Celastrol attenuates the inflammatory response by inhibiting IL-1β expression in triple-negative breast cancer cells

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Abstract. IL-1 promotes cancer cell proliferation and invasiveness in various malignancies, such as breast and colorectal cancer. In the present study, the functional roles of IL-1β (IL1B) and the inhibitory effect of celastrol on IL1B expression were investigated in triple-negative breast cancer (TNBC) cells. The data revealed that celastrol markedly decreased IL1B expression and suppressed TNBC cell proliferation in a dose-dependent manner. The levels of IL1B and IL8 mRNA were significantly increased in TNBC cells compared with non-TNBC cells. In addition, IL1B augmented the expression levels of IL8 as well as matrix metalloproteinases (MMPs), including MMP-1 and MMP-9, in TNBC cells. Furthermore, IL1B expression was decreased by a specific MEK1/2 inhibitor, MEK162. Celastrol also promoted IL1B downregulation through the suppression of the MEK/ERK-dependent pathway. Furthermore, the results also revealed a decrease in IL1B-induced IL8, MMP-1, and MMP-9 expression in response to celastrol treatment. The induction of cellular invasion by IL1B was also markedly decreased by celastrol. Collectively, the present study results suggested celastrol as an effective drug for the treatment of TNBC, involving a reduction in IL1B expression, activity or signaling pathways.

Introduction

Breast cancer is the most prevalent malignant disease among women worldwide, and the second most common cause of cancer-associated mortality (1,2). Breast cancer is a heterogeneous disease characterized by distinct molecular and morphological traits, and is classified into five subtypes based on the expression profiles of estrogen receptor α (ER-α), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (3,4). Triple-negative breast cancers (TNBCs), which do not express ER-α, PR or HER2, are some of the most aggressive breast cancers, accounting for 10-20% of all observed breast cancer cases (5,6). Due to the lack of these major target receptors, patients with TNBCs tend to have the worst overall prognosis among the luminal A, B, HER2 and TNBC breast cancer subtypes (4,6). Therefore, a number of clinical trials have assessed the efficacy of various therapeutic options for TNBCs.

Celastrol is a quinine methide triterpene isolated from root extracts of the Asian perennial vine Tripterygium wilfordii (7). Celastrol exhibits a wide range of bioactivities, including the inhibition of cellular proliferation, as well as anti-angiogenesis, antitumor and anti-inflammatory properties (7-9). Celastrol also acts as a potent inhibitor of constitutive and inducible STAT3, and contributes to the inhibition of various genes involved in cellular proliferation and survival by suppressing STAT3 activity in human hepatocellular carcinoma (8). In addition, celastrol inhibits a wide variety of inflammatory mediators, including IL10 and IL13, via suppression of the PI3K/AKT/mTOR signaling pathway (10,11). However, the regulatory mechanism by which celastrol influences TNBC cell invasiveness and migration is not known.

Elevated levels of pro-inflammatory cytokines affect tumor growth, survival, angiogenesis and metastatic potential during cancer progression (12,13). Interleukins (ILs) are representative inflammatory cytokines associated with, for example, inflammation and invasion in estrogen receptor negative (ER-) breast cancer (14,15). Abnormal IL1B induction is associated with poor prognosis in the majority of the cancer types, including breast, colon and lung cancer (16). Previously, Tulotta et al (17) reported that the endogenous production of IL1B provided a bone metastatic niche, thereby promoting tumor cell proliferation in...
breast cancer. In addition, IL1 stimulates the production of IL8, which increases cellular invasiveness and the metastatic potential of both ER- and ER+ breast cancers (18,19). Our previous study also reported that elevated IL1B expression enhances the motility of TNBC cells (15).

The aim of the present study was to investigate the pharmacological effect of celastrol on TNBC cells. Herein, the present study aimed to demonstrate the possibility of celastrol as an anti-inflammatory drug to inhibit IL1B in TNBC cells. In addition, the regulatory role of celastrol on IL1B expression was investigated.

Materials and methods

Reagents. Cell culture media and antibiotics were purchased from Thermo Fisher Scientific, Inc., and fetal bovine serum (FBS) was purchased from Hyclone; Cytiva. Celastrol was acquired from Sigma-Aldrich (Merck KGaA), and MEK162, from Selleck Chemicals. LY294002, SP600125, GM6001 and Bay11-7082 were purchased from Tocris Bioscience. All breast cancer cells were obtained from the American Type Culture Collection (ATCC; Rockville, MD, USA). The anti-matrix metalloproteinases (MMP) 1 antibody was purchased from Abcam (cat. no. ab137332; dilution, 1:1,000); anti-β-actin antibodies were purchased from Santa Cruz Biotechnology, Inc. (cat. no. sc-47778; dilution, 1:1,000); and anti-phospho (p)-ERK and total (t)-ERK antibodies (cat. no. 9102 (t); and 4370 (p); dilution, 1:1,000) were purchased from Cell Signaling Technology, Inc. The human IL8 (cat. no. K0331216) IL1B (cat. no. K1331800) ELISA kits were purchased from Koma Biotec, Inc.

Cell culture. All breast cancer cells were obtained from the American Type Culture Collection. T47D, ZR75-1, BT-474, SK-BR-3, HCC1143 and HCC1806 human breast cancer cells were cultured in RPMI1640 medium supplemented with 10% FBS, 2 mM glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin, and maintained at 37°C in a humidified atmosphere (95% air and 5% CO2). MCF7, MDA-MB-157, MDA-MB-231, and Hs578T human breast cancer cells were maintained in DMEM under the same culture conditions.

MTT assay. As previously described (15), TNBC cells were trypsinized and counted using a Countess™ automated cell counter (Invitrogen; Thermo Fisher Scientific, Inc.). Each cell line was seeded into 96-well plates at a density of 1x10^4 cells/well. After 24 h at 37°C in a cell culture incubator, fresh culture media with the indicated concentrations of celastrol were added, followed by further incubation for 24 h. Viable cells were photometrically quantified at 570 nm using a SpectraMax 190 microplate reader (Molecular Devices, LLC).

Colony formation assay. Hs578T TNBC cells were plated into 6-well culture plates (1x10^6 cells/well). After 24 h at 37°C, the cells were treated with celastrol at the indicated concentrations, followed by an additional 7 days of incubation. The colonies were subsequently fixed with 10% ethanol for 5 min at RT and stained with 0.01% crystal violet for 30 min at RT (20).
at room temperature (RT), the blots were washed three times, and ECL prime reagents (Amersham; Cytiva) were used for development. The levels of protein expression (p/t-ERK ratio) were quantified using ImageJ version 2 (National Institutes of Health).

Zymography. Conditioned culture media (serum-free) were mixed with loading buffer and run on a 10% SDS-PAGE gel containing 0.5 mg/ml gelatin without prior denaturation. After electrophoresis, the gels were washed to remove residual SDS, and incubated in renaturing buffer (50 mM Tris, 5 mM CaCl₂, 0.02% Na₂, and 1% Triton X-100) for 30 min at RT. Next, the gels were incubated for 48 h at 37°C in developing buffer (50 mM Tris, 5 mM CaCl₂, 0.15 M NaCl and 1% Triton X-100), and subsequently stained with Coomassie brilliant blue G-250, destained in 30% methanol, and flooded with 10% acetic acid until bands can clearly be visible (19).

Boydren chamber assay. Matrigel-precoated filter inserts (pore size, 8-µm; Becton, Dickinson and Company) were inserted into 24-well invasion chambers. Breast cancer cells were resuspended in culture medium (2x10⁵ cells/well) and added to the upper compartment of the invasion chamber in the presence or absence of 20 ng/ml IL-1β, and/or 0.5 µM celastrol or 10 µM GM6001. Fresh culture medium (700 µl) was added to the lower compartment of the chamber. The chambers were incubated at 37°C for 24 h. After incubation, the cells on the upper side of the filter were removed using cotton swabs, and the lower filters were fixed in 4% paraformaldehyde for 10 min and stained in 0.5% Toluidine blue for 1 h at RT (Sigma-Aldrich; Merck KGaA). The cells on the underside of the filter were photographed in four separate fields per condition using a CK40 inverted microscope (Olympus Corporation). The values obtained were calculated by averaging the total number of cells from four filters (15,21).

Statistical analysis. Data analysis was performed using Excel 2016 (Microsoft Corporation) and GraphPad Prism version 8 (GraphPad Software, Inc.). Statistical significances between two groups of data were calculated using unpaired two-tailed Student’s t-test and Tukey’s multiple comparison test was used for comparisons among multiple groups. Results are presented as the mean ± S.E.M. All quoted P-values are two-tailed, and P<0.05 was considered to indicate a statistically significant difference (20).

Results

Celastrol decreases basal levels of IL1B expression in Hs578T TNBC cells. To investigate the effect of celastrol on TNBC cells, Hs578T cells that had been subjected to serum starvation for 24 h were treated with celastrol at the indicated concentrations for a further 24 h, after which cell viability was evaluated. The chemical structure of celastrol is shown in Fig. 1A. As shown in Fig. 1B, cell viability was significantly decreased following treatment with 2 and 4 µM celastrol. Moreover, the colony formation capacity of Hs578T TNBC cells treated with 2 and 4 µM celastrol was markedly reduced, compared with that of the untreated cells (Fig. 1C). Therefore, 0.25 and 0.5 µM celastrol were used for subsequent experimentation. Using the Proteome Profiler Human Cytokine Array Kit, the effect of celastrol on cytokine expression was evaluated using Hs578T TNBC cells. As shown in Fig. 1D, the amount of secreted IL1B protein was considerably decreased by celastrol treatment. Under similar conditions, the levels of IL1B mRNA and protein expression were examined in Hs578T TNBC cells. As predicted, treatment with celastrol significantly decreased the basal levels of IL1B mRNA and protein expression (Fig. 1E and F). Treatment with 0.5 µM celastrol decreased the levels of IL1B mRNA and protein expression 0.49±0.03- (Fig. 1E) and 0.58±0.04-fold (Fig. 1F), respectively, relative to the control. Celastrol also reduced the levels of IL1B mRNA expression (Fig. S1) in HCC1143, MDA231 and HCC1806 TNBC cells. Consequently, these results demonstrate that celastrol attenuated the inflammatory response in TNBC cells by suppressing IL1B expression.

Elevated IL1B upregulates the levels of IL8 and MMPs in TNBC cells. In the present study, IL1B and IL8 mRNA expression were found to be significantly higher in TNBC cells (MDA-157, Hs578T, MDA-231, HCC1143 and HCC1806) compared with non-TNBC cells (MCF7, T47D, ZR75-1, BT474 and SK-BR-3) (Fig. 2A). The effect of IL1B on IL8 expression in Hs578T and HCC1143 TNBC cells was also determined. After serum starvation for 24 h, the two cell lines were treated with or without 20 ng/ml IL1B for 24 h in fresh serum-free media. An increase in IL8 expression was observed subsequent to IL1B treatment in Hs578T and HCC1143 TNBC cells (Fig. 2B and C). By contrast, IL8 treatment had no effect on IL1B expression (Fig. S2A and B). Compared with the control, treatment with 20 ng/ml IL1B led to a 14.9±2.8-fold and 585.6±50.6-fold increase in IL8 mRNA expression in Hs578T and in HCC1143 cells, respectively (Fig. 2B). In addition, the expression of secreted IL8 protein in the conditioned culture medium was assessed. IL1B treatment increased the level of secreted IL8 protein to 71.4±0.4 pg/ml in Hs578T cells and 72.9±1.2 pg/ml in HCC1143 cells, compared with the control (Fig. 2C). Under similar conditions, IL1B significantly increased the levels of MMPs, including MMP-1 and MMP-9, which play a pivotal role in the metastatic and invasion abilities of various cancer cell types (Fig. 2D and E). Moreover, a significant increase in TNBC cell invasiveness was observed in response to IL8 treatment (Fig. S2C). These results indicate that IL1B functions as a key mediator of inflammation and TNBC cell invasiveness through the induction of IL8, MMP-1 and MMP-9.

Celastrol regulates IL1B expression through the MEK/ERK-dependent pathway in TNBC cells. The mechanism underlying celastrol-regulated IL1B expression in TNBC cells was investigated. The cells that had been previously subjected to serum starvation for 24 h, both in the absence and presence of 5 µM specific inhibitors, were selected for analysis. As shown in Fig. 3A, MEK162, a MEK1/2-specific inhibitor, significantly decreased IL1B mRNA expression in Hs578T cells, though no effect was observed following treatment with Bay11-7082, LY294002 or SP600125. MEK162 decreased IL1B mRNA expression 0.53±0.02-fold (Hs578T cells) and 0.5±0.01-fold (HCC1143 cells), respectively (Fig. 3A). Under
similar conditions, the amount of secreted IL1B protein in response to MEK162 treatment was analyzed in Hs578T and HCC1143 cells. As shown in Fig. 3B, basal levels of IL1B protein expression were decreased following treatment with 5 µM MEK162. These findings demonstrate that basal levels of IL1B expression are regulated through a MEK/ERK-dependent pathway in TNBC. After serum starvation for 24 h, the cells were treated with celastrol at the indicated concentrations for a further 24 h. As shown in Fig. 3C, ERK phosphorylation was suppressed by celastrol treatment in both Hs578T and HCC1143 TNBC cells. In addition, the effect of celastrol was investigated at shorter time points, indicating that the levels of ERK phosphorylation began to decrease from 2 h in Hs578T cells (Fig. 3D). These results suggest that celastrol downregulated IL1B expression through the suppression of the MEK/ERK signaling pathway in TNBC cells.

Celastrol decreases IL1B-induced IL8, MMP-1 and MMP-9 expression, and the invasive ability of TNBC cells. Finally, the pharmacological effects of celastrol on IL1B-induced IL8 expression and cellular invasiveness were investigated. Cells that had been subjected to serum starvation for 24 h were pretreated with 0.5 µM celastrol for 3 h, followed by the addition of 20 ng/ml IL1B with incubation for a further 24 h. The effect of celastrol on MMP-1 and -9 expression was determined, as both proteins play an important role in cellular invasive and metastatic potential. The induction of IL1B-associated MMP-1 and -9 mRNA expression was decreased in response to celastrol treatment in Hs578T and HCC1143 TNBC cells (Fig. 4A). As anticipated, IL1B-induced MMP-1 and -9 protein expression was also decreased in the presence of celastrol (Fig. 4B). Furthermore, the effect of celastrol on IL1B-induced IL8 expression was investigated. As
Figure 2. Elevated levels of IL1B upregulate the levels of IL8 and MMPs in triple-negative breast cancer cells. (A) Levels of IL1B and IL8 mRNA were quantified by RT-qPCR. After serum starvation for 24 h, cells were treated with 20 ng/ml IL1B for a further 24 h. Levels of (B) IL8 and (D) MMP-1, MMP-2 and MMP-9 mRNA were quantified by RT-qPCR. (C) Levels of secreted IL8 protein were analyzed by ELISA, and (E) MMP-1 protein expression was analyzed by western blotting. Levels of MMP-2 and MMP-9 protein expression were analyzed by Zymography. Results represent the mean ± S.E.M of three independent experiments. *P<0.05 and **P<0.01. Con, control; MMP, matrix metalloproteinase; RT-qPCR, reverse transcription-quantitative PCR.

Figure 3. Celastrol regulates IL1B expression through a MEK/ERK-dependent mechanism in TNBC cells. After serum starvation for 24 h, cells were treated with 5 µM specific inhibitors for 24 h. (A) IL1B mRNA expression was determined by reverse transcription-quantitative PCR. (B) Conditioned culture media from the TNBC cells were harvested to detect secreted IL1B, which was analyzed by ELISA. Values shown are the mean ± S.E.M. (C) After serum starvation for 24 h, cells were treated with celastrol for a further 24 h. (D) After serum starvation for 24 h, cells were treated with 0.5 µM celastrol for the indicated time. Using the whole cell lysates, p-ERK and t-ERK expression levels were determined by western blotting. Results represent the mean of three independent experiments. *P<0.05 and **P<0.01. Con, control. TNBC, triple-negative breast cancer; p-, phosphorylated; t-, total; MEK, MEK162; Bay, Bay11-7082; LY, LY294002; SP, SP600125.
shown in Fig. 4C, celastrol decreased IL1B-induced IL8 mRNA expression. Under the control conditions (no celastrol), IL1B increased IL8 mRNA expression 133.5±6.9-fold in Hs578T TNBC cells and 765.4±127.6-fold in HCC1143 TNBC cells. Pretreatment with 0.5 µM celastrol decreased IL1B-induced IL8 expression by 64.8±4.3-fold in Hs578T TNBC cells and 7.6±1.9-fold in HCC1143 TNBC cells (Fig. 4C). In addition, celastrol suppressed IL1B-induced cell invasiveness (Fig. 4D). Furthermore, the effect of GM6001 (a reversible broad-spectrum MMP inhibitor) on IL1B-induced cell invasiveness was investigated, which was found to be suppressed (Fig. 4E). Therefore, it was demonstrated that celastrol suppressed cellular invasiveness by inhibiting IL1B-induced IL8, MMP-1 and MMP-9 expression in TNBC cells.

Discussion

In the past few decades, various researchers have revealed that inflammation plays a pivotal role in tumor development and progression (22). ILs are involved in mediating both acute and chronic inflammatory responses, as well as intercellular communication (including in cellular invasion, proliferation and adhesion) in various cancer cell types (23,24). IL1A, IL1B and IL1 receptor antagonist (IL-1RA) are frequently expressed in breast cancer cells, tissues and in the tumor microenvironment (24,25). In particular, IL1B plays a major role in human malignancy and is often associated with tumor invasiveness (26). The levels of IL1B expression have been reported to be significantly higher in TNBC compared with non-TNBC cells, although IL1B protein expression could not be quantified due to the radical proliferation rates of the cancer cell lines. However, no notable difference in IL1A mRNA expression was observed in breast cancer cells (data not shown). Therefore, it has been demonstrated that aberrant IL1B induction may be associated with the aggressiveness of TNBC cells in association with an increase in inflammatory responses.

Secreted IL1B binds to IL1R, which triggers multiple signaling pathways that involve p38, MAPK, JNK and NF-κB activation (28,29). Elevated levels of IL1Bβ promote the expression of multiple inflammatory genes, such as cyclooxygenase-2 (COX2), phospholipase A2, prostaglandin E2 and IL-8 (13,30). Hou et al (31) reported that IL1B-induced COX2 expression was decreased by IL1RA in a dose-dependent manner. Although the effectiveness of cellular invasion through the knockdown/overexpression of IL1B was not verified due to technical limitations, IL1RA decreased the invasiveness of Hs578T and MDA-MB231 TNBC cells (13). Therefore, we hypothesized that IL1B production was essential for cellular migration and invasiveness of these TNBC cell types.

Previous studies have reported IL8 as a multifunctional pro-inflammatory chemokine, and demonstrated a correlation between IL8 expression and breast cancer metastasis and poor prognosis (15,19,32). In addition, it has been demonstrated that aberrant IL8 expression significantly increases cellular invasion and migration ability in tamoxifen-resistant and TNBC cells (15,19). Consistent with a previous report, in the present study, it was observed that IL1B treatment markedly increased IL8 expression in TNBC cells, and elevated IL8-associated invasiveness. However, IL8 had no effect on IL1B expression

Figure 4. Celastrol decreases IL1B-induced IL8, MMP-1 and MMP-9 expression in TNBC cells. After serum starvation for 24 h, cells were pretreated with the indicated celastrol concentrations for 1 h, and then treated with 20 ng/ml IL1B for 24 h. Levels of IL8, MMP-1, MMP-2 and MMP-9 mRNA expression in (A) Hs578T and (C) HCC1143 cells were determined by reverse transcription-quantitative PCR. (B) Conditioned culture media from the TNBC cells were harvested to detect MMP-1, MMP-2 and MMP-9 expression, and then analyzed by western blotting and Zymography. After being seeded into Transwell chambers, cells were treated with 20 ng/ml IL1B and/or (D) 0.5 µM celastrol or (E) 10 µM GM6001 for 24 h. Invasive cells on the underside of the filter were photographed using a CK40 inverted microscope. Scale bars, 20 µm. Results represent the mean ± S.E.M of three independent experiments. *P<0.05 and **P<0.01. Con, control; NS, not significant; TNBC, triple-negative breast cancer; MMP, matrix metalloproteinase.
Therefore, the results of the present study revealed that IL1B was directly associated with cellular invasiveness and migration through the induction of IL8 expression in TNBC cells.

The expression of MMPs is regulated by various stimuli, including growth factors, cytokines, chemical agents and oncogenic transformation (33). MMPs play a role in tumor growth and metastasis by degrading matrix barriers and enhancing angiogenesis (33). Excessive induction of MMP-1 protein has been reported in several tumors, with the development of more aggressive characteristics such as cellular invasion and migration (34). MMP-9 acts as a tumor promoter in the process of carcinogenesis and has been demonstrated to decrease the incidence of carcinogenesis in MMP-9-knockdown mouse models (35). Consistent with these reports, it was observed that IL1B triggered the induction of MMP-1 and MMP-9, but not MMP-2 in the present study. These results suggest that IL1B may enhance the metastatic potential of TNBC cells by promoting MMP-1 and -9 production.

Celastrol is a triterpene with numerous pharmacological properties, including demonstrable anticancer and anti-inflammatory activities in various cancer cell types, such as breast, lung, myeloma and gastric cancer cells (8,36,37). In addition, celastrol has been reported to completely block epithelial-to-mesenchymal transition in A549 non-small cell lung cancer cells by inhibiting the TGF-β1 signaling pathway (38), and to promote inflammatory responses in orbital fibroblasts and retinal pigment epithelial cells (39,40). Consistent with these reports, the results of the current study showed that celastrol suppressed TNBC cell proliferation in a dose-dependent manner. In particular, celastrol dramatically reduced basal levels of IL1B and IL8 expression (important mediators of the inflammatory response) in TNBC cells. Furthermore, IL1B-induced MMP-1 and -9 expression was also decreased by celastrol. Consequently, celastrol is proposed as an effective drug for reducing inflammatory responses in TNBC cells.

In addition, previous studies have demonstrated the possible potential of celastrol in modulating different signaling cascades, including the STAT3, 5’AMP-activated protein kinase, NF-κB and AKT/mTOR pathways (37,41). Park et al (42) reported that ERK1/2 activation was closely associated with cancer cell migration, invasiveness and metastatic potential. In a previous study, Hashimoto et al (43) reported that the IL1B promoter contains various transcription factor binding sites, such as those for AP-1 and NF-kB. The results of the present study showed that IL1B expression was reduced by Bay11-7082 in HCC1143 cells, while there was no significant change in Hs578T cells. However, the effect of MEK inhibition commonly suppresses IL1B expression in both cell types. Based on previous reports, it is also believed that the activity of AP-1 is regulated by the MAPK (MEK/ERK) pathway, and increases IL1B promoter activity in TNBC cells. Herein, it was observed that celastrol decreased the level of ERK phosphorylation in TNBC cells, and that basal levels of IL1B expression were decreased through inhibition of the MEK/ERK-dependent pathway. Thus, it is hypothesized that celastrol suppresses IL1B expression by inhibiting ERK1/2 activity.

Furthermore, it was found that IL1B-induced IL8, MMP-1 and -9 expression was completely suppressed by celastrol. The MEK inhibitor, MEK162, completely suppressed IL1B-induced IL8, MMP-1 and MMP-9 expression. Furthermore, it was revealed that IL1B-dependent activation of the MEK/ERK pathway plays an important role in IL8, MMP-1 and MMP-9 expression, which subsequently inhibits TNBC cell motility.

In conclusion, the pharmacological effects of celastrol in TNBC cells were investigated. IL1B mRNA expression levels were observed to be higher in TNBC cells compared with non-TNBC cells. As shown in Fig. 5, elevated IL1B enhances TNBC cell invasiveness through the secretion of IL8 and MMPs. Currently, extensive clinical research is being conducted with a variety of agents that reduce IL-1 activity. In the current study, celastrol was found to suppress basal expression of IL1B in TNBC cells, and to inhibit IL1B-induced IL8, MMP-1 and MMP-9 expression. Taken together, the results of the present study demonstrated that celastrol is an effective drug for the treatment of TNBC by reducing IL-1 activity or associated signaling pathways.
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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SK, SWK, SJN and JEL contributed to the experimental design and analyzed the results. SK and JEL wrote the manuscript. SK, DY, YJ, SYY and SAK performed the experiments and analyzed the results. All authors are responsible for the authenticity of the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References


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