Review Article

Low-Dose-Whole-Lung Radiotherapy for Older Patients with Coronavirus Disease (Covid-19) Pneumonia: A Phase I-II Prospective Non-Randomized Protocol by the International Geriatric Radiotherapy Group

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Abstract

Background: Coronavirus disease 19 (COVID-19) carries a high mortality rate among older patients and minorities such as ethnic Africans and Latinos. These patients suffer from chronic inflammation that may turn into a cytokine storm when infection occurs, in addition to frequently possessing multiple comorbidity factors that may also account for their higher mortality. Even though multiple organ failure results from the cytokine storm, it is pneumonia and respiratory failure that often lead to death. Low-dose-whole-lung radiotherapy (LDWLRT) may modulate the inflammatory response and decrease the need for artificial ventilation, thus improving the mortality rate.

Methods: A phase I-II prospective trial, enrolling 500 patients, aged 65 years old or above from 25 countries, will be conducted to investigate the impact of LDWLRT on the mortality rate in COVID-19 patients. Selected patients will have developed viral pneumonia that does not require artificial ventilation. These patients will be followed for a year after receiving radiotherapy. The impact of the residual inflammation will be assessed using the ordinal scale. Mortality rates will also be compared among different ethnic groups and correlated with their cytokine response to the virus and number of co-morbidities.

Results: Patients have been recruited in an institution in Mexico as per protocol. Patient recruitment is scheduled at another institution in Canada pending Institutional Review Board approval. The preliminary results will be used to apply for funding.

Discussion and importance of the study: We postulate that LDWLRT may improve survival rates in all patients by preventing the need for artificial ventilation, which is associated with a high mortality. The differences in inflammatory response among ethnic groups prior to and following radiotherapy will serve as a valuable baseline for future prospective pandemic studies.

Keywords: COVID-19; Low-Dose radiotherapy; Pneumonia; Cytokines; Ordinal scale

1. Introduction

Coronavirus Disease 19 (COVID-19) is a pandemic of unprecedented epic proportion. The number of patients infected across the globe increased exponentially from the first case reported in Wuhan in December 2019. Even though the mortality rate is multifactorial, one of the main causes of death is virus-induced pneumonia resulting in respiratory failure despite artificial ventilation. Older patients, defined as those aged 65 years or above, have a disproportionately higher mortality rate as compared with younger patients [1,2]. Among those admitted to intensive care units, a higher rate of mortality has been reported in older patients [3]. Mortality rates are also increased in minority patients such as African and Latino Americans in comparison with other ethnicities. According to the Centers for Disease Control and Prevention (CDC), death rates per 100,000 population are 92.3, 74.3, 45.2, and 34.5 among Africans, Latinos, Caucasians, and Asians, respectively (https://www.cdc.gov). Many vaccines are currently being administered but may not be available due to limited supply: thus, an effective therapy to decrease the COVID-19 mortality rate should be introduced for these patients.

To date, few medications have been proven to be effective for COVID-19 pneumonia. An antiviral medication, remdesivir, has been shown to reduce the length of hospitalization, but mortality was not significantly improved as compared with the placebo. In addition, in a subgroup analysis, among patients who required high oxygen flow or artificial ventilation to assist their breathing, remdesivir was no more effective than the placebo [4]. The cost of this medication and

its limited availability may restrict its use in developing countries due to their modest socio economic resources [5]. Another medication, dexamethasone, may reduce mortality rates among patients who require artificial ventilation for their pneumonia but not for those requiring oxygen [6]. Both remdesivir and dexamethasone were approved for the treatment of a variety of diseases long before the pandemic. According to the World Health Organization (WHO), developing countries are currently experiencing an increased rate of infection as a result of crowded conditions and the economic impact of lock-down. Measures such as quarantine and social distancing to slow infection rates may not be realistic in these situations. Infected patients may be forced to work because of the lack of social support in developing countries.

Thus, an alternate effective treatment to decrease the COVID-19 mortality rate should be investigated and made available to the global community. Low-dose-whole-lung irradiation (LDWLRT) may be a potential solution since it was effective in treating pneumonia before the introduction of antibiotics [7]. As an international research organization devoted to older cancer patients, women, and minorities, the International Geriatric Radiotherapy Group (http://www.igrg.org) would like to propose a simple and practical protocol for LDWLRT to allow the participation of all countries worldwide regardless of their resources [8].

2. Scientific Rationale

Infection of the airway epithelial cells with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) produces a severe inflammatory form of programmed cell death, pyroptosis, which begins with the formation of a supramolecular complex termed the inflammasome followed by activation of caspases, which in turn activate several pro-inflammatory cytokines and pore-forming gasdermin proteins [9]. Cytolysis ensues due to cell membrane damage leading to the release of many damage-associated molecular pattern (DAMP) molecules such as DNA and ATP. As a result, further pro-inflammatory cytokines and chemokines such as interleukin 6 (IL6), interferon γ (IFNγ), monocyte chemoattractant protein-1 (MCP-1), and IFNγ-inducible protein 10 (IP-10) are liberated into the blood [10-12]. Blood monocytes and lymphocytes are in turn attracted into the alveoli, leading to global lymphopenia predominantly of the CD8+ T cell type. Monocytes differentiate into M1 macrophages, further increasing the inflammatory reaction through the production of IL1, IL6, IL18, and tumor necrosis factor (TNF).

Subsequently, neutrophils are attracted into the alveoli and produce reactive oxygen species (ROS) in an effort to clear the virus. Normally, this inflammatory reaction subsides after viral clearance, and the M1 macrophages are transformed into the M2 subtype that produce IL10, an anti-inflammatory cytokine, to return the lungs to their normal state. Under the pathological conditions of COVID-19, which remains poorly understood, the excessive inflammatory reaction continues unabated, as characterized by increased cytokine and chemokine (IL1, IL6, IL8, IL17, CCL-2, TNFα, G-CSF, IP-10, MCP-1, MIP) concentrations and blood ferritin levels [13,14]. This cytokine storm not only leads to lung damage, but also to multiple organ failure involving the heart, kidneys, and central nervous system, among others. In the lungs, inflammatory cytokines and chemokines cause increased vascular permeability, decreased oxygen diffusion, and in severe cases, death from respiratory failure despite artificial ventilation. Autopsy reports of patients dying from COVID-19 respiratory failure demonstrate pulmonary edema, infiltration of inflammatory cells, and fibrosis of the pulmonary alveoli in late-stage disease [15,16]. IL6 is believed to play a central role in the cytokine storm since its serum level has been correlated with a higher mortality rate and has successfully predicted the need for artificial ventilation in COVID-19 patients [17-19]. Thus, any therapeutic intervention that may reduce the cytokine storm, in particular the level of IL6, may potentially improve the COVID-19 mortality rate which is the purpose of this international protocol.

3. Low-Dose-Whole-Lung Radiotherapy Efficacy as a Potential Modulator of the Cytokine Storm

Long before radiotherapy was used as an effective modality to treat cancer, its anti-inflammatory efficacy at low doses

was employed in the treatment of a variety of diseases characterized by excessive inflammation [19]. Indeed, various animal experiments have demonstrated that the production of inflammatory cytokines is reduced following the administration of low-dose radiotherapy (LD-RT) [20-25]. Mice injected with a pro-inflammatory stimulus, such as lipopolysaccharide (LPS), demonstrate an infiltration of leukocytes into their intestinal venules. However, the number of adherent leukocytes is significantly suppressed following receipt of whole-abdominal-irradiation at a dose of 30 cGy as compared with sham irradiation. The anti-inflammatory properties of LD-RT are mediated through transforming growth factor beta 1 (TGF-β1) stimulation [20,21]. In another study, murine endothelial cell lines were activated with TNF-α. The TNF-α-induced release of inflammatory cytokine such as keratinocyte chemoattractant (KC), MCP-1, and RANTES was significantly suppressed by LD-RT at a dose of 1-10 cGy [26]. Irradiation of lung macrophages at 50-100 cGy has been shown to stimulate the production of the anti-inflammatory cytokine IL10 and decrease the production of the pro-inflammatory cytokine IFNγ [27].

In addition, the percentage of macrophages producing IL6 was also reduced [27]. These data are in agreement with the shift of M1 macrophages responsible for the inflammatory reaction toward M2 macrophages that regulate lung homeostasis following LD-RT [28]. Other LD-RT experiments also corroborate its beneficial anti-inflammatory effect through a significant reduction in TNF-1α, IL1-β, and IL6 levels [29,30]. Following stimulation with LPS, peritoneal macrophages isolated from mice showed a significant reduction in TNF-α, IL6, and IL1-β levels as compared with the control group after subsequent irradiation at 50 cGy [29]. A similar dose of LD-RT has been demonstrated to reduce the production of the proinflammatory cytokine IL-1β, and stimulate the production of the anti-inflammatory cytokine TGF-β by macrophages [30]. Thus, in theory, LDWLRT could modulate the inflammatory response generated by viral infection and prevent respiratory failure induced by the cytokine storm. Historical data strongly support the use of LDWLRT for COVID-19-induced pneumonia. Before the introduction of antibiotics, pneumonia and bronchopneumonia had a high mortality rate. In the 19th century, Sir William Osler, considered by many as the father of modern medicine, described pneumonia as the most fatal of all acute diseases with a mortality rate of 24% [31]. However, radiotherapy pioneers in the early 20th-century successfully used LDWLRT for pneumonia of diverse etiology due to its anti-inflammatory efficacy and the lack of effective treatment, which is similar to the situation involving the COVID-19 pandemic [32]. A single dose ranging from 20 cGy to 200 cGy has been reported as an effective cure for pneumonia by various institutions with radiotherapy technology that is now considered obsolete by current standards [32-35]. As an illustration, a single LDWLRT produced immediate relief of fever and dyspnea caused by lobar pneumonia in 1933. Among the 104 patients treated with LD-RT for pneumonia, only 5 deaths were reported (4.8%), which was a remarkable improvement compared to half a century earlier [32]. Patients aged 2-70 years-old immediately benefited from LDWLRT: the chest-X-ray infiltrate from lobar pneumonia completely resolved which was attributed to its cytocidal effect on the neutrophils causing lung inflammation. Radiotherapy was the standard care for pneumonia at that time, until the introduction of antibiotics. No randomized study was performed comparing LDWLRT with a control since it was believed to be unethical not to treat with radiotherapy, as most patients experienced immediate relief of their respiratory distress following treatment.

Preliminary evidence suggests that LDWLRT may be safe for the treatment of COVID-19 pneumonia. Among five patients who developed pneumonia following SARS-CoV-2 infection, four had immediate relief of their breathing after a single dose of 150 cGy applied to both lungs and within 96 hours no longer needed supplemental oxygen [36]. Even though the follow-up was short, the efficacy of LDWLRT was corroborated by subsequent studies [37-39]. It has also been reported that four out of five patients who were oxygen-dependent as a result of COVID-19 pneumonia improved significantly following whole-lung irradiation at 50 cGy [37]. The improvement in their oxygen saturation was linked to a

marked reduction in inflammatory cytokines immediately following treatment. Previously elevated IL6 and CRP levels were significantly decreased afterward. None of the treated patients received steroids. Another study also reported a significant improvement in a 65 year-old patient infected with SARS-CoV-2 who experienced deterioration of oxygen saturation despite oxygen supplementation, after one application of 100 cGy to both lungs [38]. This patient also received no steroids. In a further study, two patients who deteriorated clinically following standard treatment with antiviral medication, antibiotics, oxygen, and steroids, experienced significant improvement of their lung function immediately after receiving 80 cGy to both lungs [39]. Both patients were discharged and still remained in good clinical condition two months later: their inflammatory cytokine levels were also decreased following LD-RT. Taken together, these data show that LDWLRT at 50-150 cGy produces a significant decrease in pro-inflammatory cytokine levels, leading to improved lung function.

4. The International Geriatric Radiotherapy Group Protocol to Improve the Mortality Rate of Covid-19 Pneumonia with Low-Dose-Whole-Lung Radiotherapy

4.1 Objective

Primary endpoint: Mortality rates in all patients aged 65 years or above who develop pneumonia following infection with SARS-CoV-2 as compared to historical data. These patients may or may not require oxygen following infection with SARS-CoV-2 but are at a high risk of death following viral infection, possibly due to preexisting co-morbidities. The mortality rate at 14 days, 30 days, 3 months, 6 months, and one year following radiotherapy will be evaluated for the whole group, and compared among three subgroups of patients to determine the optimal time for LD-RT to avoid the need for artificial ventilation which is associated with a high mortality rate.

1 Patients with COVID-19 pneumonia who do not require oxygen.
2 Patients with COVID-19 pneumonia who require low-flow oxygen (2 liters/minute or less)
3 Patients with COVID-19 pneumonia who require high-flow oxygen (> 2 liters/minute) or non-invasive ventilation.

4.2 Secondary endpoints

1 Comparison of the mortality rate among different ethnic groups with COVID-19 pneumonia, whether LDWLRT improves survival in Africans and Latinos, who have the worst prognosis as compared with other ethnic groups. The number of co-morbidity factors, such as high blood pressure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), history of myocardial infarction, arrhythmia, chronic renal disease, liver disease, sickle cell disease, history of smoking and alcohol consumption, and co-existing infection (human immune virus (HIV) disease, hepatitis viruses, and malaria), will be recorded and compared among different ethnic groups to determine their influence on mortality rate. The number of co-morbidity factors in each ethnic group will be compared to evaluate whether they account for any difference in mortality. In cases where no difference in the number of co-morbidity factors is found to account for any difference in mortality, other factors such as genetics may be the cause.
2 Duration of hospitalization after viral infection for the whole group and each subgroup.
3 Time to recovery, defined as the first day, during the 28 days after LD-RT on which the patient satisfies categories 1, 2, or 3 on the 8 category ordinal scale as follows:
   - Not hospitalized, no limitations of activities.
   - Not hospitalized, limitations of activities, home oxygen requirement, or both.
   - Hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care (used if hospitalization is required for infection-control reasons).
   - Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19-related or other medical conditions).
   - Hospitalized, requiring low-flow-oxygen (2

liters/minute or less).

- Hospitalized, requiring high-flow-oxygen (>2 liters/minute) or non-invasive ventilation.
- Hospitalized, requiring endotracheal intubation or tracheostomy and ventilators or extra-corporeal membrane oxygenation (ECMO)
- Dead.

The patient ordinal scale will be defined at the time of receiving radiotherapy and 28 days following radiotherapy. The ordinal scale has been established as the gold standard to measure patient outcome following antiviral medication for COVID-19 pneumonia [4].

4 Oxygen saturation rate at the time of radiotherapy, weekly following radiotherapy until the 28th day, and 3 months, 6 months, and one year following radiotherapy. The patient ordinal scale will be defined at each point. An oxygen saturation rate of 90% or above on room air or on oxygen would be defined as satisfactory [40].

5 Identification of the patient inflammatory status using biomarkers such as sedimentation rate, C-reactive protein (CRP), ferritin, and IL6 levels, before radiotherapy, weekly following radiotherapy until the 28th day, and 3 months, 6 months, and one year following radiotherapy. The inflammatory status will be compared among the four subgroups of patients to determine whether it correlates with patient respiratory status and/or time to recovery. The data obtained may be helpful in assessing the natural history of patient recovery following COVID-19 pneumonia and whether further treatment such as anti-inflammatory medication may be necessary to expedite the patient clinical recovery. Preliminary evidence suggests that COVID-19 patients may experience a prolonged period of convalescence characterized by chronic fatigue similar to that seen during previous viral epidemics.

4.3 Study design

The present paper describes a phase I-II single-arm prospective international study involving 45 institutions in 25 countries. A phase I study is currently being conducted by one of our participating institutions. Preliminary results will be published after a minimum of 30 patients are treated. The current protocol is based on the experience acquired during that phase I study. The data obtained may be used to design a phase III randomized study comparing LDWLRT alone with remdesivir treatment in patients not requiring artificial ventilation or LDWLRT plus dexamethasone with dexamethasone alone in patients requiring artificial ventilation.

4.4 Inclusion criteria

Patients aged 65 years or above who develop pneumonia observed on chest-X-ray or diagnostic chest computerized tomography (CT) scan following infection with SARS-CoV-2 diagnosed from nasopharyngeal, oropharyngeal, or sputum secretions. Patients may or may not require oxygen but are not on artificial ventilation. Patients may receive antiviral, antibiotic, or anti-inflammatory medications as deemed necessary by the attending physician outside of a clinical trial. Patients admitted to the ICU but not on artificial ventilation are eligible. Patients who are mentally confused may be eligible if their power of attorney (POW) or family member consent to the treatment: however, such patients need to be cooperative during treatment.

4.5 Time frame for radiotherapy

1 Patients who are admitted for shortness of breath but do not require oxygen due to an oxygen saturation rate above 90% on room air. Radiotherapy intervention on admission may prevent the need for oxygen, leading to earlier hospital discharge.

2 Patients who require low-flow oxygen on admission (2 liters/minute or less) to maintain an oxygen saturation rate above 90%. Radiotherapy intervention may prevent the need for high- flow-oxygen or non-artificial ventilation.

3 Patients who require high-flow oxygen on admission (more than 2 liters/minute or non-artificial ventilation). Radiotherapy intervention may prevent the need for artificial ventilation.

Radiotherapy should be initiated as soon as possible after hospital admission to prevent deterioration of the clinical condition, circumventing the need for artificial ventilation, which carries a high mortality rate.

4.6 Exclusion criteria

1 Patients who do not have a proven diagnosis of SARS-CoV-2 infection.

2 Infected patients who are hemodynamically unstable to undergo radiotherapy due to uncontrolled cardiac arrhythmia and/or hypotension despite vasopressors (defined as systolic pressure below 90). These patients may develop cardiac arrest and require cardio-pulmonary resuscitation during radiotherapy.

3 Infected patients who have an oxygen saturation rate below 90% despite oxygen therapy.

4 Patients who are mentally confused and cannot consent to treatment. Consent from POW or family members is necessary before treatment in such cases.

5 Patients already enrolled in another clinical trial to assess the efficacy of an anti-viral treatment.

4.7 Mandatory requirements

This protocol is designed to allow institutions with limited resources in developing countries to participate since it involves 25 countries worldwide. However, to ensure patient quality of care and to protect hospital care workers (HCW) from potential infection that may be fatal, these following conditions are mandatory:

1 Authorization from the Institution Review Board (IRB) of the participating institution prior to recruiting patients or by default, the local Government Health Agency in the respective country.

2 Signed informed consent from the patient in the local language or dialect, or by default, through a translator fluent in the patient's language. For patients unable to sign the consent due to their mental status, consent may be obtained through the POW or a designated family member, or a court-appointed POW if the patient has no relatives.

3 Personal protective equipment (PPE) made available to HCW and worn during patient treatment: N95 respiratory mask, face shield or eyes goggles, disposable gown, and gloves. In addition, HCW must be trained on how to don and doff PPE before taking care of patients with a view to avoiding mistakes that lead to potential contamination during patient treatment.

4 Thorough disinfection of the treatment area must be conducted following treatment.

4.8 Radiotherapy protocol

The protocol is designed to minimize the amount of time that the patient undergoes radiotherapy. Patients on oxygen are at risk of adverse events such as arrhythmia, cardiac arrest, and oxygen desaturation which may occur as a result of infection (myocarditis) or underlying patient comorbidities.

1. Infected patients requiring oxygen. These patients are difficult to set up due to their shortness of breath, and may not collaborate with the staff as a result of their mental condition. A clinical set-up is recommended to avoid the need for planning a chest CT scan. Radiotherapy treatment may be performed with the patient in either the supine or prone position. The prone position may allow improved ventilation and oxygenation in COVID-19 patients with pneumonia [41]. No immobilization device is necessary. The radiation oncologist uses the predetermined field size to set up the patient clinically and to verify that the upper border includes the supraclavicular area or cricoid, 1 cm flash on each lateral side. Two anteroposterior and postero-anterior films are taken to ensure that the lower border is 1 cm below the costophrenic angle and the whole lung is included in the treatment fields. A single treatment of 100 cGy is delivered to the mid plane. This radiation dose is based on the promising results of an unpublished phase I study by our IGRG partner albeit in a small number of patients. Alternatively, if the patient is non-cooperative, a single anteroposterior field is also allowed to shorten treatment time. However, each participating institution must record how radiotherapy is prescribed to assess whether radiotherapy technique affects patient outcome.

Patient vital signs, cardiac rhythm, and oxygen saturation should be monitored throughout the treatment.

2. Infected patients not requiring oxygen. A chest CT scan may be performed either in the Radiation Oncology Department or Diagnostic Radiology. The patient may be either in the supine or prone position. The arms are ideally elevated to avoid irradiation: however, if the patient has severe arthritis, an akimbo position is preferred. A vacuum bag or alternative device is used for immobilization. The patient should wear a surgical mask during a CT scan without contrast.

Following chest CT, the lungs are contoured as CTV. The planning target volume is obtained by expanding CTV 5 mm in all directions: except for the supero-inferior direction, which will be 1 cm. Lung density correction and pneumonia density will be used for the planning process. Density correction with CT planning is the preferred method of planning patients who are able to cooperate because the dose prescribed may change by 10-15% if density correction is not performed based on preliminary phantom data. Planning will aim to achieve a homogeneous distribution in the area to be treated that meets ICRU criteria : 95- 107% of the prescribed dose of 100 cGy. However, older patients with COVID-19 may not be cooperative due to altered mental status and may not be able to undergo a CT scan for planning. In that case, a cone beam CT scan may be performed at the linear accelerator, and the diagnostic CT scan fused to the cone beam CT scan for planning. If that scenario is also not possible, a clinical set-up with adequate sedation may be necessary, with the dose prescribed to the mid plane or to an antero-posterior field. Again, meticulous record keeping should be performed with respect to how the patient is being treated. During the procedure, two radiotherapy technologists, the radiation oncologist in charge of the patient, a nurse, a physicist, and a dosimetrist should ideally be available for rapid intervention. However, we realize that radiotherapy legislation varies across countries. Participating institutions should follow the rules established by their country's legislation for radiotherapy treatment.

4.9 Statistical analysis

We anticipate to recruit a total of 500 patients enrolled during the study course. Since the COVID-19 pandemic is unpredictable with respect to timing and location, with 45 centers scattered in 25 countries, we may be able to achieve that number to allow comparison of survival among different ethnic groups and among the three subgroups. Assuming uniform accrual of patients over a six-month period and a one-sided type I error rate of 0.05, 500 patients will provide 100% power to detect a difference in mortality of at least 10% when comparing patients one month post-radiation therapy intervention with historical controls under exponential, survival curves and using a one-sided single sample log-rank test [42]. This study will have 100% power assuming both a mortality rate of 25- 65% in historical controls and a Weibull distribution with shape parameters of 0.5- 2. Power calculations were conducted using Performance Analysis of Systems and Software (PASS) 2020 (v20.0.2) power analysis and sample size software.

Descriptive statistics, including the mean, median, standard deviation, interquartile range, and proportions, will be used to summarize the patient characteristics of the study population. The primary endpoint for the study is mortality. Patients in the study population will be described using the Kaplan-Meier method, and a single sample log-rank test will be used to compare the treatment arm in this study population with historical controls [43] by independent analyses at 14 days, 30 days, 3 months, 6 months, and one year following radiotherapy intervention. To compare our results to historical data, the difference in the proportion of patients experiencing mortality and the corresponding 95% confidence intervals will also be reported at 14 days, 30 days, 3 months, 6 months, and one year following radiotherapy. We acknowledge that we do not know how many patients may benefit from radiotherapy since the mortality rate is currently improving with better management. In addition, as the COVID-19 vaccine is further introduced, the mortality rate is likely to decrease as vaccinated patients may experience less severe infection. However, since developing countries may experience a delay in vaccination and may not have the resources to treat infected patients effectively, LDWLRT may

still be an effective treatment. Secondary analysis will be conducted using the Kaplan-Meier method in subgroups of patients categorized by respiratory status (patients not requiring oxygen, patients requiring low-flow oxygen , and patients requiring high-flow oxygen or non-invasive ventilation) and by ethnicity (Africans, Latinos, other). In addition, the Cox proportional- hazards model will be used to estimate crude and adjusted hazard ratios and 95% confidence intervals with ethnic group and patient respiratory status modelled as categorical exposure variables. The adjusted model will include tentative confounders including age, comorbidities, and history of smoking and alcohol consumption. Additional analysis using the Kaplan- Meier method will also be conducted for time to recovery as a second endpoint. Mixed ordinal logistic and Cox proportional-hazards regression models with an autoregressive correlation structure for repeated measures will be used to examine the association of patient inflammatory status using biomarkers with respiratory status and time to recovery, respectively [44]

4.10 Ethical aspects

No financial compensation will be provided to patients who participate in the project. The protocol needs to be approved by the IRB of the participating institutions or the local Government Agency of the country responsible for overseeing trials. Informed consent in the local language or translated through a competent translator must be signed by the patient, or POW or family members if the patient is unable to consent.

5. Results

Patient recruitment is underway at a Mexican institution as per protocol. Another institution in Canada is scheduled to recruit patients in May 2021 pending IRB approval. The preliminary results will be used to apply for funding. All recruited patients should have their medication, and, clinical data, including side effects and complications, recorded, encrypted, and stored in a cloud-based computer system. The clinical data will be monitored by an independent research company specialized in international clinical trials, which is figured in the grant budget. A template to record patient data will be sent to all participating institutions for standardization of data collection

6. Discussion

Aging is associated with a chronic inflammatory state. In comparison with younger patients, older adults have significantly increased levels of inflammatory biomarkers, such as IL-6, CRP, and TNF-α, in the absence of infection. [45]. Among older adults aged 65 and above, those who had an elevation of the inflammatory cytokines were frail in comparison with their healthy counterparts [46]. In the Cardiovascular Health Study involving 4735 adults aged 65 years and above, frail patients not only displayed elevated CRP but also had significantly higher levels of the coagulation factors, VIII and D dimer, as compared with non-frail patients [47]. Elevation of IL-6 and CRP has also been reported among older adults with limited morbidity as compared with those with normal physical activity [48]. As a result, frail patients are at risk of increased thromboembolism, leading to stroke and cardiovascular disease. Not only does this chronic inflammation lead to limited physical activity, but it also results in psychomotor slowing [49]. The mechanism underlying chronic inflammation in older patients is complex and postulated to be due, in part, to the accumulation of senescent cells in every organ which are generally cleared in younger individuals [50].

Thus, it is not surprising that coronavirus infection induces a hyper-inflammatory state among older patients as compared with younger patients, leading to multiple organ failure. It may also explain why African and Latino Americans have a higher mortality rate in comparison with Caucasians. It is currently hypothesized that the high mortality rate may be due to co-morbidity factors that are prevalent among these two minorities [51]. As an illustration, a 70.6% mortality rate has been reported following hospital admission for COVID-19 in African Americans [52]. These patients had a higher rate of obesity, diabetes mellitus, hypertension, and chronic renal failure as compared with their Caucasians counterparts. However, the influence of genetic factors on mortality could not be excluded since biomarker studies have demonstrated a higher level of systemic inflammation among African

Americans as compared with Caucasians. A significantly higher level of IL6, CRP, fibrinogen, and E-selectin have been reported in fasting blood serum from African Americans [53,54]. This chronic elevation in biomarker levels has also been reported among Mexican immigrants to the US and in Porto Ricans. In a study in 6652 American children, CRP blood levels were significantly higher among children of African and Latino descent as compared with those of Caucasians descents [55]. Among Americans whose parents immigrated from Mexico, the levels of IL6, CRP, and TNFα increased progressively and were the highest in the third generation as compared with the previous generations [56]. Among Latino Americans, Porto Ricans have the worst inflammatory profile [57]: thus, our study may be able to distinguish the contribution of co-morbidities and ethnicity to the mortality rate through the respective inflammatory biomarker profile.

Our study also emphasizes that rapid radiotherapy intervention should be started as soon as the patient is admitted to the hospital in order to avoid deterioration of their clinical status and circumvent respiratory failure and artificial ventilation, which are associated with a high mortality rate (26-61%) [3,58,59]. Recently, the Recovery Trial (www.recoverytrial.net) from the United Kingdom reported a significant reduction in the mortality rate among patients who required artificial ventilation or oxygen after administration of low-dose dexamethasone (6 mg for 10 days) for COVID-19 pneumonia [6]: however, for patients who did not require oxygen, the medication showed no benefit. For these patients, our trial may demonstrate a benefit of LDWLRT on the mortality rate since it is very well tolerated [36] and has little morbidity based on preliminary results from various institutions [35-39]. We will also evaluate the time to recovery in accordance with the remdesivir trial, which reported a reduction in recovery time among patients not on oxygen. If our study demonstrates a similar decreased rate of hospitalization, we may consider a future randomized trial comparing LDWLRT with remdesivir, since this medication is expensive and may not be a good fit for developing countries. According to Gilead Science which produces this medication, remdesivir will cost 520 dollars per vial, or 3,120 dollars per treatment course, for patients with private insurance. For those with government-sponsored insurance or for countries with a national health-care system, the price will be 390 dollars per vial or 2,340 dollars per treatment course. Time to recovery also allows us to determine whether LDWLRT can reduce ICU admission among patients who do not require oxygen or who are on oxygen but do not require artificial ventilation. Should our study demonstrates a reduction in ICU admission of these patients, our intervention may not only be lifesaving but also cost-effective [60].

Our study may also be able to correlate the patient inflammatory status to their recovery following viral infection. Even in patients who developed mild symptoms and did not require hospital admission, up to 35% experienced chronic fatigue preventing them from resuming normal physical activity [61]. Indeed, prolonged chronic fatigue for up to 20 months has been reported in previous Severe Acute Respiratory Syndrome (SARS) infection and is currently being described after COVID-19 [62]. Among the 143 patients who were hospitalized for COVID-19 in a recent study, 55% still experienced chronic fatigue at the last follow-up [63]. It is postulated that the persistence of inflammatory cytokines in the central nervous system may be the cause of this prolonged convalescence.

In this case, anti-inflammatory medication and physical therapy may accelerate their recovery. In summary, this international research cooperation may be able to investigate many factors that may influence the mortality rate among patients with COVID-19 pneumonia besides the anti-inflammatory effect of LDWLRT.

7. Conclusion

We postulate that the mortality rate of older patients after corona-virus infection may be due to their baseline chronic inflammation in contrast to younger patients. In addition, the high death rate among African and Latin Americans may also be related to their increased baseline inflammatory status as compared with that of Caucasians. Early treatment of COVID-19 patients with LDWLRT may improve the mortality rate through the modulation of inflammatory cytokines, and may be cost-effective in comparison with

medications such as remdesivir.

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