REVIEW
INFECTION DISEASES

Diseases & Research

Co-Infection of COVID-19, Influenza and RSV: How Non-pharmaceutical Therapeutic Approaches Such as Low Dose Radiation Therapy Can be A Game Changing Strategy

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Abstract: Non-pharmaceutical interventions (NPIs), such as social distancing, were previously reported to play a significant role in diminishing the transmission of COVID-19. However, updated guidelines highlight the elimination of social distancing, quarantine, and test-to-stay for schools, which may increase the risk of a tripledemic. H3N2, a subtype of influenza type A, has caused waves of infection in the southern hemisphere. A tripledemic of RSV, COVID-19 and influenza viruses can result in the full circulation of the flu and SARS-CoV-2, especially during fall and severe flu season. Moreover, in the presence of the COVID-19 pandemic, the occurrence of recombination within influenza and SARS-CoV-2 can lead to the emergence of new variants. It has been reported that coinfection with these viruses could significantly impact health service demand, morbidity, and mortality. Patients with dual influenza A/SARS-CoV-2 infection may have a more severe illness compared to those with a single infection. Furthermore, as recombination can lead to viral evolution at a quicker rate than mutation, during a tripledemic, recombination may increase the likelihood of developing new variants with higher virulence. As early as March 2020, our research team suggested applying low-dose radiation therapy (LDRT) for patients with COVID-19. Our first report received remarkable global attention, and following this report, numerous papers were published on this topic. Moreover, more than ten clinical trials have been conducted on LDRT for COVID-19 worldwide. The wide spectrum of advantages of using LDRT for treating COVID-19/influenza-associated symptoms is discussed.

Keywords: COVID-19; Radiotherapy; Coronavirus; Influenza; Tripledemic.

Introduction

As individuals return to school and work while contemplating the discontinuation of social distancing and mask mandates, concerns are rising about a potential "tripledemic"[1]. The "tripledemic" refers to the simultaneous surge of three respiratory viruses: influenza, SARS-CoV-2 (the virus responsible for COVID-19), and respiratory syncytial virus (RSV). This phenomenon became particularly pronounced during the winter of 2022, creating significant challenges for public health systems across the United States.

Previous studies revealed a high rate of co-infections during the 2021–2022 influenza season, with variations in co-infection prevalence between the Delta and Omicron waves, underscoring the significance of influenza vaccinations in combating co-infections[2]. As patients with coinfection are at greater risk of experi-

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Received 9 August 2024; Revised 26 August 2024; Accepted 6 November 2024; Available Online 28 November 2024
DOI: 10.54457/DR.202402009

encing severe health consequences, improved detection of both viruses and personalized treatment approaches for coinfection are advised to minimize the occurrence of serious disease outcomes going forward[3]. Moreover, co-infection has been associated with higher rates of hospitalization, mechanical ventilation, and mortality[4].

Both SARS-CoV-2 and influenza A viruses, which cause COVID-19 and influenza, respectively, cause severe respiratory tract infections with overlapping symptoms[5,6]. As different variants of SARS-CoV-2, RSV and flu viruses co-spread, many specialists have highlighted the possibility of a tripledemic of influenza, RSV and COVID-19 in the coming flu seasons. Fortunately, despite previous warnings, no tripledemic outbreak was reported during the 2019-2021 flu seasons. The lack of such reports is thought to be attributable in part to the global control of COVID-19, high flu vaccination coverage, and even a lower rate of flu tests[7].

It has been reported that coinfection with SARS-CoV-2 and influenza viruses could significantly impact health service demand, morbidity, and mortality[8]. While vaccination against COVID-19 and influenza is vital, a study showed that although 80.0% of adults intended to receive influenza vaccines, only 33.0% intended to receive COVID-19 vaccines[5]. Despite the CDC's urgent warning about the potential risk of a "multidemic" in the cold months, African American women were hesitant to receive vaccines[9]. Another study also reveals that African American patients demonstrated a low likelihood of receiving the COVID-19 vaccine[5].

Multiple respiratory viruses can circulate at the same time and may infect the same host, leading to various types of interactions[10]. This co-circulation may lead to either positive interactions or negative interactions between the viruses[11]. There are a number of reports of co-circulation of the SARS-COV-2 and the Influenza viruses, especially in the Northern Hemisphere[12-14].

It has been reported that there may be no significant association between coinfection and mortality in some cases[15]. Moreover, there is an imbalance in COVID-19 vaccination rates in different countries and it ranges from 30% to 70% of the population in low and high-income countries[16].

Low-dose radiation therapy (LDRT) has been shown to serve as a non-pharmaceutical therapeutic approach. There are reports of using this method for COVID-19 patients. For example, Sharma *et al.* have applied LDRT to treat patients with COVID-19 at moderate to severe risk of disease in 2020 and 90% patients achieved full clinical recovery[17]. Sanmamed et al. have also reported clinical improvement for COVID-19 positive patients undergoing LDRT[18].

This study aims to explore the potential of low-dose radiation therapy (LDRT) as a non-pharmaceutical intervention for managing coinfections of influenza, RSV and COVID-19. Given the emerging concerns over a possible 'tripledemic' and the increasing likelihood of viral recombination, this research seeks to highlight how LDRT may mitigate severe respiratory complications, reduce mortality, and control cytokine storms in patients affected by these viruses. Furthermore, the study examines the implications of LDRT on immune response modulation and its potential role in preventing new, more virulent viral strains.

Recombination versus Mutation in Viruses

Mutation occurs due to a mistake in the viral genome, which can be harmful, neutral, or even beneficial in some cases[19]. Recombination is due to genomic exchange between members of the same virus type (e.g., between two influenza viruses) invading the same host cell[20,21]. Mutation is an alteration in the nucleotide sequence of a brief region of the genome, whereas recombination is the reorganization of a portion of the genome. Both mutation and recombination generate viruses with novel antigenic determinants, and antigenically changed viruses can cause illness in previously immune or resistant individuals[20,21]. Recombination that leads to the generation of a novel virus occurs in many viruses, including influenza, HIV, and other coronaviruses. Any type of RNA virus may undergo RNA recombination. In RNA viruses, the rate of recombination varies considerably[20–22]. Recombination may lead to the development of new variants with higher virulence since it can lead to viral evolution at a quicker rate than mutation[20].

Recombination-induced major antigenic change, called antigenic shift, can give rise to pandemics of influenza[20]. There is also rising concern about the involvement of genomic recombination across distinct SARS-CoV-2 strains. Thus, in the presence of the COVID-19 pandemic, the occurrence of recombination within the RSV, influenza A and SARS-CoV-2 viruses can result in the influenza-COVID-19 tripledemic, especially during fall and severe flu season. A "tripledemic" refers to the simultaneous occurrence of three different viruses within a population. When a person is infected with RSV, influenza A and SARS-CoV-2, the resulting illness can be more severe than with just one of these viruses[23].

SARS-CoV-2's Continued Spread

Some forecasts indicate that SARS-CoV-2 will persist in circulating within the human population. Oberemok et al.[24] propose that, over time, fatalities among individuals of reproductive age may result in future generations developing increased resistance to this virus. They also point out that due to natural genetic processes like mutations and recombination, it’s impossible to prevent the virus from generating new strains that could periodically threaten the world with new pandemics[24]. Bevelacqua and Mortazavi[25] argue that the situation is even more complex, as the extensive use of ineffective vaccines and antiviral drugs might exert selective pressure on the virus, encouraging it to evolve[26]. Kupferschmidt, in a report published in Science, noted that as the virus spreads through millions of immunologically naive individuals, there might be minimal selection pressure, but this could change with the introduction of vaccines or new therapies, potentially forcing the virus to evolve[27]. The spread of SARS-CoV-2 among humans is affected by the immune response of the host, the frequency of viral replications, and the rate at which the virus mutates[28].

Concerns Over Tripledemic

The CDC in the US announced that flu activity during 2020-2021 was at its lowest level since data gathering began in 1997. Thus, CDC director Rochelle Walensky believes that because there has been so little flu over the past years, the population may have a lower degree of immunity, putting them at increased risk of the disease[29]. This is exactly why experts believe that vaccination and other prevention methods, including wearing a mask, frequently washing/sanitizing hands, practicing social distancing, and staying home if sick, will reduce the dual risk of COVID and flu infection[29,30].

Potential Benefits of LDRT in Treating COVID-19

Low-dose radiation therapy (LDRT) has shown promise in reducing mortality rates in patients suffering from bacterial and viral pneumonia[31]. Our proposed method, LDRT, offers several advantages over existing approaches, particularly in its ability to leverage localized dynamics for more targeted intervention strategies. Unlike traditional methods, LDRT captures the spatial and temporal heterogeneity of infection spread, which allows for more precise control measures. This is particularly relevant in the context of COVID-19, where varying immunity levels, due to previous exposure or vaccination, create complex patterns of disease propagation. Studies have demonstrated the importance of immunization effects in curbing the spread of COVID-19, and LDRT's capacity to incorporate immunity data enables more efficient resource allocation and containment efforts. By accounting for localized immunity levels, our method ensures a more adaptable and responsive framework compared to global models that often overlook these critical variations. The case of a constant immunity loss rate as well as a scenario where immunity is eventually completely lost has been studied by Shang in 2021[32].

In the case of COVID-19, one of the main challenges is managing uncontrolled inflammatory responses and cytokine storms, which play a significant role in the severity of the disease[33,34]. LDRT has the ability to modulate these inflammatory responses by affecting various cell types, including leukocytes, endothelial cells, and fibroblasts, and influencing the production of cytokines and chemokines[31,35,36]. Additionally, LDRT may boost the body's antiviral defenses by enhancing the activity of natural killer (NK) cells, CD8 + T-cells, and the generation of IFN-γ[37,38].

A hypothesis regarding the use of LDRT for COVID-19 was introduced by Ghadimi-Moghadam *et al*. on April 1, 2020, and by Kirkby & Mackenzie on April 6, 2020[39,40]. However, the initial concept of using LDRT to treat severe COVID-19-induced pneumonia was first proposed by Mortazavi et al. on February 22, 2020, and further discussed on March 15, 2020, through communications with the Scientists for Accurate Radiation Information (SARI). The core idea behind this proposal is rooted in the anti-inflammatory and immune-enhancing properties of LDRT, making it a potentially effective treatment option for the severe respiratory complications associated with COVID-19. As shown in Fig. 1, these are just some of the therapeutic effects that LDRT could offer in managing COVID-19.

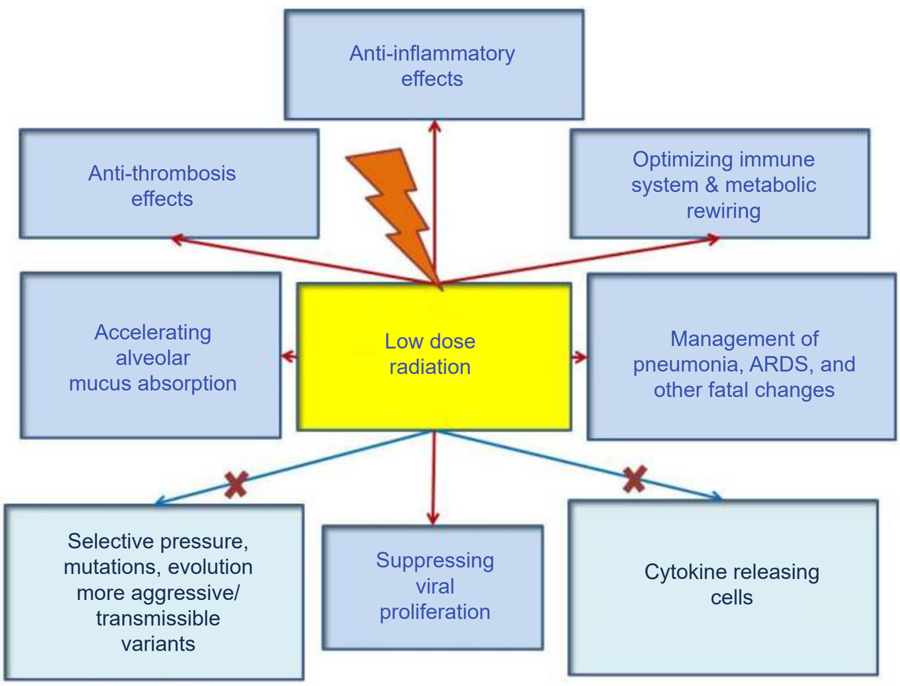

Fig. 1. Key advantages of using low-dose radiation therapy for effective management of COVID-19.

LDRT for Flu

Cuttler and Calabrese have recommended incorporating LDRT into the treatment protocol for patients hospitalized with influenza-associated pneumonia. They believe that because each year about 600,000 patients are hospitalized with pneumonia in the US, LDRT would remove the annual need to treat about 100,000 cases of ARDS in ICUs (with a mortality of ~ 40%)[41]. While people who have had the common cold are not protected against COVID-19, some studies show that in some individuals, exposure to coronaviruses that cause the common cold can lead to resistance through induction of memory T-cell-mediated responses[42].

Conclusion

Since recombination can lead to viral evolution at a quicker rate than mutation, during a tripledemic, recombination may increase the likelihood of developing new variants with higher virulence. There is increasing concern about the involvement of genomic recombination across distinct SARS-CoV-2 strains. In the presence of the COVID-19 pandemic, the occurrence of recombination within the RSV, influenza A and SARS-CoV-2 viruses can result in the influenza-COVID-19 tripledemic. Patients with dual influenza A/SARS-CoV-2 infection may have a more severe illness than those with a single infection. We provided substantial evidence indicating how low-dose radiation therapy can be introduced as an effective treatment for COVID-19 and influenza coinfection.

Abbreviations

ARDS, Acute Respiratory Distress Syndrome; CDC, Centers for Disease Control and Prevention; LDRT, Low Dose Radiation Therapy; RSV, Respiratory Syncytial Virus.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Authors' contributions

ARM, AGM, and LS were responsible for the study's conception and design. AJ, JSW, MHPM, MH, and FGM conducted the literature review, which was supervised and guided by SMJM, who also directed the interpretation of the findings. LS, ARM, AGM, and SMJM oversaw the preparation of the draft manuscript. All authors reviewed and approved the final version of the manuscript.

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