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Elevated plasma CAF22 are incompletely restored six months after COVID-19 infection in older men

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ABSTRACT

Introduction: The long-term complications of COVID-19 appear as significant health problems. However, the long-term muscle decline in these patients is poorly characterized.

Method: We investigated the age-related muscle decline, termed sarcopenia, before and following the COVID-19 infection in older male patients (n = 87). We evaluated handgrip strength (HGS) and functional capacity (short physical performance battery; SPPB) in COVID-19 patients 7–42 days before and one week and 6-month after COVID-19 infection. We used ELISA tests to measure plasma c-terminal agrin fragment-22 (CAF22), c-reactive protein (CRP), and 8-isoprostanes as markers of degraded neuromuscular junctions, inflammation, and oxidative stress, respectively.

Results: Before the COVID-19 infection, 54 patients were non-sarcopenic, and 25 patients were sarcopenic, while eight patients subsequently developed sarcopenia. All patients exhibited reduced HGS and SPPB, while elevated CAF22, CRP, and 8-isoprostane levels one week post-COVID-19 infection (all p < 0.05). At six months post-COVID-19 infection, the HGS, SPPB, CAF22, CRP, and 8-isoprostanes were partly restored to baseline levels (all p < 0.05). Correlation analysis revealed that the plasma CAF22 had a significant correlation with HGS, SPPB, and COVID-19 disease severity. CAF22 also demonstrated significant areas under the curves in diagnosing sarcopenia at all three time-points.

Conclusion: Altogether, the muscle detriment due to COVID-19 persists six months post-infection, and plasma CAF22 may be helpful to detect muscle and functional decline in these patients. Timely evaluation and intervention of sarcopenia may be critical in COVID-19 treatment.

1. Introduction

Increased fatigue sensitivity and functional dependence are common occurrences in patients infected with SARS-CoV-2 infection, the cause of the ongoing COVID-19 pandemic. It is also clear that the COVID-19 infection survivors are at an increased risk of developing muscle weakness and wasting (de Andrade-Junior et al., 2021). A large proportion of these patients are older with susceptibility to age-related muscle detriment or sarcopenia (Parvatiyar and Qaisar, 2022). In addition, several lines of evidence suggest mutually adverse effects of sarcopenia and COVID-19 on each other. First, sarcopenia is associated with immobility and a sedentary lifestyle, increasing susceptibility to respiratory infections (Bone et al., 2017). Second, sarcopenic patients demonstrate poor respiratory capacity due to diaphragm dysfunction (Nagano et al., 2021), which increases the risk of developing COVID-19 infection. Third, age-related comorbidities, chronic diseases, and cancers are important risk factors for sarcopenia and COVID-19 infection (de Luzignan et al., 2020; Yang et al., 2019). Fourth, sarcopenia impairs systemic and local immune systems, which hampers the protection against infective diseases (Kitano et al., 2019). Considering this evidence, sarcopenic patients are likely to have severe phenotypes and longer duration of COVID-19 infection.

Several studies suggest skeletal muscle involvement in COVID-19 infection. For example, biochemical evidence of muscle injury (Mao et al., 2020), myalgia and dynapenia (Carod-Artal, 2020) are reported in patients with COVID-19. Additionally, several cases of COVID-19 report rhabdomyolysis as presenting or late complication during the disease (Casey et al., 2021). Reduced physical activity, hospitalization,
anorexia, and a sedentary lifestyle can further worsen the muscle decline in these patients, leading to physical dependency and disease exacerbation. Unfortunately, the assessment of sarcopenia phenotype is not fully integrated into clinical settings despite the robust association of sarcopenia with mortality and morbidity in several diseases (Arango-Lopera et al., 2013). Additionally, most studies on COVID-19 patients investigate acute sarcopenia, and the long-term effects of COVID-19 on sarcopenia phenotype are poorly known.

The instability of neuromuscular junction (NMJ) is a common finding in sarcopenia. Our previous work using mouse models and clinical data shows that NMJ degradation can induce and/or exacerbate sarcopenia phenotype (Qaisar et al., 2018; Qaisar et al., 2020a; Karim et al., 2022a). Specifically, the work in COPD patients indicates a robust association between NMJ dysfunction and muscle decline in sarcopenic men (Karim et al., 2021; Qaisar et al., 2020b). Due to the several clinical and pathological similarities between COPD and COVID-19 infection, NMJ degradation is likely found in COVID-19 patients with muscle decline.

NMJ disintegration involves proteolytic cleavage of neuronal agrin into smaller sub-fragments. The smaller sub-fragment termed C-terminal agrin fragment 22 (CAF22) is released into circulation and has emerged as a valuable marker of NMJ degradation and sarcopenia (Qaisar et al., 2021a). Specifically, we have reported that the higher plasma CAF22 level is robustly correlated with muscle weakness and severity of sarcopenia in older patients (Karim et al., 2022b). Our recent findings indicate an elevation of plasma CAF22 in COVID-19 patients, indicating potential NMJ damage (Qaisar et al., 2021b). In addition, the elevated plasma CAF22 was associated with muscle weakness and severity of COVID-19 infection in these patients. These findings indicate the biomarker potential of CAF22 in sarcopenia and disease severity in COVID-19 patients.

To date, the long-term complications of COVID-19 are increasingly being recognized. However, the data about the chronic progression of sarcopenia in COVID-19 patients is lacking. Owing to the potential coupling of sarcopenia with complications and/or severity of COVID-19 infection, there is a need to rigorously characterize the long-term progression of sarcopenia after recovery from COVID-19 infection. We thus sought to perform a dynamic evaluation of sarcopenia using muscle mass and strength parameters, functional capacity, and plasma CAF22 during disease progression in COVID-19 patients.

2. Methods

2.1. Study design & participants

We investigated 87 patients with COVID-19 infection at the University of Gomal Medical College, Dera Ismail Khan, Hayatabad Medical Complex, and Rehman Medical Center, Peshawar, Pakistan. The regional ethical committees at these university hospitals approved this study. All patients were 51—67 year-old males and provided written informed consent. The participants were initially recruited as healthy controls for an ongoing project investigating sarcopenia biomarkers but were followed up for this study after testing positive for COVID-19 infection. COVID-19 was detected using the real-time reverse transcription PCR method, as described elsewhere (Udagama et al., 2020). The data included biochemical assays, clinical and physical examination and was collected at three time-points, including 7–42 days before (mean = 22.5 days, median = 27 days), testing positive and at two time-points after testing negative for COVID-19. The two time-points included 2–13 days (mean = 6.7 days, median = 7 days) and 171–196 days (mean = 183 days, median = 185 days) after testing negative for COVID-19 infection and were labeled as post-1 w and post-6 m, respectively. Nine patients died of COVID-19 infection, and their data were discarded from this study. The scoring for COVID-19 disease severity was based on the pulse rate, blood pressure, breathing rate, body temperature, and levels of consciousness of patients (Son et al., 2021). Each clinical parameter was assigned a score ranging from zero to three, and the cumulative score of all parameters was used to describe disease severity. A selected number of patients were provided with medications, which include lopinavir or ritonavir (n = 46), azithromycin (n = 33), heparin (n = 42), dexamethasone (n = 68) and oxygen (n = 29). Before acquiring COVID-19 infection, all patients were healthy and had no history of acute or chronic diseases, organ failure, major surgeries, or prolonged bed rest within the past eight weeks. This study was conducted under the declaration of Helsinki (World Medical, 2013).

2.2. HGS and body composition

We used a handgrip meter (CAMRY, South El Monte, CA, USA) to measure HGS, as described previously (Qaisar et al., 2020b; Qaisar et al., 2020a). Bioelectric impedance analysis was used to measure body composition, including appendicular skeletal muscle mass (ASM) (RENPHO, Dubai, UAE), which was divided by the square of the height to get appendicular skeletal muscle mass index (ASMI), as described elsewhere (Qaisar et al., 2020b).

2.3. Definition of sarcopenia and the measurement of physical performance

Sarcopenia was defined according to the criteria set by the European Working Group on Sarcopenia in Older People (EWGSOP2), including HGS ≤ 27 kg, ASM ≤ 7 kg/m², and gait speed ≤ 0.8 m/s (Sobestiansky et al., 2019; Cruz-Jentoft et al., 2019). We used the short physical performance battery (SPPB) score to assess physical capacity. This battery comprises three timed tests: 4-m walking speed (4MWT), balance, and standing from sitting position five times (5-STS). Each trial was assigned a score ranging from zero (worst performers) to four (best performers), based on the timed results, as described elsewhere (Landi et al., 2007).

2.4. Measurement of circulating biomarkers

We used ELISA to measure 8–isoprostanones (Cayman Chemical, Ann Arbor, MI, USA) and C–reactive protein or CRP (R&D Systems, Minneapolis, MN, USA) levels and biochemical assays to measure creatine kinase levels, as described previously (Qaisar et al., 2020a). Plasma CAF22 levels were measured according to the manufacturer’s instructions (NTCAF, ELISA, Neuroutine, Schlieren-Zurich, Switzerland), as described previously (Karim et al., 2022b).

2.5. Statistical analysis

Anthropometric measurements of the participants were presented using mean and standard deviation. Pearson correlation was used to determine the strength of the relationship between plasma CAF22 levels and various parameters. The receiver operating characteristics (ROC) analysis was used to measure the areas under curve (AUC) for the diagnostic potential of CAF22 in sarcopenia. Data were analyzed using GraphPad Prism 8, and the p-value < 0.05 was statistically significant. GraphPad Prism v.8.0 was used for all statistical analysis.

3. Results

3.1. Characteristics of the participants

The primary characteristics of the COVID-19 patients are summarized in Table 1.

At baseline, 62 patients were non-sarcopenic, and 25 patients were sarcopenic. During the course of the disease, eight patients developed sarcopenia and were labeled as acquired sarcopenics. Before acquiring COVID-19 infection, sarcopenic patients had lower BMI and percent body fat than non-sarcopenic patients (both p < 0.05). However, COVID-19 infection did not alter the BMI and percent body fats. The proportion
Table 1

| Body composition, clinical parameters, and plasma biomarkers according to sarcopenia status in patients with COVID-19 infection before (A, B, and C) and one week (D, E, and F) and six months (G, H, and I) after acquiring COVID-19 infection (n = 87). Values are expressed as mean ± SD, one-way analysis of variance. * and ** p < 0.05 vs. pre- and post-1 w in the same group according to sarcopenia status. $ p < 0.05 vs. non-sarcopenic group at the same time-point. (BMI: body mass index, CRP; c-reactive protein).

| Age at baseline (years) | Pre | Post-1 w | Post-6 m |
|------------------------|-----|----------|----------|
| 59.2 ± 5.8             | 59.2 ± 5.8 | 59.8 ± 5.9 |

| Body composition BMI (kg/m²) | No sarcopenia | Acquired sarcopenia | Sarcopenia | Percent fat |
|------------------------------|---------------|--------------------|-----------|-------------|
| 25.17 ± 2.95                 | 24.38 ± 2.48  | 22.77 ± 2.95       | $           |             |
| 22.74 ± 2.81 $               | 22.33 ± 2.42  | 22.82 ± 2.69       | $           |             |

| Clinical data | Co-morbidities, n (%) | Acquired sarcopenia | Sarcopenia | Pre-Post-1 w Post-6 m |
|---------------|-----------------------|--------------------|-----------|----------------------|
| No sarcopenia  | 14 (22.6)             | $                  | 44.3*     |                     |
| Acquired sarcopenia | 5 (62.5)     | 38.5 179.7 ± 44.3* | 47.6 171.2 ± 44.3* |                     |
| Sarcopenia    | 11 (44)               | $                  | 58.3      |                     |

| FEV1% (predicted) | No sarcopenia | Acquired sarcopenia | Sarcopenia |
|-------------------|---------------|--------------------|-----------|
| 97.1 ± 1.6        | 96.3 ± 2.1    | 96.1 ± 2.4         | $         |

| Length of hospital stay (days) | No sarcopenia | Acquired sarcopenia | Sarcopenia |
|--------------------------------|---------------|--------------------|-----------|
| 9.5 ± 2.4                    | 11.7 ± 2.7    | 17.3 ± 2.9$        | $         |

| Plasma biomarkers 8-Isoprostanes (pg/ml) | No sarcopenia | Acquired sarcopenia | Sarcopenia |
|-----------------------------------------|---------------|--------------------|-----------|
| 75.3 ± 19.6                             | 108.4 ± 34.8* | 93.6 ± 18.9#       | $         |
| 81.7 ± 17.5                             | 97.4 ± 23.5   | 95.3 ± 19.3        | $         |
| 104.7 ± 21.2                            | 129.7 ± 19.7* | 114.3 ± 20.9#     | $         |

| CRP (mg/l) | No sarcopenia | Acquired sarcopenia | Sarcopenia |
|-----------|---------------|--------------------|-----------|
| 2.19 ± 0.37 | 2.88 ± 0.53* | 2.79 ± 0.43#       | $         |
| 2.09 ± 0.28 | 3.02 ± 0.63* | 2.89 ± 0.49#       | $         |
| 2.78 ± 0.49| 3.65 ± 0.59* | 3.14 ± 0.44#       | $         |

| Creatine kinase (IU/l) | No sarcopenia | Acquired sarcopenia | Sarcopenia |
|------------------------|---------------|--------------------|-----------|
| 157.5 ± 38.5           | 179.7 ± 47.6  | 171.2 ± 41.1       | $         |
| 194.3 ± 49.9           | 255.4 ± 54.3* | 219.3 ± 42.3* #    | $         |

| Sarcopenia | 211.4 ± 58.3 | 249.5 ± 44.3* | 184.3 ± 39.3*#

 experi of patients with co-morbidities in sarcopenic vs. non-sarcopenic patients, while the spirometry performance was similar among the three groups and was not affected by the COVID-19 infection. Conversely, the presence of sarcopenia at baseline was associated with a longer stay in the hospital (p < 0.05) (Table 1). We next asked whether the deterioration in generalized health status and the muscle integrity by COVID-19 infection persist for a prolonged duration. We measured the circulating markers of oxidative stress (8-isoprostanes) and systemic inflammation (CRP) as the measures of generalized health and creatine kinase as the marker of muscle integrity in the study population. At the onset of COVID-19, sarcopenic patients had higher 8-isoprostanes, CRP, and creatine kinase than the non-sarcopenic patients (all p < 0.05). COVID-19 infection elevated the plasma 8-isoprostanes and CRP in the sarcopenic and non-sarcopenics group at one week and six months post-infection (all p < 0.05). However, the sarcopenic patients still demonstrated higher 8-isoprostanes and CRP levels than non-sarcopenic patients at both time points following the COVID-19 infection (all p < 0.05) (Table 1). Patients who acquired sarcopenia following COVID-19 infection also reported an elevation in CRP following COVID-19 infection, which remained elevated six months after the infection. Further, plasma creatine kinase levels were higher in sarcopenic vs. non-sarcopenic patients at all time-points irrespective of the COVID-19 status. The COVID-19 infection did not alter the plasma creatine kinase in non-sarcopenic groups but induced a significant elevation in the patients who had sarcopenia at baseline or developed sarcopenia following COVID-19 infection (all p < 0.05) (Table 1).

3.2. Alterations in plasma CAF22, indexes of sarcopenia, and functional capacity following COVID–19 infection

We next evaluated plasma CAF22, ASMI, HGS, gait speed, and SPPB scores as markers of sarcopenia and functional capacity during the COVID–19 infection. Plasma CAF22 levels were significantly elevated one week following the COVID-19 infection and remained elevated at six-month time-point, albeit with partial reduction (all p < 0.05) (Fig. 1A). One week following the COVID-19 infection, HGS was significantly reduced, but this alteration was not observed at six-month time-point (Fig. 1B). We also observed an increase in gait speed six months following COVID-19 infection (p < 0.05) (Fig. 1C). COVID-19 infection did not affect the ASMI and relative proportion of sarcopenic patients in the study population (Fig. 1D and E). We observed a reduced performance on all three SPPB indexes, including balance, 4MWT, and 5-STS, one week following the COVID-19 infection (all p < 0.05) (Fig. 1F). However, at six months, the performance on 4MWT and 5-STS was not different than baseline in the study population (Fig. 1F).

3.3. Alterations in plasma CAF22 and the indexes of sarcopenia according to sarcopenia status

We next investigated the plasma CAF22, ASMI, HGS, and gait speed according to sarcopenia status. All patients were divided into three categories, including sarcopenic, non-sarcopenic, and the patients who acquired sarcopenia during the disease course of COVID-19. Before the onset of COVID-19 infection, plasma CAF22 levels were similar among the three groups. Only the sarcopenic group showed a significant elevation of plasma CAF22 following COVID-19 infection, when compared to baseline and the non-sarcopenic groups (all p < 0.05). CAF22 levels were partially reduced at six months but were still significantly higher than the pre-COVI-19 levels (Fig. 2A).

The patients in the non-sarcopenic group had higher HGS than the sarcopenic patients at baseline, which was reduced one week after COVID-19 infection, and incomplete restored at the six-month time-point (Fig. 2B). Conversely, ASMI and gait speed was not affected by the sarcopenia status and COVID-19 infection (Fig. 2C and D).

3.4. Association of plasma CAF22 with COVID-19 disease severity

We next asked if plasma CAF22 can predict the disease severity of COVID-19 infection. The sarcopenic patients had more severe diseases than the non-sarcopenic patients (p < 0.05) (Fig. 2E). The correlation analysis between COVID-19 severity scores and plasma CAF22 at three time-points revealed significant associations between the two parameters (p < 0.05) (Fig. 2F–H). However, the most robust association of COVID-19 severity score was found with plasma CAF22 at six months after the recovery from COVID-19 (r² = 0.217, p < 0.001) (Fig. 2H).
< 0.001) (Fig. 3B) and six month ($r^2 = 0.258$, $p < 0.001$) (Fig. 3C) after acquiring COVID-19 infection. We also found relatively less robust but statistically significant associations of plasma CAF22 with SPPB scores at baseline ($r^2 = 0.159$, $p = 0.002$) (Fig. 3D) and one week ($r^2 = 0.101$, $p = 0.014$) (Fig. 3E) and six month ($r^2 = 0.142$, $p = 0.003$) (Fig. 3F) after acquiring COVID-19 infection. We next generated ROC curves to...
measure the sensitivity and specificity of plasma CAF22 in diagnosing sarcopenia. We observed significantly higher ROC curves at all three time-points, including baseline (AUC = 0.824, p < 0.001, 95% C.I = 0.731–0.915) (Fig. 3G) and at one week (AUC = 0.832, p < 0.001, 95% C.I = 0.741–0.933) (Fig. 3H) and six months (AUC = 0.803, p < 0.001, 95% C.I = 0.699–0.907) (Fig. 3I) following COVID-19 infection.

4. Discussion

The major finding of this study is a persistent elevation of plasma CAF22 and sarcopenia phenotype six months after COVID-19 infection. An elevated plasma CAF22 level was associated with higher disease severity, muscle decline, and functional dependency in COVID-19 patients. Additionally, plasma CAF22 may be a potential biomarker to predict sarcopenia and functional capacity in COVID-19 patients. Lastly, the presence or development of sarcopenia in COVID-19 patients was associated with more extended hospital stay, more severe disease phenotype, and elevated oxidative stress and systemic inflammation. The development and/or persistence of sarcopenia can induce significant long-term health problems in COVID-19 patients. Owing to the negative impact of sarcopenia on generalized health, an unnoticed and unattended muscle insufficiency may lead to exacerbation and/or death due to COVID-19 infection. Sarcopenia in COVID–19 seems to involve multiple pathogenic mechanisms (Welch et al., 2020). Among them, the disruption of muscle innervation may be of significant importance (Qaisar et al., 2021b). The elevated CAF22 levels in COVID-19 patients indicate NMJ disruption as a potential contributor to muscle wasting in COVID–19 infection. While definitive involvement of NMJ can be determined with electrophysiology and histology, our finding agrees with evidence of neuromuscular detriment in COVID–19 patients (Paliwal et al., 2020). Specifically, these patients present with development or exacerbation of myasthenia gravis (Muppidi et al., 2020). While the exact mechanisms of NMJ deterioration in COVID–19 remain elusive, several possible candidates emerge. For example, elevated oxidative stress has been implicated in the pathogenesis of COVID–19 (Cecchini and Cecchini, 2020). Our previous reports using animal models indicate the disruptive effects of oxidative stress on NMJ integrity (Blaskaran et al., 2020). Specifically, the NMJs show structural and functional defects in conditions of elevated oxidative stress, contribute to skeletal muscle atrophy and weakness. These findings are consistent with elevated oxidative stress in our patients following COVID–19. COVID–19 patients also present with heightened inflammation and increased expression of inflammatory cytokines (Udugama et al., 2020). The elevation of plasma CRP in our study cohort indicates systemic inflammation. Among the NMJ components, motor neurons are highly susceptible to inflammation-associated damage (Komine and Yamannaka, 2015), and it is possible that the NMJ deterioration in COVID–19 patients is partly due to systemic inflammation. In addition, molecular mimicry has been suggested to cause NMJ damage in COVID–19 patients (Paliwal et al., 2020).

The plasma CAF22 was only incompletely restored six months after COVID–19 infection, indicating reduced NMJ plasticity following COVID–19 infection. We have previously reported a dynamic association of plasma CAF22 with muscle strength and mass (Karim et al., 2022b). These findings suggest that plasma CAF22 can potentially mirror the alterations in NMJ integrity during health and disease. Specifically, age-related conditions such as COPD degrade the NMJs and elevate plasma CAF22, while pulmonary rehabilitation incompletely restores the NMJ integrity and plasma CAF22 (Karim et al., 2021). Importantly, these changes are partly mirrored by levels of plasma CRP and 8-isoprostane.

Fig. 3. Correlation of plasma CAF22 levels with HGS (A–C) and SPPB (D–F), and receiver operating characteristic (ROC) curves for plasma CAF22 in detecting sarcopenia (G–I) in patients with COVID-19 infection before (A, D, and G) and one week (B, E, and H) and six months (C, F, and I) after acquiring COVID-19 infection (n = 87). (CAF22; c-terminal fragment of agrin, HGS; handgrip strength, SPPB; short physical performance battery).
indicating the susceptibility of NMJs to systemic inflammation and oxidative stress. We found an incomplete reduction in plasma CRP and 8-isoprostanones, which were still higher than baseline levels. Thus, the elevated systemic inflammation and oxidative stress may account for reduced NMJ plasticity six months following COVID-19 infection. Direct toxicity of AChRs by COVID-19 has also been suggested as a membrane glycoprotein of COVID-19 can interact with nicotinic AChRs and induce their dysregulation (Lagoumintzis et al., 2021), which may contribute to the elevated CAF22 in these patients. However, the direct clinical manifestations of this interaction are not known.

The NMJ degradation may partly account for functional deterioration in COVID-19 patients. These patients present with muscle atrophy and weakness, which limit the performance of daily functional tasks. This is evident by low scores on SPPB after acquiring COVID-19 infection. This finding agrees with our previous reports showing an association between plasma CAF22 levels and SPPB scores in sarcopenic patients with co-morbidities (Karim et al., 2021).

The study has some limitations. The time intervals between the first measurements and the onset of COVID-19 varied across patients and extended up to 53 days. However, we are confident that these variations are not significantly affecting the slow, chronic process of sarcopenia.

We tried to minimize the time interval between the resolution of COVID-19 and the second measurements, although some variations exist. We could not perform similar measurements during the disease process. We did not take the muscle biopsies and cannot directly correlate plasma CAF22 levels with NMJ degradation. However, studies with isolated synaptosomes report a neurontropin-dependent cleavage of agrin into CAF22 with synaptic degeneration (Stephan et al., 2008). These findings boost our confidence in the potential association of elevated plasma CAF22 with NMJ degeneration in sarcopenic population. All patients were males, so we could not perform sex differences which play a role in sarcopenia status and the risk of acquiring COVID–19 infection (Peckham et al., 2020; Tay et al., 2015). 13 patients died during the study, and selective survival of the patients must be considered as any other cohort study. We cannot dissect out the potential contributions of a sedentary lifestyle and/or bedrest to elevated plasma CAF22 levels following the diagnosis of COVID-19 infection in these patients.

5. Conclusion and implications

This study indicates the potential contribution of NMJs degradation to sarcopenia and functional dependency in COVID-19 patients. In addition, the assessment of plasma CAF22 levels may be helpful to assess disease severity and physical capacity in COVID-19 patients. We also recommend a timely assessment and intervention of sarcopenia in older patients with COVID-19 infection. Further studies are required to investigate the molecular mechanisms of muscle loss in sarcopenic patients with COVID-19.

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CRedit authorship contribution statement

Asima Karim: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Rizwan Qaisar: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

Data is available from corresponding author upon reasonable request.

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