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Research Article

Effects of Eight-Week High-Intensity Interval Training Combined with Pomegranate Juice Supplementation on Intestinal Lipid Peroxidation and Visceral Fat Mass in Colorectal Cancer-Induced Laboratory Mice

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Abstract

Introduction: Dysregulation of lipid metabolism and increased lipid peroxidation are key contributors to colorectal cancer (CRC) progression. Considering the limited evidence on the combined effects of high-intensity interval training (HIIT) and pomegranate juice (PJ) supplementation in CRC, the present study aimed to evaluate the impact of an eight-week HIIT program combined with PJ supplementation on intestinal lipid peroxidation and visceral fat mass in CRC-induced laboratory mice.

Methods: In this experimental study, thirty-two male BALB/c mice (18–22 g, 8–10 weeks old) were induced with CRC via subcutaneous injection of 5×10^5 viable CT26 cells and randomly assigned to four groups: (1) CRC, (2) PJ, (3) HIIT, and (4) HIIT+PJ. To assess the effects of CRC itself, eight mice were allocated to a healthy control group (HC), and eight additional mice were included in a Sham group to evaluate culture medium effects. HIIT was performed five sessions per week for eight weeks, progressing from five high-intensity sets in week one to sixteen sets in week eight, at 75–90% of maximal running speed on a 15° incline. PJ supplementation consisted of 5% of the daily drinking water intake. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test ($P \leq 0.05$).

Results: Post-intervention body weight, visceral fat mass, and malondialdehyde (MDA) levels were significantly higher in the CRC group compared to HC ($P < 0.001$). In contrast, PJ, HIIT, and HIIT+PJ groups exhibited significantly lower body weight and visceral fat compared to CRC ($P < 0.001$). MDA levels were significantly reduced in HIIT and HIIT+PJ groups relative to CRC ($P < 0.05$). Moreover, post-intervention body weight, visceral fat mass, and MDA in HIIT and HIIT+PJ groups were significantly lower than in the PJ group ($P < 0.05$).

Conclusion: Both HIIT and PJ, individually and in combination, effectively improved body composition. However, HIIT alone or combined with PJ exerted more pronounced effects on reducing lipid peroxidation and enhancing body composition compared to PJ supplementation alone.

Keywords:
High-intensity interval training, Pomegranate juice supplementation, Body composition, Lipid peroxidation, Colorectal cancer

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1. Introduction

Colorectal cancer (CRC) is characterized by the abnormal and uncontrolled proliferation of epithelial cells in the colon or rectum. The global incidence of CRC is rising, with nearly two million new cases and approximately 900,000 deaths reported in recent years, making it the second leading cause of cancer-related mortality (Gonzalez-Gutierrez, 2024). Clinical studies have demonstrated that lipid peroxidation markers, such as malondialdehyde (MDA), are significantly elevated in CRC patients, highlighting the role of oxidative stress in intestinal tumorigenesis (Janion et al., 2020). Furthermore, review studies indicate that in obesity, increased visceral fat enhances reactive oxygen species (ROS) production and promotes lipid peroxidation in various tissues, including the intestine; these oxidized lipid products can induce inflammation, DNA damage, and cellular alterations, facilitating CRC development (Martinez-Useros et al., 2016; Gonzalez-Gutierrez, 2024). Meta-analyses also report a significant association between obesity or overweight and increased CRC risk (Ungvari et al., 2025).

Despite advances in surgical, chemotherapeutic, and radiotherapeutic interventions, CRC treatment remains financially burdensome and associated with high mortality. Exercise has emerged as a low-risk, cost-effective adjunctive approach that may contribute to CRC prevention and management. Evidence indicates that physical activity offers multiple benefits, including tumor growth suppression, improved overall survival, enhanced immune function, and reduced inflammation in CRC patients (Amirsasan, 2022; Jovanović, 2022).

Mechanistically, exercise can modulate oxidative status by improving insulin sensitivity and attenuating inflammatory responses. In conditions of obesity, visceral fat accumulation increases ROS generation and oxidative stress, promoting lipid peroxidation (Jovanović, 2023). Exercise, by stimulating energy expenditure, reducing visceral fat, and enhancing antioxidant capacity, can help restore weight balance and decrease oxidized lipid products. Among exercise modalities, high-intensity interval training (HIIT) is recognized for its time efficiency and potent metabolic effects, with multiple studies demonstrating its efficacy in improving body composition and reducing total and percentage body fat (Xu et al., 2025). Animal studies also show that high-intensity exercise can inhibit tumor cell growth and modulate gene expression related to oxidative resistance (Jee et al., 2022).

Recently, dietary supplements and plant extracts have gained attention as adjunctive CRC therapies due to their anti-inflammatory and antioxidant properties (Benedetti et al., 2023). Natural compounds, such as polyphenols and flavonoids, can inhibit cancer cell proliferation and activate apoptotic pathways (Seeram et al., 2005). Pomegranate juice (PJ) is particularly rich in punicalagin, ellagic acid, and antioxidant flavonoids (Banerjee et al., 2013). These compounds have demonstrated antitumor and anti-inflammatory effects in CRC models (Seeram et al., 2005; Banerjee et al., 2013). Animal studies reveal that PJ consumption reduces MDA production and lipid peroxidation in intestinal tissue (Banerjee et al., 2013) and enhances antioxidant enzyme activity, including SOD and GPx (Sohrab et al., 2015). In humans, regular PJ intake lowers oxidative markers and increases plasma antioxidant capacity (Sohrab et al., 2015; Benedetti et al., 2023).

Metabolically, PJ polyphenols may improve insulin sensitivity and lipid metabolism, contributing to weight regulation (Reguero et al., 2022). Evidence from animal models further indicates that PJ extract reduces inflammation in adipose tissue, decreases visceral fat stores, and improves energy balance (Al-Muammar, 2012; Reguero et al., 2022). Collectively, PJ exerts antioxidant, anti-inflammatory, and metabolic regulatory effects that can suppress lipid peroxidation and improve body composition (Benedetti et al., 2023).

The combination of exercise and antioxidant supplementation has been proposed as an adjunctive approach in CRC management, potentially mitigating oxidative stress, enhancing immune function, and reducing inflammation to inhibit tumor progression (Wu et al., 2025). Studies examining the combination of exercise and PJ in CRC indicate synergistic effects on reducing inflammatory markers in intestinal tissue (Omidiparsa et al., 2025). However, challenges such as differences in exercise intensity, supplement dosage and duration, and interindividual variability in treatment response may affect study outcomes (Reis et al., 2020). Therefore, the present study aimed to investigate the effects of HIIT combined with PJ supplementation on intestinal MDA levels and visceral fat mass in CRC-induced

2. Materials and Methods

This study was an experimental-basic research. A total of 40 male BALB/c mice, weighing 18–22 g and aged 8–10 weeks, were obtained from the Pasteur Institute of Iran and transferred to the Sports Physiology Laboratory at Islamic Azad University, Marvdasht Branch.

All experimental procedures were conducted in accordance with ethical guidelines for animal research based on the Helsinki Declaration. The animals were housed under standard environmental conditions, including a 12-hour light/12-hour dark cycle, ambient temperature of 22–24°C, relative humidity of 55–60%, and free access to water and standard rodent chow. Polycarbonate cages with washable surfaces were used, and sterilized wood shavings were applied to absorb moisture and excreta.

Colorectal Cancer Induction

CRC was induced using CT26 cells obtained from the Pasteur Institute of Iran. Once the cells reached confluence as a monolayer, they were trypsinized and washed three times. Cell viability and count were determined using trypan blue staining under a light microscope. Subsequently, each mouse received a subcutaneous injection of 5×10^5 viable CT26 cells in 150 µL of Hanks' solution into the right flank to induce tumor formation (Kurzejamska, 2019). Following confirmation of tumor development, mice were randomly assigned to four experimental groups:

1. CRC (diseased control)

2. Pomegranate juice supplementation (PJ)

3. High-intensity interval training (HIIT)

4. HIIT combined with PJ supplementation (HIIT+PJ)

For comparative purposes, 8 healthy mice were included in a healthy control group (HC). To evaluate potential effects of the culture medium, an additional 8 mice received injections of the culture medium alone and were designated as the Sham group.

High-Intensity Interval Training (HIIT) Protocol

Initially, mice underwent a one-week familiarization period with the treadmill. The maximal running speed of each mouse was subsequently determined. Animals were warmed up for 3 minutes at 10 m/min with a 5° incline, after which speed was increased by 3.3 m/min every minute until exhaustion. Exhaustion was defined as the mouse contacting the end of the treadmill three consecutive times within one minute. Following the test, mice were cooled down for 3 minutes at speeds below 10 m/min.

During the first two weeks, HIIT consisted of five sessions per week, each lasting 30 minutes. Each session began with a 10-minute warm-up at less than 50% of maximal speed, followed by 5 sets of 1-minute high-intensity running (>75% maximal speed) and 4 sets of 2-minute low-intensity running (<50% maximal speed), concluding with a 10-minute cool-down. From the second week onward, the protocol included 8 sets of 1-minute high-intensity running (85–90% maximal speed) and 7 sets of 1-minute low-intensity running. This regimen continued until the eighth week, with treadmill incline increased to 15° during weeks 6–8 to respect the principle of overload, and high-intensity sets gradually increased to 16 sets by week eight (Caru, 2019).

Pomegranate Juice (PJ) Supplementation

Pomegranate juice was prepared every three days using 500 g of locally sourced, certified pomegranates. After washing and deseeding, the arils were blended to yield approximately 250 mL of juice. The juice was filtered through paper and centrifuged to separate the clear supernatant, resulting in 120 mL of clear extract. The extract was stored at –20°C and administered daily at a dose of 2.5 mL per mouse in the drinking water of the PJ and HIIT+PJ groups. Due to the limited stability of pomegranate juice, fresh extracts were prepared every three days (Mortada, 2020).

Dissection and Sampling

Forty-eight hours after the last training session, following a 12-hour fasting period, mice were anesthetized with ketamine (55 mg/kg) and xylazine (15 mg/kg). Cardiac blood was collected directly from the ventricle using a 2 mL syringe. Target tissues, including the intestine, were carefully excised and stored at –70°C for subsequent analyses.

Measurement of Variables

Lipid peroxidation, assessed via MDA, was measured in intestinal tissue using a ZellBio ELISA kit (CAT No. ZB-MDA-96A, Germany) in micromolar units. Visceral fat weight was determined by carefully dissecting all white adipose tissue from the abdominal cavity and weighing it using a precision scale (0.001 g sensitivity, Merk, Germany).

Statistical Analysis

Normality of data distribution was assessed using the Shapiro–Wilk test. One-way ANOVA was performed to compare group means, followed by Tukey's post-hoc test to determine pairwise differences. All analyses were conducted using GraphPad Prism 8.3.3, with significance set at $P \leq 0.05$

3. Results

Paired t-test results indicated that post-test body weight was significantly higher than pre-test values in the HC (P=0.001), CRC (P=0.001), Sham (P=0.001), PJ (P=0.001), and HIIT (P=0.001) groups. Furthermore, one-way ANOVA revealed significant differences in post-test body weight among the experimental groups (F=38.20, P=0.001). Tukey's post-hoc analysis showed that body weight in the CRC group was significantly higher than in the HC group (P=0.001), whereas no significant difference was observed between the HC and Sham groups (P=0.99). Body weight in the PJ (P=0.001), HIIT (P=0.001), and HIIT+PJ (P=0.001) groups was significantly lower than in the CRC group. Additionally, body weight in the HIIT (P=0.002) and HIIT+PJ (P=0.001) groups was significantly lower than in the PJ group (Figure 1).

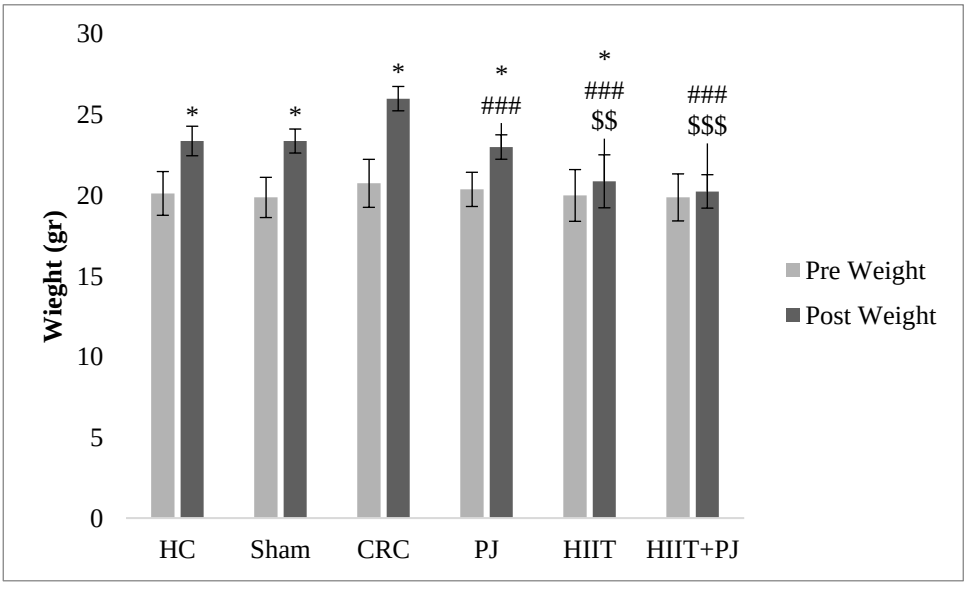
Visceral fat weight was significantly higher in the CRC group compared to the HC group (P=0.001), whereas no significant difference was observed between the Sham and HC groups (P=0.99).

In contrast, visceral fat weight in the PJ (P=0.001), HIIT (P=0.001), and HIIT+PJ (P=0.001) groups was significantly lower than in the CRC group.

Moreover, visceral fat weight in the HIIT (P=0.001) and HIIT+PJ (P=0.001) groups was significantly lower than in the PJ group (Figure 2).

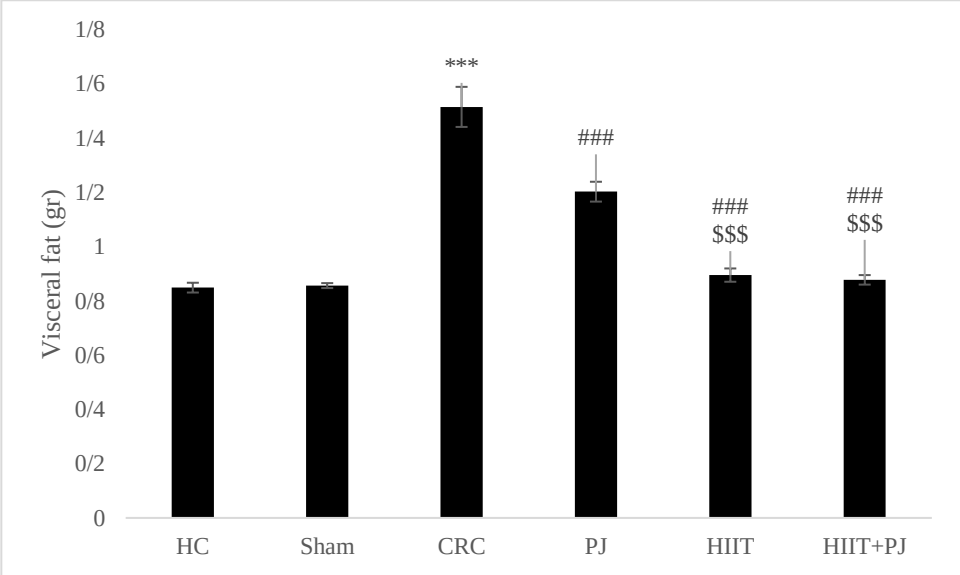
Additionally, one-way ANOVA indicated significant differences in intestinal MDA levels among the experimental groups (F=24.58, P=0.001). Post-hoc analysis revealed that MDA levels in the CRC group were significantly higher than in the HC group (P=0.001), while no significant difference was observed between the Sham and HC groups (P=0.99). Although MDA levels did not differ significantly between the PJ and CRC groups (P=0.99), they were significantly lower in the HIIT (P=0.012) and HIIT+PJ (P=0.001) groups compared to the CRC group. Furthermore, MDA levels in the HIIT (P=0.031) and HIIT+PJ (P=0.001) groups were significantly lower than in the PJ group (Figure 3)

Figure 1. Pre- and post-test body weight of laboratory mice across the experimental groups.



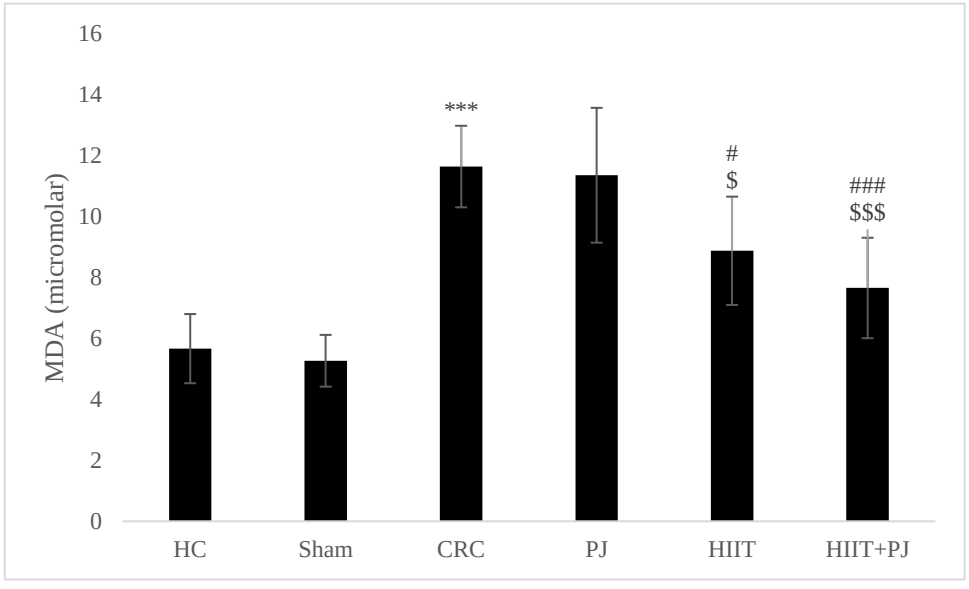
***P=0.001 indicates a significant increase in post-test body weight compared to pre-test values. ###P=0.001 indicates a significant decrease in post-test body weight compared to the CRC group. $$P=0.01 and $$$P=0.001 indicate significant decreases in post-test body weight compared to the PJ group

Figure 2. Visceral fat weight of laboratory mice across the experimental groups.



***P=0.001 indicates a significant increase compared to the HC group. ###P=0.001 indicates a significant decrease compared to the CRC group

Figure 3. MDA levels in the intestinal tissue of laboratory mice across the experimental groups.



***P=0.001 indicates a significant increase compared to the HC group. ###P=0.001 and #P=0.05 indicate a significant decrease compared to the CRC group.

3. Discussion

The results indicated that post-test body weight, visceral fat mass, and MDA levels in the CRC group were significantly higher than those in the HC group. Colorectal cancer (CRC) is among the most common malignancies and is associated with severe alterations in cellular oxidative status, leading to increased production of reactive oxygen species (ROS) (Catalano, 2025). Accumulation of ROS causes DNA damage, lipid peroxidation, and disruption of cellular membranes in colorectal tissues (Skrzydlewska, 2005). Studies have shown that levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), as markers of lipid peroxidation, are significantly elevated in both patients and animal models of colorectal cancer (Koren et al., 2021). This elevation is partly due to overactivation of NADPH oxidase and inflammatory pathways such as NF-κB, which stimulate pro-inflammatory cytokine production (Takiguchi et al., 2023). Moreover, tumor-related metabolic alterations can induce insulin resistance and disrupt lipid homeostasis, ultimately increasing visceral fat accumulation (Ye et al., 2020). Visceral fat accumulation, through secretion of inflammatory adipokines such as TNF-α and IL-6, activates a feedback loop of inflammation and oxidative stress in colorectal tissues (Gonzalez-Gutierrez, 2024). In the present study, a significant increase in body weight, visceral fat, and MDA levels was observed in CRC mice compared to healthy controls, consistent with the aforementioned mechanisms and previous findings (Sun et al., 2023).

In the PJ group, post-test body weight and visceral fat mass were significantly lower than in the CRC group; however, PJ supplementation alone did not significantly reduce MDA levels. These findings indicate the limited efficacy of pomegranate polyphenols alone under complex pathological conditions such as colorectal cancer. Similar studies support this observation: Taghavinia et al. (2022) reported that phenolic compounds from *Nasturtium* reduced body weight and slightly lowered MDA in a CRC mouse model; moreover, administration of pomegranate by-products in Apc-mutated Pirc rats over six weeks reduced cancer risk and predictive biomarkers, yet the decrease in blood MDA was not significant (Tortora, 2017). Concordant findings include Aviram et al. (2000) in healthy humans, where pomegranate intake reduced oxidized LDL but did not significantly affect MDA, and Basu (2013), who observed MDA reduction only in type 2 diabetic patients but not in healthy individuals. Variations in dose, duration, baseline antioxidant capacity, and experimental model likely explain discrepancies among studies. The cellular and molecular mechanisms of pomegranate involve potent antioxidant activity of polyphenols and anthocyanins, which scavenge free radicals, reduce lipid peroxidation, and protect cellular membranes. Ellagic acid can modulate apoptotic and inflammatory pathways by downregulating NF-κB, COX-2, and TNF-α, and stimulate endogenous antioxidant enzymes such as SOD and GPx. Pomegranate tannins and flavonoids further mitigate oxidative stress in intestinal tissue, limiting membrane damage and formation of oxidized lipid products. Collectively, these findings suggest that pomegranate supplementation alone can reduce body weight and visceral fat, but attenuation of lipid peroxidation may require combination with exercise or longer intervention duration (Aviram et al., 2000).

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This study demonstrated that combining high-intensity interval training with pomegranate supplementation improved MDA levels more effectively than pomegranate alone. These findings align with Omidiparsa et al. (2025), who reported that HIIT combined with pomegranate intake reduced inflammatory markers in CRC mouse models, while pomegranate alone had no significant effect. Similarly, Akbarpour et al. (2022) showed that exercise combined with pomegranate improved apoptotic biomarkers in men with prostate cancer. These results highlight the synergistic effect of exercise and pomegranate supplementation in reducing oxidative stress and improving metabolic status under pathological conditions such as colorectal cancer (Akbarpour et al., 2022). Further studies support this observation: Aytac et al. (2023) reported that a combination of pomegranate and black carrot with endurance exercise reduced MDA levels in laboratory mice, demonstrating a synergistic effect between polyphenolic compounds and exercise. Yildirim et al. (2024) also showed in non-athlete humans that consumption of pomegranate and black carrot along with an exercise program significantly reduced MDA and improved biochemical parameters. These findings emphasize that the protective effects of antioxidant supplements can be enhanced in the presence of regular exercise and suggest that combined behavioral and nutritional interventions are more effective in reducing oxidative stress and improving metabolic health under pathological conditions. In the present study, exercise and pomegranate appeared to exert interactive effects on lipid oxidation, visceral fat, and MDA improvement.

One limitation of this study is its exclusive focus on lipid peroxidation markers and visceral fat, with direct assessment of molecular signaling pathways such as NF-κB, COX-2, and TNF-α only indirectly inferred.

This limits a detailed analysis of the combined effects of exercise and pomegranate on apoptosis, inflammation, and antioxidant pathways. Additionally, the study design employed a fixed dose and an 8-week intervention, which may be insufficient to fully capture cellular and molecular responses, and the bioavailability of polyphenols was limited. Furthermore, the use of a single animal model (BALB/c mice) may restrict the generalizability of the findings to other laboratory models or humans. Based on these limitations, future studies should investigate signaling pathways related to oxidative stress and inflammation using direct molecular methods, over longer periods, with different doses or higher bioavailability forms, and include diverse animal models as well as human clinical trials to evaluate the combined effects of exercise and antioxidant supplementation.

4. Conclusion

The present study demonstrated that eight weeks of high-intensity interval training, alone or combined with pomegranate supplementation, significantly reduced body weight, visceral fat mass, and lipid peroxidation in colorectal cancer mice, with exercise exerting a more pronounced effect

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: R.N.A., S.A.H, F.T, K.J ; Methodology: S R.N.A., S.A.H, F.T, K.J ; Software: R.N.A., S.A.H, F.T, K.J ; Validation: R.N.A., S.A.H, F.T, K.J; Formal analysis: R.N.A., S.A.H, F.T, K.J ; Investigation: R.N.A., S.A.H, F.T, K.J ; Resources: R.N.A., S.A.H, F.T, K.J ; Data curation: R.N.A., S.A.H, F.T, K.J ; Writing - original draft: R.N.A., S.A.H, F.T, K.J; Writing - review & editing: R.N.A., S.A.H, F.T, K.J ; Visualization: R.N.A., S.A.H, F.T, K.J ; Supervision: R.N.A., S.A.H, F.T, K.J ; Project administration: R.N.A., S.A.H, F.T, K.J ;Funding acquisition: R.N.A., S.A.H, F.T, K.J.

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