MiR-27a-3p Regulated the Aggressive Phenotypes of Cervical Cancer by Targeting FBXW7

Background: Abnormally expressed microRNAs (miRNAs) contribute greatly to the initiation and development of human cancers, including cervical cancer, by regulating the target mRNAs. MiR-27a-3p was up-regulated and acted as an oncogene in multiple cancers. However, the function of miR-27a-3p in cervical cancer has not been fully understood.

Methods: The expression of miR-27a-3p in cervical cancer tissues and cell lines was detected by RT-qPCR. MTT assay, colony formation assay and flow cytometry analysis were performed to determine the effects of miR-27a-3p on the growth of cervical cancer cells. The targets of miR-27a-3p were predicted using the miRDB database. Luciferase reporter assay was utilized to confirm the binding between miR-27a-3p and the 3'-untranslated region (UTR) of targets. The expression of target proteins was determined by RT-qPCR and Western blot.

Results: Our results found that miR-27a-3p was overexpressed in cervical cancer tissues and cell lines. Down-regulation of miR-27a-3p significantly inhibited the proliferation, colony formation and promoted apoptosis of cervical cancer cells. Overexpression of miR-27a-3p enhanced the cell proliferation. MiR-27a-3p was found to bind the 3'-UTR of F-box and WD repeat domain containing 7 (FBXW7) and resulted in the down-regulation of FBXW7. The up-regulated level of miR-27a-3p was inversely correlated with that of FBXW7 in cervical cancer tissues. Additionally, reintroducing of FBXW7 significantly attenuated the promoting effect of miR-27a-3p on the proliferation of cervical cancer cells.

Conclusion: These results indicated the growth-promoting function of miR-27a-3p in cervical cancer via targeting FBXW7. Our finding suggested the potential application of miR-27a-3p/FBXW7 axis in the diagnosis and treatment of cervical cancer.

Keywords: cervical cancer, miR-27a-3p, FBXW7

Introduction

Cervical cancer is one of the most prevalent malignancies and the leading cause of cancer-related death among women worldwide. Although technical progress has been made in the management of cervical cancer in recent decades, the mortality rate of cervical cancer still remains high. The related pathogenic mechanisms contributing to the carcinogenesis and progression of cervical cancer are incompletely elucidated. Exploring the molecular mechanisms that are responsible for the development of cervical cancer is critical to establish novel therapeutic strategies for the diagnosis and treatment of cervical cancer.

MicroRNAs (miRNAs) are evolutionary conserved, non-coding single-stranded small molecules. MiRNAs regulate the expression of protein-coding genes via binding to the 3'-untranslated region (UTR) of targets, which leads to mRNA degradation or translation blockage. An increasing body of evidence has
demonstrated the critical roles of miRNAs in both physiological and pathological conditions.\(^{10,11}\) Aberrant expression of miRNAs is involved in the progression of cervical cancer via modulating the expression of oncogenes or tumor suppressors.\(^{12}\) MiR-27a-3p is located at chromosome 19 and is frequently aberrantly expressed in human cancers.\(^{13-16}\) MiR-27a-3p has been identified as an oncogene given its abilities to promote the malignant behaviors of cancer cells, including colorectal cancer, gastric cancer, and esophageal cancer.\(^{14-16}\) Overexpression of miR-27a-3p was associated with the poor disease-free survival of cancer patients. However, the biological role of miR-27a-3p in cervical cancer still remains largely unknown.

The ubiquitin-proteasome system (UPS) plays important roles in multiple cellular processes, including cell proliferation, differentiation and apoptosis.\(^{17}\) The F-box and WD repeat domain containing 7 (FBXW7), belonging to the F-box protein family, acts as the substrate recognition components of the SCF E3 ubiquitin ligase.\(^{18}\) Given the essential role of FBXW7 in UPS, the critical involvement of FBXW7 in cancer has been emerged.\(^{19}\) It has been documented that FBXW7 suppressed the tumorigenesis by controlling the proteasome-mediated degradation of oncoproteins, such as Cyclin E, c-Myc, mTOR and Notch.\(^{20-24}\) Interestingly, considering the inhibitory effect of FBXW7 in cancer, long non-coding RNAs and miRNAs have been found to inactivate FBXW7 and promoted the tumorigenesis.\(^{25-29}\)

In this study, we found that miR-27a-3p was significantly up-regulated in cervical cancer. MiR-27a-3p served as a potential target to modulate the malignant behaviors of cervical cancer cells via regulating FBXW7.

**Materials and Methods**

**Tumor Tissues and Cell Lines**

A total of 50 patients with cervical cancer were recruited into this study at the first affiliated Hospital of Harbin Medical University between January 2013 and September 2015. None of these patients received anti-tumor treatment prior to the surgical resection. Paired cancer tissues and adjacent non-cancerous tissues (>5 cm distant from the cancer tissues) were collected and frozen at −80°C immediately. All procedures performed involving human participants were conducted in accordance with the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the first affiliated Hospital of Harbin Medical University. Written informed consents were received from all participants.

Human cervical cancer cell lines including Hela, SiHa, Caski, C33A, and the normal human cervical epithelial cell line HCerEpic were purchased from the Shanghai Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM; Gibco, Thermo Fisher Scientific, Inc., Waltham, MA, USA) supplemented with 10% of fetal bovine serum (FBS; Gibco, Thermo Fisher Scientific, Inc., Waltham, MA, USA), 100 μg/mL streptomycin, and 100 U/mL penicillin (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany). Cells were maintained at 37°C with 5% CO₂.

**Oligonucleotides and Transfection**

The miR-27a-3p inhibitor and a negative control inhibitor (NC inhibitor), the miR-27a-3p mimic and control miRNA were purchased from Ribobio Co., Ltd. (Guangzhou, China). Cell transfection was performed using the Lipofectamine 2000\(^{\text{TM}}\) reagent (Invitrogen, Thermo Fisher Scientific, Inc., Waltham, MA, USA) following the manufacturer’s instructions. Cells were harvested for further analysis after cultured for 48 h.

**RNA Isolation and RT-qPCR**

Total RNA was isolated from cells or tissues using TRIzol reagent following the manufacturer’s protocol. All-in-One\(^{\text{TM}}\) miRNA First-Strand cDNA Synthesis Kit was used to synthesize cDNA (GeneCopoeia, Inc., Rockville, MD, USA) according to the manufacturer’s instructions. qPCR was performed on the Applied Biosystems 7900 Sequence Detection system (Applied Biosystems) with SYBR Premix Ex Taq Kit (Takara, Tokyo, Japan). U6 small nuclear RNA was also detected as an internal reference for the normalization of miR-27a-3p expression. The primers of miR-27a-3p and U6 RNA were designed as follows: miR-27a-3p forward, 5′-CCGCTCGAGACTGGCTGCTAGGAAGGTG-3′ and reverse, 5′-GCGAATTCTTGCTGTAGCCTCCTTGTC-3′; U6 forward, 5′-GCACCTAGGCTGAACA-3′ and reverse, 5′-AGCTATGGCCAGTCTTTG-3′. The thermocycling conditions were set as: 95°C for 5 min followed by 40 cycles for 95°C for 15s and 60°C for 45s. The relative expression of miR-27a-3p was analyzed using the 2\(^{-\Delta\Delta CT}\) method.

**Cell Proliferation**

The proliferation of cervical cancer cells transfected with the indicated miRNA was determined via Methyl Thiazolyl Tetrazolium (MTT) assay. Cells were seeded into 96-well plates and cultured for 1-, 2-, 3-, 4- and 5 days, respectively. 20 μL of MTT (5 mg/mL, Sigma-Aldrich, St. Louis, MO,
USA) was added into the medium and incubated for 4 h at 37°C. The MTT medium was replaced by 100 μL of DMSO and incubated for additional 10 min. The absorbance of each well was measured at 490 nm with the microplate reader (Bio-Rad Laboratories Inc., Hercules, CA, USA). The experiment was performed in three replicate.

**Flow Cytometry Analysis**

The cell apoptosis was determined using the FITC Annexin-V apoptosis Detection Kit (R&D systems, Inc., USA) according to the manufacturer’s instructions. Briefly, cells transfected with miR-27a-3p inhibitor or NC miRNA were harvested and washed twice with pre-cold PBS. Cells were then stained with Annexin-V-FITC and propidium iodide (PI) for 15 min at room temperature (RT) in the dark. The percentage of cell apoptosis was determined by flow cytometry using a fluorescence-activated cell sorting vantage cytometer (BD Biosciences). The data was analyzed using the FlowJo version 10.5.0 software (FlowJo LLC).

**Western Blot**

Total proteins were extracted from cervical cancer cells or tissues using RIPA buffer (Beyotime, Shanghai, China) containing proteinase inhibitors (Beyotime, Shanghai, China). The protein concentration was detected by the BCA reagent kit (Beyotime, Shanghai, China). 20 μg of protein was loaded and separated by 15% SDS-PAGE, and transferred to the PVDF membranes (Millipore, Billerica, MA, USA). The membrane was blocked with 5% skim milk at RT for 1 h followed by incubating with the primary antibodies at 4°C overnight. Subsequently, the HRP-conjugated secondary antibodies were added in and incubated for 1 h at RT. The signals were detected with the enhanced chemiluminescence kit (ECL, Millipore, Billerica, MA, USA) according to the manufacturer’s instruction. GAPDH was detected as the loading control.

**Dual Luciferase Reporter Assay**

The wild-type or mutant 3′-UTR sequence of FBXW7 that contained the putative seeding sites of miR-27a-3p was amplified and constructed into the pMIR-reporter luciferase vector, respectively. Cervical cancer cells were transfected with miR-27a-3p mimics or control miRNA and the luciferase vector of FBXW7 using Lipofectamine 2000. After transfection for 48 h, cells were harvested and the luciferase activity was measured with the Dual Luciferase Reporter Assay System (Promega, Madison, WI, USA) according to the manufacturer’s instruction.

**Statistical Analysis**

All experimental data was presented as mean ± standard deviation (S.D.). Student’s t test or One-way Analysis of Variance (ANOVA) was performed to determine the P value using GraphPad Prism 5.02 Software (GraphPad Software, Inc.). P<0.05 was considered as statistical significance.

**Results**

**MiR-27a-3p Was Overexpressed in Cervical Cancer Tissues and Cell Lines**

To evaluate the involvement of miR-27a-3p in cervical cancer, the expression of miR-27a-3p in 50 paired cervical cancer tissues and adjacent normal tissues was determined using RT-qPCR analysis. As shown in Figure 1A, a significant increase of miR-27a-3p level was observed in cervical cancer tissues, compared with that in matched adjacent tissues. The expression of miR-27a-3p was further detected in cervical cancer cell lines (Hela, SiHa, Caski, C33A) and normal cervical epithelial cell HcerEpiC. The level of miR-27a-3p was obviously higher in cervical cancer cells than that of normal cells (Figure 1B). These results suggested the up-regulated expression of miR-27a-3p in cervical cancer.

**Down-Regulation of miR-27a-3p Inhibited the Growth of Cervical Cancer Cells**

To investigate the function of miR-27a-3p in the malignancy of cervical cancer, miR-27a-3p was down-regulated by transfecting miR-27a-3p inhibitor into both Hela and C33A cells. The knockdown efficiency of miR-27a-3p inhibitor was monitored by RT-qPCR assay after transfection for 48 h. The data showed that the expression of miR-27a-3p was significantly reduced in miR-27a-3p inhibitor-transfected cells (Figure 2A). MTT assay was performed to evaluate the impact of miR-27a-3p on the proliferation of cervical cancer cells. The results indicated that down-regulation of miR-27a-3p inhibited the proliferation of both Hela and C33A cells (Figure 2B and C). Colony formation assay further confirmed the suppressed growth of cervical cancer cells with the knockdown of miR-27a-3p (Figure 2D). To investigate whether the reduced growth of cervical cancer cells was associated with the apoptosis, the cell apoptosis with depleted miR-27a-3p was determined by flow cytometry. The results revealed that blockage of miR-27a-3p significantly increased the apoptosis of cervical cancer cells compared with the corresponding control cells.
Figure 1 MiR-27a-3p was overexpressed in cervical cancer. (A) miR-27a-3p expression was determined by RT-qPCR in 50 paired cervical cancer and adjacent non-cancerous tissues. (B) The level of miR-27a-3p was determined in the indicated cervical cancer cell lines and normal HCeEpC cells. **P<0.01, ***P<0.001.

Figure 2 Down-regulation of miR-27a-3p inhibited the growth of cervical cancer cells. (A) MiR-27a-3p inhibitor was transfected into HeLa and C33A cells. MiR-27a-3p expression was measured using RT-qPCR. (B, C) MTT assay was performed to determine the cell proliferation of HeLa and C33A cells expressing depleted miR-27a-3p. (D) Down-regulation of miR-27a-3p suppressed the colony formation of cervical cancer cells. (E) Representative images of apoptosis were shown in left panel and the statistical analysis of apoptosis was presented in the right panel. ***P<0.001.
Overexpression of miR-27a-3p Promoted the Proliferation of Cervical Cancer Cells

To provide more evidence for the function of miR-27-3p in the growth of cervical cancer cells, miR-27a-3p was overexpressed in HeLa and C33A cells by transfecting miR-27a-3p mimic. The overexpression of miR-27a-3p was validated by RT-qPCR (Figure 3A). The MTT assay showed that ectopic expressed miR-27a-3p promoted the proliferation of both HeLa and C33A cells (Figure 3B and C). Additionally, to determine whether the up-regulated proliferation of cervical cancer cells was associated with cell cycle progression. The cell cycle distribution of cervical cancer cells with miR-27a-3p overexpression was detected. The results showed that overexpression of miR-27a-3p significantly reduced the cell percentage of cells in G1 phase and increased in S phase, suggesting accelerated cell cycle progression with the transfection of miR-27a-3p (Figure 3D and E). These results indicated the promoting effects of miR-27a-3p on the growth of cervical cancer cells.

FBXW7 Was a Target of miR-27a-3p in Cervical Cancer

Given the significant effects of miR-27a-3p on the growth of cervical cancer cells, the underlying mechanism was investigated by predicting the targets of miR-27a-3p using web-based resources (http://www.mirdb.org). Among the putative targets, the 3′-UTR of FBXW7 was found to harbor the complementary binding sites of miR-27a-3p (Figure 4A and Supplementary Table 1). To test whether miR-27a-3p bound the 3′-UTR of FBXW7 via the seed sequences, the wild-type or mutated seed sequence of FBXW7 3′-UTR was constructed into the luciferase reporter vector. As shown in Figure 4B and C, transfection of miR-27a-3p significantly inhibited the luciferase activity of vectors expressing WT 3′-UTR of FBXW7. However, when cells were co-transfected with miR-27a-3p and mutated 3′-UTR, the luciferase activity remained the same to that of control cells (Figure 4B and C). These results suggested the specific binding between miR-27a-3p and the 3′-UTR of FBXW7. Since the 3′-UTR plays important role in the mRNA stability and translation, qPCR and Western blot were employed to examine the influence of miR-27a-3p on the mRNA and protein levels of FBXW7, respectively. The results uncovered that compared with the corresponding control cells, overexpression of miR-27a-3p in both HeLa and C33A cells significantly decreased the mRNA and protein levels of FBXW7 (Figure 4D and E). To further confirm the negative regulation of FBXW7 by miR-27a-3p, miR-27a-3p was down-regulated in cervical cancer cells by transfecting miR-27a-3p inhibitor. The results showed that depletion of miR-27a-3p increased the mRNA, as well as the protein expression of FBXW7 in HeLa and C33A cells (Figure 4F and G). These data indicated that miR-27a-3p bound the 3′-UTR of FBXW7 and negatively regulated the expression of FBXW7 in cervical cancer cells.

Recovered FBXW7 Expression Reversed the Increased Cell Proliferation by miR-27a-3p

To further support the conclusion that FBXW7 was a target of miR-27a-3p, the abundance of FBXW7 in cervical cancer tissues was detected. The results showed that the mRNA level of FBXW7 in cervical cancer tissues was significantly lower than the paired normal tissues (Figure 5A). The relationship between the expressions of miR-27a-3p and FBXW7 in cervical cancer tissues was evaluated by Spearman test. The result showed that the abundance of miR-27a-3p was reversely correlated with that of FBXW7 in cervical cancer tissues (Figure 5B). Additionally, the protein levels of FBXW7 in both cervical cancer tissues and adjacent normal tissues were also evaluated, which showed that consistent with the mRNA level, the protein expression of FBXW7 was significantly decreased in cervical cancer tissues (Figure 5C). Reduced FBXW7 expression was associated with the lymph node metastasis of patients with cervical cancer (Figure 5D). Similarly, the down-regulation of FBXW7 in cervical cancer cells was also obtained compared with that of the normal cells (Figure 5E). These findings supported the observation that FBXW7 was a target of miR-27a-3p in cervical cancer.

To investigate whether FBXW7 mediated the regulatory effects of miR-27a-3p on the proliferation of cervical cancer cells, the expression of FBXW7 was restored by transfecting Flag-FBXW7 into HeLa and C33A cells. The MTT assay showed that the overexpression of FBXW7 significantly abrogated the promoting effects of miR-27a-3p on the proliferation of HeLa and C33A cells (Figure 5F and G). The overexpression of FBXW7 was confirmed by Western blot with anti-Flag antibody. These results suggested the critical role of FBXW7 in mediating the function of miR-27a-3p in cervical cancer.
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Figure 3 Overexpression of miR-27a-3p promoted the proliferation of cervical cancer cells. (A) The overexpression of miR-27a-3p was confirmed by RT-qPCR. (B, C) Ectopic expressed miR-27a-3p promoted the proliferation of cervical cancer cells. (D, E) Transfection of miR-27a-3p significantly promoted the cell cycle progression from G1 to S phase in HeLa (D) and C33A cells (E). ***P<0.001.
Figure 4. FBXW7 was a target of miR-27a-3p in cervical cancer. (A) The binding sites of FBXW7 and miR-27a-3p were predicted using bioinformatics analysis. (B, C) Overexpression of miR-27a-3p decreased the luciferase reporter activity of cells carrying wild-type 3'-UTR of FBXW7. (D, E) The expression of FBXW7 was determined by RT-qPCR and Western blot within cells expressing overexpressed miR-27a-3p or control miRNA. (F, G) Down-regulation of miR-27a-3p increased both the mRNA (F) and protein (G) level of FBXW7 in both HeLa and C33A cells. ***P<0.001.
Figure 5 Transfection of FBXW7 attenuated the effects of miR-27a-3p on the cervical cancer cells. (A) The mRNA level of FBXW7 in paired cervical cancer tissues and adjacent normal tissues was detected by RT-qPCR. (B) Spearman rank correlation analysis showed an inverse correlation between the level of FBXW7 and miR-27a-3p in cervical cancer tissues. (C) The protein level of FBXW7 in paired cervical cancer tissues and adjacent normal tissues. (D) Patient with lymph node metastasis showed lower level of FBXW7. (E) The protein abundance of FBXW7 was compared in cervical cancer cells and normal cell. (F, G) Transfection of FBXW7 abrogated the promoting effects of miR-27a-3p on the proliferation of cervical cancer cells. The expression of Flag-tagged FBXW7 in both HeLa and C33A cells was examined by Western blot with anti-Flag antibody. (H) Overexpression of miR-27a-3p increased the expression of FBXW7 targets in HeLa and C33A cells. ***P<0.001.
It has been well documented that FBXW7 acts as the substrate recognition component of the SCF E3 ubiquitin ligase and controls proteasome-mediated degradation of oncogenes, such as cyclin E, c-Myc and Notch. Given miR-27a-3p negatively modulated the level of FBXW7 in cervical cancer, the abundance of cyclin E, c-Myc and Notch was detected. The Western blot data indicated that overexpression of miR-27a-3p dramatically up-regulated the protein expression of Cyclin E, c-Myc and Notch, which was inversely associated with that of FBXW7 (Figure 5H). These results indicated that miR-27a-3p targeted FBXW7 and modulated the expression of several oncogenes that may play a role in the tumorigenesis of cervical cancer.

Discussion

Cervical cancer has been one of the most prevalent malignancies in women worldwide. Mounting evidence suggested that aberrant expression of miRNAs affected the initiation and development of cervical cancer. To get an overview of the miRNA expressions in cervical cancer, we performed a miRNA sequence analysis to obtain the aberrantly expressed miRNAs (Unpublished data). Our results showed that miR-27a-3p was significantly increased in cervical cancer tissues compared with that of paired adjacent normal tissues. The fold change of miR-27a-3p rank top among all the candidates. Since the function of miR-27a-3p in cervical cancer was not fully reported, we performed this study to investigate the role of miR-27-3p in the progression of cervical cancer. We found that miR-27a-3p was significantly overexpressed in clinical cervical cancer tissues and cell lines. Down-regulation of miR-27a-3p inhibited the proliferation of cervical cancer cells and promoted apoptosis, indicating the critical function of miR-27a-3p in the progression of cervical cancer.

Emerging studies have shown that miR-27a-3p was frequently up-regulated in many types of cancers and promoted the malignant behaviors of cancer cells. For example, miR-27a-3p was overexpressed in ovarian cancer and enhanced the cell migration, invasion and reduced cell apoptosis. Inhibition of miR-27a-3p suppressed the proliferation and invasion of osteosarcoma cells, suggesting miR-27a-3p as a potential target for the treatment of osteosarcoma. Similarly, down-regulated miR-27a-3p expression induced cell cycle arrest at G1/S transition in esophageal squamous cell carcinoma (ESCC), which indicated that miR-27a-3p could be considered as a potential therapeutic strategy for ESCC. The oncogenic function of miR-27a-3p was also supported by the finding that miR-27a-3p modulated the Wnt/β-catenin signaling pathway and promoted the epithelial-mesenchymal transition in oral squamous carcinoma. Interestingly, miR-27a-3p was experimentally verified as a new pharmacogenomics biomarker for metformin in MCF-7 and MDA-MB-231 cells. In the current study, miR-27a-3p was highly expressed in cervical cancer tissues and cell lines. Down-regulation of miR-27a-3p significantly inhibited the proliferation, colony formation and induced apoptosis of cervical cancer cells. These results suggested the pro-proliferative role of miR-27a-3p in the tumorigenesis of cervical cancer. Further in vivo validation might be necessary to support the oncogenic function of miR-27a-3p in cervical cancer.

Additionally, it was also reported that some mutant p53 acquires novel oncogenic functions via modulating the expression of specific miRNAs. Previous study showed that miR-27a-3p was a novel downstream transcriptional target of mutant p53-273H and suppressed the expression of miR-27a-3p. It would be interesting to determine whether restoration of p53 or mutants affects the function of miR-27a-3p in the progression of cervical cancer.

MiRNAs are known to silence the translation of target mRNAs via binding to the 3’-UTR recognition sequences. To better understand the mechanism of miR-27a-3p in cervical cancer, bioinformatics analysis was performed and FBXW7 was predicted as a putative target of miR-27a-3p. The binding between miR-27a-3p and the 3’-UTR of FBXW7 was further confirmed by the luciferase reporter assay. Overexpression of miR-27a-3p significantly decreased the mRNA and protein levels of FBXW7 in cervical cancer cells. The tumor suppressive role of FBXW7 in cancers was reported by previous studies. Consistently, we found that FBXW7 was down-regulated in cervical cancer tissues and associated with the advanced progression of cervical cancer patients. The abundance of FBXW7 in cervical cancer was inversely correlated with that of miR-27a-3p. Increasing evidence has suggested FBXW7 as potential target of miRNAs in cancers. For example, FBXW7 was targeted by miR-223 and promoted the proliferation of oral squamous cell carcinoma. MiR-182 enhanced the cell growth of non-small cell lung cancer by regulating FBXW7. These reports suggested FBXW7 as a downstream target of miRNAs and modulated tumorigenesis. Collectively, our results demonstrated that miR-27a-3p was up-regulated in cervical cancer and depletion of miR-27a-3p significantly inhibited the malignant behaviors of cervical cancer cells. Mechanism study uncovered that...
miR-27a-3p bound the 3′-UTR of FBXW7 and decreased the expression of FBXW7 in cervical cancer cells. Our findings suggested miR-27a-3p/FBXW7 axis might serve as a promising target for the diagnosis and treatment of cervical cancer. Further study would be necessary to characterize how miR-27a-3p is up-regulated and affects the progression of cervical cancer.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declared that they have no conflicts of interest in this work.

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