/advancements in technology contribute to minimizing the risk while enhancing the benefits. The same is the case for CT imaging; a recent low-dose chest CT protocol has been proposed to reduce the dose up to 89% when compared to the standard-dose protocol without compromising the diagnostic accuracy of COVID-19-induced pneumonia in CT images[69]. Despite those developments, the medical uses of IR are not devoid of criticism owing to the projected risk for different health effects. The reported studies suggest that CXR contributed significantly toward initial rapid diagnosis and CT- imaging to monitor the disease.

## CONCLUSION

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. 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 X-ray-based technology continues to evolve and play a significant role even during the COVID-19 pandemic.

## FOOTNOTES

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