

# Tudor-staphylococcal nuclease regulates the expression and biological function of alkylglycerone phosphate synthase via nuclear factor- $\kappa$ B and microRNA-127 in human glioma U87MG cells

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Received September 7, 2017; Accepted February 20, 2018

DOI: 10.3892/ol.2018.8484

**Abstract.** Glioma is one of the malignant tumor types detrimental to human health; therefore, it is important to find novel targets and therapeutics for this tumor. The downregulated expression of Tudor-staphylococcal nuclease (SN) and alkylglycerone phosphate synthase (AGPS) can decrease cancer malignancy, and the overexpression of them can increase viability and migration potential of various tumor cell types; however, the role of AGPS in the proliferation and migration of glioma, and the association of Tudor-SN and AGPS in human glioma is not clear. In the present study, it was determined that AGPS silencing suppressed the proliferation and migration potential of glioma U87MG cells, and suppressed the expression of the circular RNAs circ-ubiquitin-associated protein 2, circ-zinc finger protein 292 and circ-homeodomain-interacting protein kinase 3, and the long non-coding RNAs H19 imprinted maternally expressed transcript (non-protein coding), colon cancer-associated transcript 1 (non-protein coding) and

hepatocellular carcinoma upregulated long non-coding RNA. Furthermore, Tudor-SN silencing suppressed the expression of AGPS; however, nuclear factor (NF)- $\kappa$ B and microRNA (miR)-127 retrieval experiments partially reduced the expression of AGPS. Additionally, it was determined that Tudor-SN silencing suppressed the activity of the mechanistic target of rapamycin (mTOR) signaling pathway, and NF- $\kappa$ B and miR-127 retrieval experiments partially reduced the activity of mTOR. Therefore, it was considered that NF- $\kappa$ B and miR-127 may be the mediators of Tudor-SN-regulated AGPS via the mTOR signaling pathway. These results improve on our knowledge of the mechanisms underlying Tudor-SN and AGPS in human glioma.

## Introduction

Gliomas are a type of tumor formed by neoplastic transformation of neural stem cells, progenitor cells and differentiated glial cells, including astrocytes, oligodendrocytes and ependymal cells (1). Neoplastic cells may spread diffusely to normal brain tissues and damage normal neurological functions, which is the reason why malignant gliomas are detrimental to human health (2). In China, gliomas constitute 44.69% of primary intracranial tumors and 1-3% of generalized malignancies (3). According to the World Health Organization, malignant glioma causes the second highest amount of mortalities in sufferers <34 years old, and the third highest amount of mortalities in sufferers aged 35-54 years old (4). It is estimated that the survival time of the majority of glioma sufferers is ~1 year. Although there are currently various treatments available, including excision, chemotherapy and radiotherapy, the characteristic of strong invasiveness has severely influenced the effectiveness of glioma treatment.

MicroRNAs (miRNAs/miRs) are an important molecular mediator of cell genetic changes, and are directly or indirectly associated with the occurrence and development of a number

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**Key words:** Tudor-staphylococcal nuclease, alkylglycerone phosphate synthase, glioma, circular RNAs, long non-coding RNAs

of tumor types, including glioma, when the miRNAs are abnormally expressed in the tumors (5).

Human Tudor-staphylococcal nuclease (SN), also known as P100, is a multi-functional protein with overexpression in various malignant tumor types, including breast cancer, prostate cancer, colorectal cancer and melanoma (6-10). Previous studies have indicated that Tudor-SN has a close association with lipid metabolism, and that the expression of lipoprotein in liver cells can be affected through adjustment of lipid metabolism-associated genes (11,12). Inactivation of alkylglycerone phosphate synthase (AGPS) can lower the ether ester level in the tumor cell and cancer pathogenicity, while overexpression of AGPS can increase the ether ester level, viability and migration potential of various tumor cells, including 231MFP, C8161 melanoma, PC3 prostate cancer and primary breast cancer cells, and advance the growth and migration of the tumor cells (13,14). The aforementioned studies demonstrated that Tudor-SN and AGPS serve an important role in tumor development.

In the present study, the role of Tudor-SN and AGPS in the proliferation and migration of glioma U87MG cells and the association of Tudor-SN with AGPS in this process was investigated.

## Materials and methods

**Cell lines and cell culture.** Human glioma U87 cells were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China) and cultured in Dulbecco's modified Eagle's medium (Corning Life Sciences, Manassas, VA, USA) with 10% fetal bovine serum (Corning Life Sciences) at 37°C, with an atmosphere containing 5% CO<sub>2</sub>. The AGPS and Tudor-SN silencing U87 cell line [Tudor-SN short hairpin (shRNA) group] was established by the Basic Medical College, Tianjin Medical University (Tianjin, China).

A total of 3x10<sup>5</sup> cells/well were seeded onto a 6-well plate and cultured at 37°C for 24 h. A total of 2.5 µg AGPS shRNA plasmid, 2.5 µg Tudor-SN shRNA plasmid (Santa Cruz Biotechnology, Inc., Dallas, TX, USA), 2.5 µg NF-κB p65 expression plasmid (Santa Cruz Biotechnology, Inc.) and 2.5 µg miR-127 siRNA plasmid (OBIO Biotechnology, Inc., Shanghai, China) were transfected using GeneJuice® (Merck KGaA, Darmstadt, Germany), according to the manufacturer's protocol, for another 6 h. Fresh Dulbecco's modified Eagle's medium (Corning Life Sciences, Manassas, VA, USA) was then added and the cells were harvested after 72 h for all experiments.

**Cell proliferation assay.** A total of 3,000 cells/well (negative control and AGPS shRNA, n=5) were seeded into a 96-well plate and cultured at 37°C for 72 h. The BrdU cell proliferation kit (ab126556, Abcam, Cambridge, UK) was used to determine the optical density value to reflect the cell proliferation, according to the manufacturer's instructions. Briefly, 20 µl of BrdU label (negative BrdU control for determining assay background) was added at 37°C for 12 h, and cells were fixed by 200 µl/well fixing solution (3.7% formaldehyde in PBS) at room temperature for 30 min, then washed for 3 times using PBS, and 100 µl/well anti-BrdU monoclonal detector antibody (1:2,000, supplied in the BrdU cell proliferation kit) was added

and incubated for 1 h at room temperature. Then, they were washed 3 times using PBS, and 100 µl/well peroxidase-conjugated goat anti-mouse IgG antibody (1:2,000, also supplied in the BrdU cell proliferation kit) was added and incubated for 30 min at room temperature. Subsequently the cells were washed 3 times using PBS, and 100 µl/well TMB peroxidase substrate was added and incubated for 30 min at room temperature in the dark. Finally, 100 µl of stop solution (also supplied in the BrdU cell proliferation kit) was added, and the OD value was measured every 24 h using the Multiskan™ Spectrum at 450 nm (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

**Cell migration assay.** A total of 3x10<sup>6</sup> cells/well were seeded into the insert of the Transwell kit (Cell Biolabs, Inc., San Diego, CA, USA) with 200 µl 10% bovine serum albumin (BSA, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) in the upper chamber and 600 µl Dulbecco's modified Eagle's medium with 10% fetal bovine serum, cultured at 37°C for 72 h, according to the manufacturer's instructions. Non-migratory cells were then washed off using PBS, and migratory cells were stained by 0.1% crystal violet at 37°C for 10 min and counted using a light microscope (Olympus Corporation, Tokyo, Japan) to determine the cell migration (magnification, x200).

**Western blotting assay.** Cells were co-transfected with AGPS shRNA plasmid, and Tudor-SN shRNA plasmid, NF-κB p65 expression plasmid (retrieval experiment) or miR-127 siRNA plasmid (retrieval experiment) in order to explore the affect of Tudor-SN, NF-κB p65 and miR-127 on the AGPS, p-mTOR and mTOR by western blotting assay.

A total of 3x10<sup>5</sup> cells/well were seeded onto a 6-well plate and cultured for 24 h. Cells were lysed and total proteins were extracted by centrifugation at 12,000 x g for 10 min at 4°C with protein extraction buffer (Bioo Scientific, Austin, TX, USA). Protein was measured by Bradford assay (Beyotime Institute of Biotechnology, Haimen, China) and 50 ng protein were separated via 12% SDS-PAGE and transferred onto a polyvinylidene fluoride membrane. The membrane was then blocked using 1% BSA for 1 h at 37°C. The membrane was incubated with antibodies against AGPS (sc-374201; 1:2,000 dilution), phosphorylated mechanistic target of rapamycin (sc-293133, p-mTOR; 1:1,000 dilution) and mTOR (sc-8319; 1:1,500 dilution) (all Santa Cruz Biotechnology, Inc., Dallas, TX, USA) overnight at 4°C, and then incubated for 1 h at 37°C with mouse peroxidase-labeled anti-rabbit immunoglobulin G (cat no. sc-2357; 1:2,000 dilution; Santa Cruz Biotechnology, Inc.). Following this, the membrane was washed with PBS plus 0.05% Tween20 three times. The membrane was visualized using Immobilon Western chemiluminescent horseradish peroxidase substrate (EMD Millipore, Billerica, MA, USA). β-actin (A5441; 1:5,000 dilution; Sigma-Aldrich; Merck KGaA) was used as the control.

**Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay.** Cells were co-transfected with AGPS shRNA plasmid, and Tudor-SN shRNA plasmid, NF-κB p65 expression plasmid (retrieval experiment) or miR-127 siRNA plasmid (retrieval experiment) in order to explore the effect of Tudor-SN, NF-κB p65 and miR-127 on the AGPS by RT-qPCR.

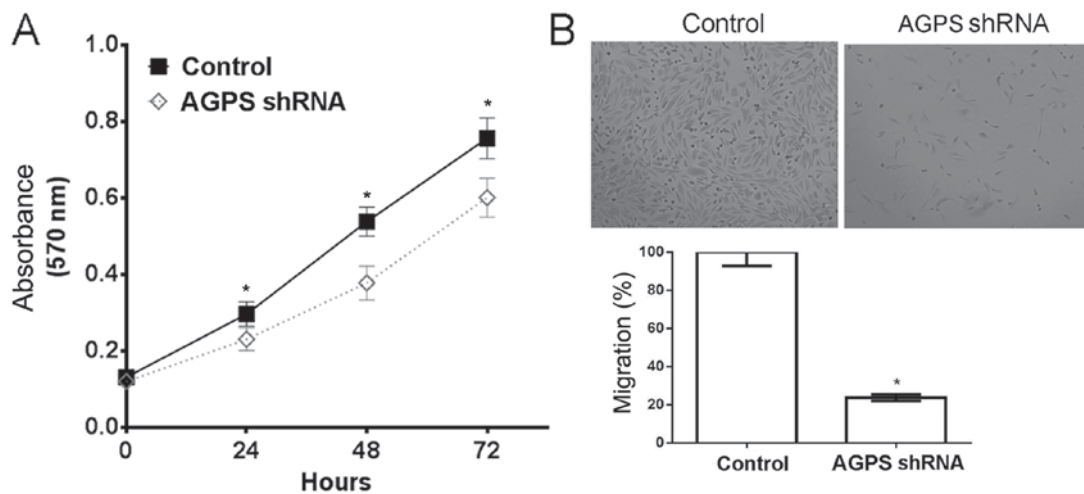


Figure 1. Tudor-SN silencing reduces the proliferation and migration in human glioma U87MG cells. (A) The cell proliferation assay demonstrated that the potential for proliferation was reduced by Tudor-SN silencing in human glioma U87MG cells. (B) The Transwell assay indicated that the potential for migration was reduced by Tudor-SN silencing in human glioma U87MG cells. \* $P \leq 0.05$ , compared with control group. AGPS, alkylglycerone phosphate synthase; Tudor-SN, Tudor-staphylococcal nuclease; shRNA, short hairpin RNA.

A total of  $3 \times 10^5$  cells/well were seeded onto a 6-well plate and cultured for 24 h. Cells were lysed and total RNA was extracted using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). Total RNA was then reverse transcribed using PrimeScript™ RT reagent Kit (Takara Biotechnology, Dalian, China) and mRNA, circular RNA (circRNA) and long non-coding RNA (lncRNA) expression of the target genes were detected using a qPCR assay (ABI7500; Applied Biosystems; Thermo Fisher Scientific, Inc.) and the  $2^{-\Delta\Delta C_q}$  method using a qRT-PCR SYBR® Kit (Takara Biotechnology) (15). The RT-qPCR primers used were as follows: AGPS, forward, 5'-ACC AGATTCCCTGGAGTTCA-3' and reverse, 5'-GAACCA CCAGTCCCTCGATA-3'; circ-ubiquitin-associated protein 2 (UBAP2) forward, 5'-AGCCTCAGAAGCCAACTCCTT TG-3' and reverse, 5'-TCAGGTTGAGATTTGAAGTCAAGA T-3'; circ-zinc finger protein 292 (ZNF292) forward, 5'-GCT CAAGAGACTGGGGTGTG-3' and reverse, 5'-AGTGTGTGT TCTGGGGCAAG-3'; circ-homeodomain-interacting protein kinase 3 (HIPK3) forward, 5'-TATGTTGGTGGATCCTGT TCGGCA-3' and reverse, 5'-TGGTGGGTAGACCAAGAC TTGTGA-3'; H19 imprinted maternally expressed transcript (non-protein coding) (H19) forward, 5'-ATCGGTGCCTCA GCGTTCGG-3' and reverse, 5'-CTGTCCTCGCCGTCA CACCG-3'; colon cancer-associated transcript 1 (non-protein coding) (CCAT1) forward, 5'-CATTGGGAAAGGTGCCGA GA-3' and reverse, 5'-ACGCTTAGCCATACAGAGCC-3'; hepatocellular carcinoma upregulated long non-coding RNA (HULC) forward, 5'-CAGGAAGAGTCGTCACGAGAA CCAG-3' and reverse, 5'-CTTCTTGCTTGATGCTTTGGT CTGT-3'; and  $\beta$ -actin forward, 5'-AGGCACCAGGGCGTG AT-3' and reverse, 5'-GCCACATAGGAATCCTTCTGAC-3'.  $\beta$ -actin was used as the control. The PCR conditions were as follows: Denaturation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 sec, 60°C for 60 sec and a final elongation at 95°C for 15 sec, followed by 60°C for 60 sec and 95°C for 15 sec.

**Statistical analysis.** SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data are presented

as the mean  $\pm$  standard deviation. The statistical analysis was performed using analysis of variance with Tukey's post-hoc test.  $P \leq 0.05$  was considered to indicate a statistically significant difference.

## Results

**AGPS silencing reduces proliferation and migration in human glioma U87MG cells.** The cell proliferation assay demonstrated that the potential for proliferation was significantly reduced by AGPS silencing in human glioma U87MG cells ( $P < 0.05$ ) (Fig. 1A). Furthermore, the Transwell assay indicated that the potential for migration was reduced by 23.7% as a result of AGPS silencing in human glioma U87MG cells, compared with that in the control group (Fig. 1B).

**AGPS silencing regulates the expression of circRNAs and lncRNAs in human glioma U87MG cells.** The RT-qPCR assay demonstrated that AGPS silencing significantly downregulated the expression of the circRNAs circUBAP2, circZNF292 and circHIPK3, and the lncRNAs H19, CCAT1 and HULC (Fig. 2).

**Silencing Tudor-SN decreases the expression of AGPS by NF- $\kappa$ B and miR-127 in human glioma U87MG cells.** The western blotting and RT-qPCR assay indicated that silencing Tudor-SN decreased the expression of AGPS. Furthermore, it was determined that the expression of AGPS was partially restored by NF- $\kappa$ B and miR-127 retrieval experiments (Fig. 3). Therefore, it was considered that the effect of Tudor-SN-regulated AGPS may be partially dependent on NF- $\kappa$ B and miR-127.

**Silencing Tudor-SN decreases the activity of the mTOR signaling pathway via NF- $\kappa$ B and miR-127 in human glioma U87MG cells.** The western blotting assay demonstrated that Tudor-SN silencing decreased the activity of the mTOR signaling pathway. Furthermore, it was determined that the activity of the mTOR signaling pathway was partially

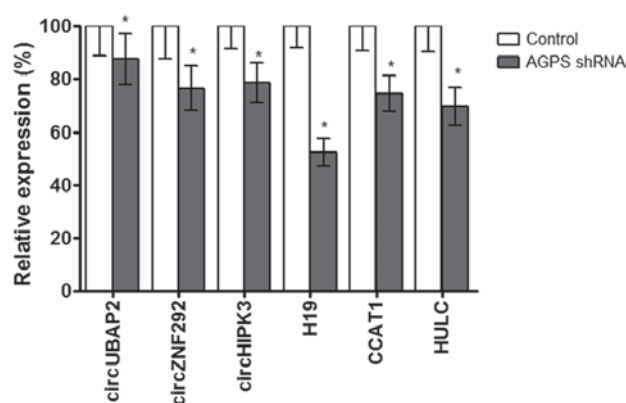


Figure 2. AGPS silencing regulates the expression of circRNAs and lncRNAs in human glioma U87MG cells. The reverse transcription-quantitative polymerase chain reaction assay demonstrated that AGPS silencing regulated the expression of circRNAs (circUBAP2, circZNF292 and circHIPK3) and lncRNAs (H19, CCAT1 and HULC) in human glioma U87MG cells. \* $P \leq 0.05$ , compared with control group. AGPS, alkylglycerone phosphate synthase; shRNA, short hairpin RNA; circ, circular; UBAP, ubiquitin-associated protein 2; ZNF292, zinc finger protein 292; HIPK3, homeodomain-interacting protein kinase 3; H19, H19 imprinted maternally expressed transcript (non-protein coding); CCAT1, colon cancer-associated transcript 1 (non-protein coding); HULC, hepatocellular carcinoma upregulated long non-coding RNA.

restored by NF- $\kappa$ B and miR-127 retrieval experiments (Fig. 4). Therefore, it was considered that the effect of the Tudor-SN-regulated mTOR signaling pathway may be partially dependent on NF- $\kappa$ B and miR-127.

## Discussion

AGPS and Tudor-SN serve a key role in the adjustment of tumor angiogenesis, and are expressed highly in multiple tumor tissue types and are associated with the prognosis of patients (16). In the present study, it was determined that AGPS silencing or suppression inhibited the proliferation and migration of glioma U87MG cells, validating the biological function of AGPS in glioma (17). circRNAs and lncRNAs are considered to serve a key role in tumor progression, and their altered expression can improve or suppress the potential for proliferation and migration in glioma. Therefore, circRNAs and lncRNAs are considered to be important targets for glioma therapeutics (18,19). The present study determined that the silencing of AGPS downregulated the expression of the circRNAs circUBAP2, circZNF292 and circHIPK3, and the lncRNAs H19, CCAT1 and HULC. All the aforementioned circRNAs and lncRNAs have been reported to be oncogenes (20-24).

It was also determined that Tudor-SN silencing suppressed the expression of AGPS; however, the mechanism underlying Tudor-SN-regulated AGPS in human glioma was not clear. Tudor-SN is a type of multi-functional protein that is widely expressed in tumor cells. Tudor-SN has the ability to activate various transcription factors, including NF- $\kappa$ B, and is involved in adjusting the expression of miRNAs (11).

miRNAs serve an important role in the progression of cancer, and a number of miRNAs are tumor suppressors, such as miR-127 (25). Inhibiting Tudor-SN promotes the expression of miR-127, and miR-127 has the ability to inhibit

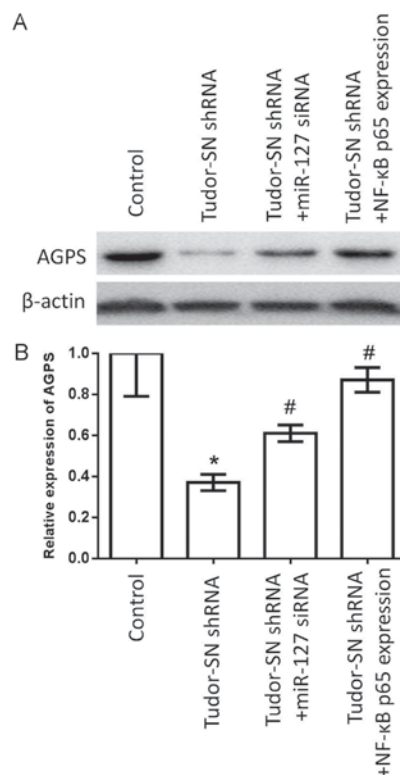


Figure 3. Tudor-SN silencing decreases the expression of AGPS via NF- $\kappa$ B and miR-127 in human glioma U87MG cells. (A) The western blotting assay indicated that Tudor-SN silencing decreased the protein expression of AGPS, and that the expression of AGPS was partially recovered via NF- $\kappa$ B and miR-127 retrieval experiments. (B) The reverse transcription-polymerase chain reaction assay demonstrated that Tudor-SN silencing decreased the mRNA expression of AGPS, and that the mRNA expression of AGPS was partially recovered via NF- $\kappa$ B and miR-127 retrieval experiments. \* $P \leq 0.05$ , compared with control group; # $P \leq 0.05$ , compared with Tudor-SN silencing group. AGPS, alkylglycerone phosphate synthase; Tudor-SN, Tudor-staphylococcal nuclease; NF, nuclear factor; miR, microRNA; shRNA, short hairpin RNA.

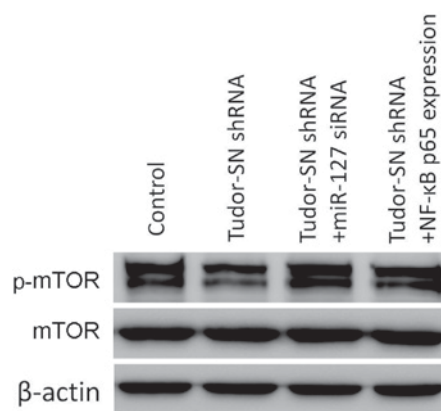


Figure 4. Tudor-SN silencing decreases the activity of the mTOR signaling pathway via NF- $\kappa$ B and miR-127 in human glioma U87MG cells. The western blotting assay demonstrated that Tudor-SN silencing decreased the activity of the mTOR signaling pathway, and that the activity of mTOR signaling pathway was partially recovered via NF- $\kappa$ B and miR-127 retrieval experiments. Tudor-SN, Tudor-staphylococcal nuclease; NF, nuclear factor; p-mTOR, phosphorylated mechanistic target of rapamycin; miR, microRNA.

the migration of tumor cells (26); therefore, Tudor-SN is considered to have the ability to adjust the expression of AGPS



in glioma cells through miR-127 adjustment and further control of the biological function of glioma cells. The present study determined that AGPS expression decreased following the inhibition of Tudor-SN.

Following a retrieval experiment to inhibit miR-127, the expression of AGPS was partially recovered, similar to that of NF- $\kappa$ B. The aforementioned results confirmed the alteration of AGPS expression through control of NF- $\kappa$ B and miR-127 by Tudor-SN in glioma cells. In the present study, it was also determined that Tudor-SN regulates the activity of the mTOR signaling pathway via miR-127 and NF- $\kappa$ B, indicating that Tudor-SN may regulate the expression of AGPS via the mTOR signaling pathway.

The data demonstrated that silencing AGPS reduced the potential for the proliferation and migration of glioma U87MG cells, and use of NF- $\kappa$ B and miR-127 may be the manner in which Tudor-SN regulates AGPS expression via the mTOR signaling pathway, laying a theoretical foundation and experimental basis for further investigation of the pathogenesis and therapeutics of malignant gliomas.

### Acknowledgements

Not applicable.

### Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 31501159), the Tianjin Public Health Key Research Project (grant no. 15KG108), the Tianjin Science and Technology Key Project on Chronic Diseases Prevention and Treatment (grant no. 16ZXMSY00020), the Tianjin Research Program of Application Foundation and Advanced Technology (grant no. 16JCYBJC27200) and the Special Program of Talents Development for Excellent Youth Scholars in Tianjin, China (TJZJH-QNBJRC-2-9).

### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

YZhu was responsible for study conception and design. YZha, YL, JJ and YQ were responsible for acquisition of data. HH and Y-GC performed analysis of the data.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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