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Mini Review

Frailty in the COVID-19 Pandemic and the Potential of Stem Cells

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ABSTRACT

The concept of frailty is common knowledge but it is a relatively new scientific discipline due its extensive study in the last two decades [1]. Measured in terms of the accumulation of deficits/ Frailty Index (FI) approach or the frailty phenotype/ syndromic approach, the results of frailty are adverse health outcomes and innumerable challenges to health care resources and health systems including emergency room visits, hospitalization and institutionalization [2, 3]. The ongoing COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has imposed unprecedented pressures on the current health care systems globally [4]. There have been several indications of a connection between frailty, and COVID-19 and associated co-morbidities. In this direction, several clinical trials against COVID-19 have shed significant focus on frailty metrics. One of the common connections in clinical trials addressing frailty and those that address COVID-19 is the therapeutic potential of stem cells. Hence, this mini-review discusses the frailty in the clinical context of COVID-19, related clinical trials, and the promise of stem cells in addressing frailty.

Note: National Clinical Trial (NCT) Identifiers mentioned in parenthesis in the following text.

INTRODUCTION

Although most patients (~ 81%) infected with COVID-19 show clinically mild symptoms, an alarming percentage manifests severe (14%) to critical symptoms (5%) requiring hospitalization [5]. Among patients infected with COVID-19, although a small percentage have pre-existing co-morbidities (25%), a significant percentage of these patients require hospitalization (60- 90%) [5]. A rise in multimorbidity, polypharmacy, and certain ethnicities are associated with a being more prone to developing COVID-19 [6]. Comorbidities and age predict mortality in COVID-19 [7]. Since frailty and co-morbidities are strongly interlinked [8], providing optimal health care to frail patients during the current circumstances has become both a priority and a challenge. An in-depth understanding of the inter-relationship between COVID-19 and frailty, and knowing how stem cells can be harnessed as a common solution to both problems, would assist in better disease management, decision making and utilization of health care resources while reducing the burden on health systems (Figure 1).

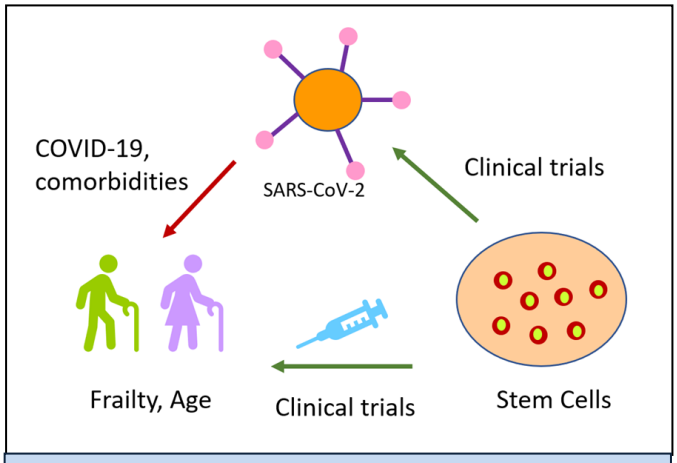

Figure 1: Stem Cells show promise in therapeutic developments against COVID-19 and frailty.

Inferences from Clinical and Hospitalization Data

Several studies have tried to look at outcomes of COVID-19 in frail patients, widely categorized on the basis of the Clinical Frailty Scale (CFS), where patients having CFS ≥5 are considered frail [9]. An observational cohort study from hospitals in UK and Italy (n= 1564 COVID-19 patients) suggested that patients with CFS ≥5 had a longer length of stay at the hospital and higher mortality compared to those below CFS 5, with both outcomes increasing with progressive frailty [4]. A retrospective, singe- centre observational study (n= 48) from Belgium showed that CSF was independently associated with mortality in COVID-19 patients [10].

A similar prospective observational cohort from Italy (n= 105) showed that FI was an independent predictor of ICU admission or in- hospital mortality [11]. Frailty, categorized by the FRAIL scale, was also associated with a higher risk of developing severe disease among COVID-19 positive frail patients (n= 114), as shown by a study in China [12]. On the contrary, a retrospective, single centre cohort study using electronic records in a hospital in UK (n= 1071 patients, both COVID-19 positive and negative) showed that CSF had little incremental contribution to mortality in patients hospitalized due to COVID-19 [13]. Similar results were reflected in another prospective study in UK (n= 217 COVID-19 positive, 160 COVID-19 patients) [14].

Clinical trials on frailty

Several COVID-19 clinical trials have focused on frailty. In one clinical trial from Canada (NCT04392115), one of the secondary outcomes is the measure of Clinical Frailty Scale (CFS) which provides a global assessment of frailty. In this study, CFS will be measured from baseline to 12 monthly scores for participants who are subjected to exercise intervention against COVID-19. Another clinical trial from Italy aims at developing a tool to measure frailty to determine if that is a superior way to predict clinical states than age and comorbidity for COVID-19 patients (NCT04412265). In the United Kingdom, a clinical trial will be measuring changes in frailty and quality of life scores in COVID-19 patients to identify prognostic markers (NCT04459351). Another United Kingdom-based clinical trial will be measuring frailty in lung cancer patients to understand the impact of COVID-19 on them (NCT04538456). Important features of the above clinical trials are presented in Table 1.

Table 1: Clinical Trials focused on frailty and COVID-19.

Identifier	Title	Size and Type	Conditions	Intervention
NCT04392115	The PREPARE for COVID Trial	372, Interventional	Comorbidities and Coexisting Conditions, Social Isolation	Behavioural, estimate effectiveness of remotely-supported exercising for aged
NCT04412265	Frailty in Elderly Patients With COVID-19 (FRA-COVID)	300, Observational	COVID related pneumonia	tool built to measure frailty in elderly COVID-19 patients
NCT04459351	PHenotyping patiENts Admitted to Hospital With cOvid-19 Infection and idenTifYing Prognostic markErs (PHENOTYPE)	500, Observational	COVID-19 infection	evaluate respiratory, cardiac, renal and psychological outcomes of patients, analyse severity
NCT04538456	Impact of COVID-19 on Lung Cancer Patients	800, Observational	non-small cell lung cancer (NSCLC) or SCLC	physical, social and psychological impact of COVID-19 on frail patients

Promise of cellular potency of stem cells in addressing frailty

To address the concerns of frailty in disease, one of the promising approaches has been the use of stem cells. The multipotency and pluripotency of stem cells have enabled their applications in several therapies including those against frailty. Regenerative therapies have been proposed to ameliorate frailty because patients with frailty show changes and abnormal functioning of stem cells [15]. Further, age causes a

reduction in the capacity of stem cells to self-renew, maintain, and regenerate. In this direction, Mesenchymal Stem Cells (MSCs) show certain characteristics that empower them to combat frailty-related issues. MSCs have anti-inflammatory and immunomodulatory functions. They are attracted to locations of injury to mitigate inflammation and aid in cellular repair through various mechanisms, such as by secreting anti-inflammatory chemokines and cytokines like transforming growth factor beta, Il-10 and prostaglandin E2, and transcriptionally through Heme Oxygenase-1 and Inducible T Cell Costimulator Ligand, to name a few (https://www.nature.com/articles/s41536-020-00105-z)These properties of stem cells can be important in harnessing them for COVID-19 therapies. This is because MSCs reduce the levels of proinflammatory cytokine and an inflammation marker in cardiomyopathies [15], which constitute a major group of comorbidities in COVID-19 [16]. In the context of frailty, a clinical trial NCT02065245 reported that intravenous delivery of allogeneic MSCs to aged and frail participants, caused significant benefits to physical performance and levels of inflammatory biomarkers [17]. In this randomized, double-blinded study, patients were injected with placebo or two doses (100 and 200 million) or allogenic MSCs and followed-up for six months. Frailty, measured through the 6 Minute Walk Test (6MWT) and Short Physical Performance Battery (SPPB) showed significant improvement in patients treated with MSCs. Immune biomarkers also showed improvement, especially a significant decrease in the CD8 T- cell marker, whose increase is observed during ageing. The CRATUS study also aims to explore the safety and efficacy for using MSCs for reversing frailty [18]. Consisting of a non-blinded phase I and a blinded, randomized phase I/II, the study focuses on the changes in symptom-related quality of life, improvement of cardiovascular status, endothelial function, decrease in inflammatory biomarkers and 1 year survival. As these parameters are grossly affected in COVID-19 infection and even more so in frail adults, the results of this study would shed light on the relevance of stem cell therapy in the current pandemic and its benefits, especially in the frail/ vulnerable population. The observations also supported that MSCs are safe therapeutic options, and further support their potential for therapies against frailty, whose benefits can be extended to anti-COVID-19 therapies. Although, challenges like stability, cost, accessibility, and maintenance of desired biological characteristics of the stem cells remain long term challenges [19]. However, the overall observation of the anti-inflammation roles of stem cells and promise in clinical trials against frailty indicate their benefits towards therapies against COVID-19 where abnormal upregulation of immune response and cytokine storm are seen.

CONCLUSION

Considering the contextual nature of the different methods of frailty assessments and the lack of sufficiently large studies on outcomes in COVID-19 infected frail patients, it is difficult to conclude how strongly frailty predicts patient outcomes. However, since frailty is an established risk factor in health care resource utilization [3], prevention of frailty is of paramount importance in order to ease an already strained health care system due to COVID-19 [20]. As suggested by the SAVE model, frailty progression can be delayed during the current pandemic using Socialization (social media, telephone or video calls), Adequate nutrition, Vitamin D and Exercise [20]. In the context of nutrition, obesity and diabetes are prominent co-morbidities for COVID-19, hence care needs to be taken for nutritional and food processing-related measures against COVID-19 [21]. Similar multi-dimensional frailty prevention/ reversal strategies suggested during the pre- COVID-19 era could also be useful if tailored to the current circumstances, including physical activity, nutrition, cognitive training, prehabilitation, home modifications, psycho-social intervention/ support and geriatric evaluations and management [22-24]. Further studies like Woolford et al., infer that more investigation is needed to assess the prognostic value of frailty and multimorbidity for detrimental clinical conditions resulting from a previous disease or injury. Their inference is based on a study on 4510 participants where 1326 are COVID-19 positive and 3184 are negative [25]. In addition to the above, in the near future, MSC therapies might play an equally, if not more important role in the management of frail individuals. On one hand, MSCs would be preventive in reducing/ reversing frailty in individuals unaffected by COVID-19. On the other hand, in frail patients infected with COVID-19, MSC therapy would play a dual role- the therapeutic alleviation of systemic inflammation and cardiovascular symptoms associated with

COVID-19 (32200663), as well as the simultaneous preventive role in reversal of the frailty phenotype. However, a more detailed understanding of the connection between frailty, COVID-19, and its associated co-morbidities are required to better inform ongoing research on anti-COVID-19 therapies using MSCs.

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