Impact of COVID-19 on Fatigue and Exercise Capacity in Patients Treated at a Dedicated COVID Hospital

Chhaya V Verma¹, Sayali D Mhatre²*, Anagha N Mangaonkar², Mala V Kaneria³, Ramesh N Bharmal⁴

Abstract

Objectives: COVID-19 is an ongoing pandemic of highly contagious respiratory disease caused by the novel corona virus SARS-CoV-2. Along with fever and respiratory symptoms of dyspnea and dry cough, musculoskeletal symptoms like fatigue, myalgia have also been reported. COVID-19, primarily affecting the lungs, takes a toll on the exercise capacity. The aim is to study the impact of COVID-19 on fatigue and exercise capacity.

Methods: Seventy five stable adult inpatients who tested positive for COVID-19 on RT PCR were recruited. Serum CPK and CRP levels were recorded. Patients rated their level of fatigue on Fatigue Assessment Scale (FAS) and were then asked to perform the One Minute Sit to Stand test (1MSTS). Pearson’s correlation coefficient (r) was used to test the correlation of fatigue with serum CPK, serum CRP and exercise capacity respectively.

Results: Mean level of fatigue rated on FAS was 16.90±4.36. Serum CPK levels were observed to be raised in 8% of the patients with a mean level of 106.34±65.52 IU/L. Raised CRP levels with a mean of 48.61±30.20 mg/L were observed in 98.66% patients. Mean number of repetitions completed during the 1MSTS were 17.69±6.00 repetitions. A significant positive correlation of FAS score with Serum CPK and CRP levels respectively was observed (p value <0.01) and a significant negative correlation was observed (p value <0.01) between FAS score and number of repetitions completed during 1MSTS.

Conclusion: Fatigue showed a significant positive correlation with Serum CPK and Serum CRP levels and a significant negative correlation with exercise capacity.

Introduction

COVID-19 is an ongoing pandemic of respiratory disease caused by the novel corona virus SARS-CoV-2. This highly contagious disease presents with early symptoms of upper respiratory tract affection like fever (84.49%), dyspnea (22.3%), dry cough (56.39%) or cough with expectoration (20.72%) due to a strong affinity of SARS-CoV-2 with ACE-2 receptors in the lungs.¹ Musculoskeletal symptoms like fatigue, myalgia have been proved to be prevalent in patients with COVID-19.²

The Oxford English and Spanish Dictionary defines fatigue as “extreme tiredness resulting from mental or physical exertion or illness”. Evidence has shown that SARS-CoV-2 activates adaptive and immune responses leading to uncontrolled inflammatory changes which ultimately cause a cytokine storm. These pro-inflammatory changes compromise the oxygen delivery to the tissues causing fatigue and myalgia.³ Additionally, fatigue is said to occur as a result of changes in high-energy phosphates (i.e., ATP and ADP) and accumulation of by-products of rapid energy metabolism. An imbalance in the ATP/ADP ratio is responsible for elevated level of CPK causing lack of ATP production which leads to anaerobic metabolism. Literature has shown that excessive accumulation of lactic acid, a by-product of anaerobic metabolism, is one of the prime reasons of fatigue.⁴ Similarly, inflammatory processes occurring as a result of cytokine storm with elevated levels of pro-inflammatory cytokines like CRP have been shown to be responsible for fatigue.⁵ The Fatigue Assessment Scale (FAS) has been proven to be the most promising patient rated outcome measure with good psychometric properties to assess fatigue. It is a 10 item self-reporting measure with 5 items reflecting physical fatigue and 5 reflecting mental fatigue. The scale gives a total score of 10-50 with each item scored on a 5 point Likert scale.⁶,⁷

A decline in the TLC (Total Lung Capacity) and subsequent reduction in exercise capacity in COVID-19 has been observed in early convalescence phase.⁸ Exercise capacity, defined as the maximum amount of physical exertion that a patient can sustain, improves the function of immune and respiratory systems in patients with COVID-19.⁹,¹⁰ First described by Koufaki et al in 2002, the One minute sit to stand test (1 MSTS) is an easy to administer, inexpensive, and space efficient test used to quantify exercise capacity.¹¹,¹² It is shows good efficacy in measuring the exertional desaturation commonly observed in COVID-19.¹³

Limited evidence is, however, available which highlights the impact of COVID-19 on fatigue and exercise capacity in patients with COVID-19. Hence, through this study, we aim to explore this relationship of fatigue and exercise capacity with COVID-19.

Methods

A cross-sectional, observational study was conducted at a 1047 bedded municipal tertiary care hospital dedicated to COVID-19 management in a metropolitan city. After seeking

¹Professor & Head, ¹Final Year Postgraduate Student, Physiotherapy School and Centre, ²Additional Professor and Unit Head, Department of Medicine, ³Dean, TNMC and BYL NCH, Mumbai, Maharashtra; ⁴Corresponding Author
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approval from the Institutional Ethics Committee (ECARP/2020/85), the study was registered with Clinical Trials Registry-India under CTRI/2020/09/027993. Written consent was obtained and 75 adult inpatients who tested positive for COVID-19 on RT-PCR were recruited using non purposive sampling over a period of 4 weeks. Stable patients fulfilling the discharge criteria practiced by the hospital were included in the study after consulting the treating physician. Patients were excluded if (i) they were on immune-compromising drugs, (ii) presence of cognitive impairment, and (iii) reported pre-existing neuromuscular disorders. Written Informed Consent of the patients fulfilling the eligibility criteria was obtained after which their demographic data was recorded along with the co-morbidities, symptoms, medications, serum CPK and serum CRP levels. The patients rated their level of fatigue on Fatigue Assessment Scale and were then asked to perform the One Minute Sit to Stand test under supervision as described in Figure 1.

Statistical analysis
The data was collected and statistical analysis was performed using SPSS version.24 (2016). Kolmogorov Smirnov test was used to test normality of the data. As the data of all the variables showed normal distribution, correlation of Fatigue Assessment Scale Score with Serum CPK, Serum CRP levels and One Minute Sit to Stand respectively was measured using Pearson’s correlation co efficient.

Results
A total of 75 patients were included in the study within the age group of 20-75 years with a mean age of 52.36±13.36 years. The study comprised of 72 males which accounted for 96% of the total sample, while females accounted to 4%. The patients were categorized into 3 categories (mild, moderate, and severe) based on severity of the disease at the time of admission by the treating physician. Out of the total sample, maximum patients (N=32, 43%) were classified under the moderate category, 38% (N=29) were classified as mild, while 19% (N=14) were classified under the severe category of affection. Patients in this study most commonly reported co morbidities in the form of Diabetes Mellitus (N=11, 14.66%) and Hypertension (N=16, 21.33%) whereas 13.33% (N=10) reported both. However, majority of the patients reported no co morbidities accounting to 48% (N=36) of the total sample.

Mean level of fatigue rated by the patients on Fatigue Assessment Scale was 16.90±4.36 with 89.33% (N=67) reporting ‘No Fatigue’ (FAS score: 10-21) and 10.66% (N=8) reporting ‘Fatigue’ (FAS score: 22-34). None of the patients reported a FAS score ≥ 35 indicative of ‘extreme fatigue’. Serum CPK levels were observed to be raised (> 200 IU/L) in 8% (N=6) of the patients with a mean level of 106.34±65.52 IU/L. However, raised CRP levels with a mean of 48.61±30.20 mg/L were observed in majority of the patients (98.66%, N=74). Mean number of repetitions completed during the One minute Sit to Stand test were 17.69±6.00 repetitions.

Fatigue Assessment Scale Score was correlated with Serum CPK, Serum CRP, and One minute sit to stand test respectively using Pearson’s Correlation Co efficient. A statistically significant positive correlation of FAS score with Serum CPK (r = 0.349) and CRP levels (r = 0.450) respectively was observed (p value < 0.01) as shown in Figures 2 and 3. A statistically significant negative correlation was observed (r = -0.320) between FAS score and number of repetitions completed during One Minute Sit to Stand test (p value < 0.01) as depicted in Figure 4.

Discussion
The COVID-19 pandemic has been a matter of international concern owing to its unpredictable and nonspecific nature of affection. A report from the Chinese Center for Disease Control and
10.66% reporting psychological as well as physical fatigue. The fatigue levels in this study positively correlated with serum CPK levels which was in conjunction with two researches conducted by Dahlstedt AJ et al (2000) and Marianne F et al (2012) who stated the primary reason of fatigue to be accumulation of lactic acid formed due to lack of regeneration of cellular ATP caused by elevated CPK. Elevated inflammatory biomarkers such as ferritin, interleukin-6 (IL-6) and C-reactive protein (CRP) were the commonly observed laboratory abnormalities associated with COVID-19. This can be attributed to the wide spectrum of pathogenetic mechanisms triggered by SARS-CoV-2 inclusive of cytokine storm, inflammatory and coagulation cascades. Higher CRP values (48.61±30.20 mg/L) were observed in majority patients in this study similar to a retrospective study wherein the epidemiological and clinical characteristics of COVID-19 were studied. Serum CRP levels of the patients in the present study showed a significant positive correlation with their perceived level of fatigue. Serum CRP is an indicator of pro-inflammatory activity. These inflammatory processes affect the central nervous system through cytokine effects causing fatigue. Furthermore, physical and psychological stressors activate the peripheral immune system which transduces peripheral inflammatory signals (pro-inflammatory cytokines) to the brain which eventually leads to perception of fatigue. The systemic inflammatory responses occurring as a result of COVID-19 infection pose a considerable burden on the cardiopulmonary system causing reduction in exercise capacity. The patients in the present study were able to complete an average of 17.69±6.00 repetitions on the One minute sit to stand test (1 MSTS) showing a decline in the exercise capacity when compared to the population based reference values given by A. Strassman (2013). The patient rated fatigue levels correlated negatively with their exercise capacity as measured by the repetitions performed during 1 MSTS. A similar finding was reported in a study wherein exercise capacity showed negative correlation with physical, cognitive and psychosocial dimensions of fatigue. Fatigue can cause an impact on exercise capacity...
due to increased work of breathing, insufficient regular physical activity, probable systemic inflammatory response, and muscle depletion and dysfunction. Additionally, patients with impaired peripheral muscle strength are more fatigued and demonstrate lower exercise capacity as compared to the patients without reduced peripheral muscle strength.

**Conclusion**

The present study conducted in patients with COVID-19 at a municipal tertiary care hospital dedicated to COVID-19 management explored the relationship of their perceived level of fatigue rated on the Fatigue Assessment Scale with their Serum CPK level, serum CRP level, and exercise capacity. Fatigue showed a significant positive correlation with Serum CPK and Serum CRP levels and a significant negative correlation with exercise capacity measured by the repetitions performed on the One Minute Sit to Stand test.

**Ethics approval and consent to participate**

The study was approved by the Institutional Ethics Committee (ECARP/2020/85) and a written consent was obtained from all the participants.

**Authors’ Contribution**

The concept and design of the study were given by CVV. She contributed in the data analysis as well as in the editing of the manuscript for intellectual content. SDM and ANM acquired the data and contributed in the analysis of the same and also drafted the manuscript. CVV, SDM and ANM contributed to the literature search. MVK has contributed to data acquisition and reviewing the manuscript along with CVV. All the authors have contributed in preparing and editing the manuscript for publishing. RNB is the guarantor of the study.

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**Abbreviations**

**SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2; RT-PCR: Reverse Transcription Polymerase Chain Reaction; COVID-19: Corona Virus Disease 19; FAS: Fatigue Assessment Scale; CPK: Creatinine Phosphokinase; CRP: C-Reactive Protein; 1 MSTS: One Minute Sit to Stand test**

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