



Lidocaine inhibits the proliferation and metastasis of epithelial ovarian cancer through the Wnt/ β -catenin pathway

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Background: Lidocaine, an amide local anesthetic, has recently been found to have anticancer action in various cancer cells. However, the role of lidocaine in epithelial ovarian cancer (EOC) remains largely unknown. In the present study, we investigated how lidocaine regulates the progression of EOC.

Methods: Real-time polymerase chain reaction was used to examine the expression of Snail, Wnt, β -catenin, E-cadherin, vimentin, matrix metalloproteinase (MMP)-7, MMP-9, and vascular endothelial growth factor in lidocaine-treated cells. Cell proliferation assays, cell apoptosis assays, and cell migration assays were employed to verify the function of lidocaine in EOC cells. Cell proliferation and cell migration assays were employed to verify the function of Wnt/ β -catenin signaling in lidocaine-treated EOC cells together with Wnt-overexpressing plasmids or inhibitor NVP-XAV939.

Results: Lidocaine could inhibit proliferation, migration, and invasion, and induce apoptosis in ovarian cancer cells lines in a dose-dependent manner. Wnt/ β -catenin signaling was involved in the suppression of epithelial–mesenchymal transition progression of ovarian cancer cells, which resulted in the downregulation of Snail and vimentin, as well as the upregulation of E-cadherin. Furthermore, overexpressed Wnt could reverse the carcinostatic effect of lidocaine, while Wnt inhibitor XAV-939 synergistically enhanced the antitumor effect of lidocaine.

Conclusions: Mechanistically, lidocaine could inhibit the proliferation and metastasis of EOC by the Wnt/ β -catenin pathway to regulate the progression of EOC.

Keywords: Lidocaine; epithelial ovarian cancer (EOC); Wnt/ β -catenin; metastasis

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Introduction

Epithelial ovarian cancer (EOC) is the seventh most common cancer and eighth most common cause of cancer death among women (1,2). Approximately 230,000 women worldwide are diagnosed and 150,000 die from EOC annually (3). Some deleterious mutations in breast cancer type (BRCA)1 and BRCA2 are largely associated with

high-grade serous EOC subtype susceptibility (4). The World Health Organization classification guidelines list 7 EOC histotypes: high-grade serous, low-grade serous, endometrioid, mucinous, clear cell, carcinosarcoma, and malignant Brenner tumors (5). Considerable efforts have been made to implement early screening and detection of EOC in patients; however, EOC oncogenesis in different

pathological patterns is distinct. Understanding the detailed molecular mechanism is imperative for developing more effective strategies for EOC diagnosis and treatment.

Lidocaine, a derivative of cocaine, is an amide local anesthetic (6). It has a biphasic effect of excitation and inhibition on the central nervous system, and there is no precursory excitation. It is widely used in regional anesthesia, peripheral nerve blocks, and epidural anesthesia with excellent effects on pain management. Lidocaine also has many other pharmacological effects, such as strong anti-inflammatory effects, and can inhibit pyroptosis, protect neurons, and prevent mitochondrial dysfunction (7-10). In a recently published study, lidocaine was found to have antitumor properties in diverse cancers, including hepatocellular carcinoma, malignant glioma, transient receptor potential cation channel subfamily V member 6 (TRPV6)-expressing cancer, colon adenocarcinoma, bladder cancer, gastric cancer, breast cancer, and lung cancer (6,11-17). Lidocaine can alleviate cytotoxicity resistance in lung cancer cells via the downregulation of microRNA-21, and also significantly inhibit the proliferation of lung cancer by regulating the expression of Golgi transport 1A (GOLT1A) (17,18). Another study found that lidocaine can also inhibit the proliferation and metastasis of lung cancer cell via the regulation of the miR-539/epidermal growth factor receptor (EGFR) axis (16). In a recent study, lidocaine could inhibit the metastatic potential of EOC cell via inhibiting EMT and FAK/Paxillin pathway, which indicating the potential of lidocaine in treat EOC (19). However, whether there were other potential mechanisms remains to be clarified.

β -Catenin is a crucial signaling transducer in Wnt signaling. Mutations of canonical Wnt signaling pathway genes frequently occur in cancer and lead to abnormal accumulation of the key effector β -catenin (20). Wnt/ β -catenin signaling mainly affects the maintenance of cancer stem cells, metastasis, and immune control (21). Small molecular inhibitors of the Wnt/ β -catenin pathway have been shown to inhibit Wnt secretion, leading to a size reduction of mouse mammary tumor virus (MMTV)-Wnt1-driven tumors and head and neck cancer xenotransplants (22). Therefore, Wnt signaling is strongly associated with cancer.

In the present study, we found that lidocaine could inhibit proliferation, migration, and invasion, and induce apoptosis in ovarian cancer cells lines in a dose-dependent manner. Further investigations demonstrated that lidocaine also could inhibit epithelial-mesenchymal transition (EMT)

of ovarian cancer cells via regulation of Wnt/ β -catenin pathway signaling and EMT-related genes. Furthermore, Wnt overexpression reverses the carcinostatic effect of lidocaine, while Wnt inhibitor XAV-939 enhances it. This suggests that lidocaine could inhibit the proliferation and metastasis of EOC through the Wnt/ β -catenin pathway.

We present the following article in accordance with the MDAR reporting checklist (available at <https://dx.doi.org/10.21037/tcr-21-1047>).

Methods

Cell culture

Human ovarian cancer cell line, SKOV3 and COC1 were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured in McCoy's 5A medium supplemented with 10% fetal bovine serum, America) for transient transfection. Samples were collected after 24 h to quantify the mRNA expression of the target gene.

Real-time polymerase chain reaction (PCR)

TRIzol and microRNA isolation kit were purchased from Qiagen (Valencia, CA, USA). Samples were homogenized in TRIzol, and total RNA extract and reverse transcription were performed according to the manufacturer's protocol. For PCR amplification of the cDNA fragment coding target genes, sense and antisense primer sequences for matrix metalloproteinase (MMP)-7, MMP-9, vascular endothelial growth factor (VEGF), Wnt, β -catenin, E-cadherin, vimentin, and β -actin were as described previously (Table 1).

Apoptosis analysis by fluorescence-activated cell sorting

The Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) detection kit (TransGene Biotech, Winooski, VT, USA) was used for the apoptosis assays. The cells were treated and then labelled with Annexin V-FITC and PI at room temperature under dark conditions for 20 min. The apoptosis percentage was tested using a FACSCalibur flow cytometer (Becton Dickinson, San Jose, CA, USA).

Cell counting kit-8 (CCK-8) assay

SKOV3 and COC1 cells were seeded in a 96-well plate (3,000/well). Cell proliferation was examined by CCK-8,

Table 1 The primers in this study

Primer sequence	Sense	Anti-sense
MMP-7	TCGGAGGAGATGCTCACTTCGA	GGATCAGAGGAATGTCCCATAACC
MMP-9	GCCACTACTGTGCCTTTGAGTC	CCCTCAGAGAATCGCCAGTACT
VEGF	TTGCCTTGCTGCTCTACCTCCA	GATGGCAGTAGCTGCGCTGATA
Wnt	ATGAACCGCCACAACAACGAGG	GTCCTTGAGGAAGTCACCGATG
β -catenin	CACAAGCAGAGTGCTGAAGGTG	GATTCCTGAGAGTCCAAAGACAG
E-cadherin	GCCTCCTGAAAAGAGAGTGGAAG	TGGCAGTGTCTCTCCAAATCCG
vimentin	AGGCAAAGCAGGAGTCCACTGA	ATCTGGCGTTCCAGGGACTCAT
β -actin	CACCATTGGCAATGAGCGGTTC	AGGTCTTTGCGGATGTCCACGT

as per the kit's instructions. Absorbance of 450 nm at 48 h after seeding was measured by a microplate reader (Bio-Rad, Hercules, CA, USA).

Terminal deoxynucleotidyl transferase-mediated digoxigenin-dUTP nick-end labeling (TUNEL) assays

TUNEL assay kit was purchased from Abcam (ab66108, Cambridge, USA). Treated cells and fixed cells in 4% PFA, next 0.1% Triton X-100 was used to permeabilize cells for 2 min. Cells were incubated with TUNEL reaction mixture under dark conditions for 1 h, and then incubated with Hoechst 33342 for 15 min. Mounted cells with ProLong Gold antifade overnight and imaged cells by a fluorescence microscope.

Cell migration and invasion assays

SKOV3 and COC1 cells were transfected with Wnt recombinant and blank plasmid, as well as 100 μ M lidocaine, and Wnt recombinant plasmid+100 μ M lidocaine in 12-well plates (10,000 cells/well) for 24 h. Then 5,000 cells per well were seeded in the inserts pre-equilibrated of 8- μ m pore Transwell for migration assays (Corning, NY, USA). Another, for invasion assay, the insert was coated with Matrigel before the cells were inoculated. After 24 h of incubation, the inserts were rinsed, fixed in 2% paraformaldehyde for 10 min, and then stained with crystal violet (Beyotime, Jiangsu, China). Migrated cells were counted under a microscope (ECLIPSE Ti; Nikon, Japan).

Statistical analysis

Each experiment was performed 3 times, and data were

analyzed with GraphPad Prism 8.0 software by 2-tailed test, unpaired Student's *t*-test or one-way analysis of variance. Differences with $P < 0.05$ were considered statistically significant.

Results

Lidocaine inhibits proliferation and induces apoptosis in ovarian cancer cells

To examine the effect of lidocaine in ovarian cancer, we selected the SKOV3 and COC1 cell lines and treated the cells with different doses of lidocaine (1, 10, and 100 μ M) and found that lidocaine inhibits the proliferation of SKOV3 and COC1 cells in a dose-dependent manner (*Figure 1A*). Furthermore, we performed BrdU (5-Bromodeoxyuridine) test to confirm the effect of lidocaine, and also found that the proliferation of SKOV3 and COC1 cells was inhibited in a dose-dependent manner (*Figure 1B*). In addition, the apoptosis analysis of SKOV3 cells with 1, 10, and 100 μ M lidocaine revealed that lidocaine could promote apoptosis in a dose-dependent manner (*Figure 1C*). These data indicated that lidocaine can suppress the progression of ovarian cancer cells.

Lidocaine inhibits the migration and invasion of ovarian cancer cells lines SKOV3 and COC1

To determine the effect of lidocaine in the migration and invasion of ovarian cancer cells, we treated SKOV3 and COC1 cells with different doses of lidocaine to analyze migration by Transwell assay. As shown in *Figure 2A*, the migration rate in SKOV3 or COC1 cells with 1 μ M lidocaine began to decline compared with that of the

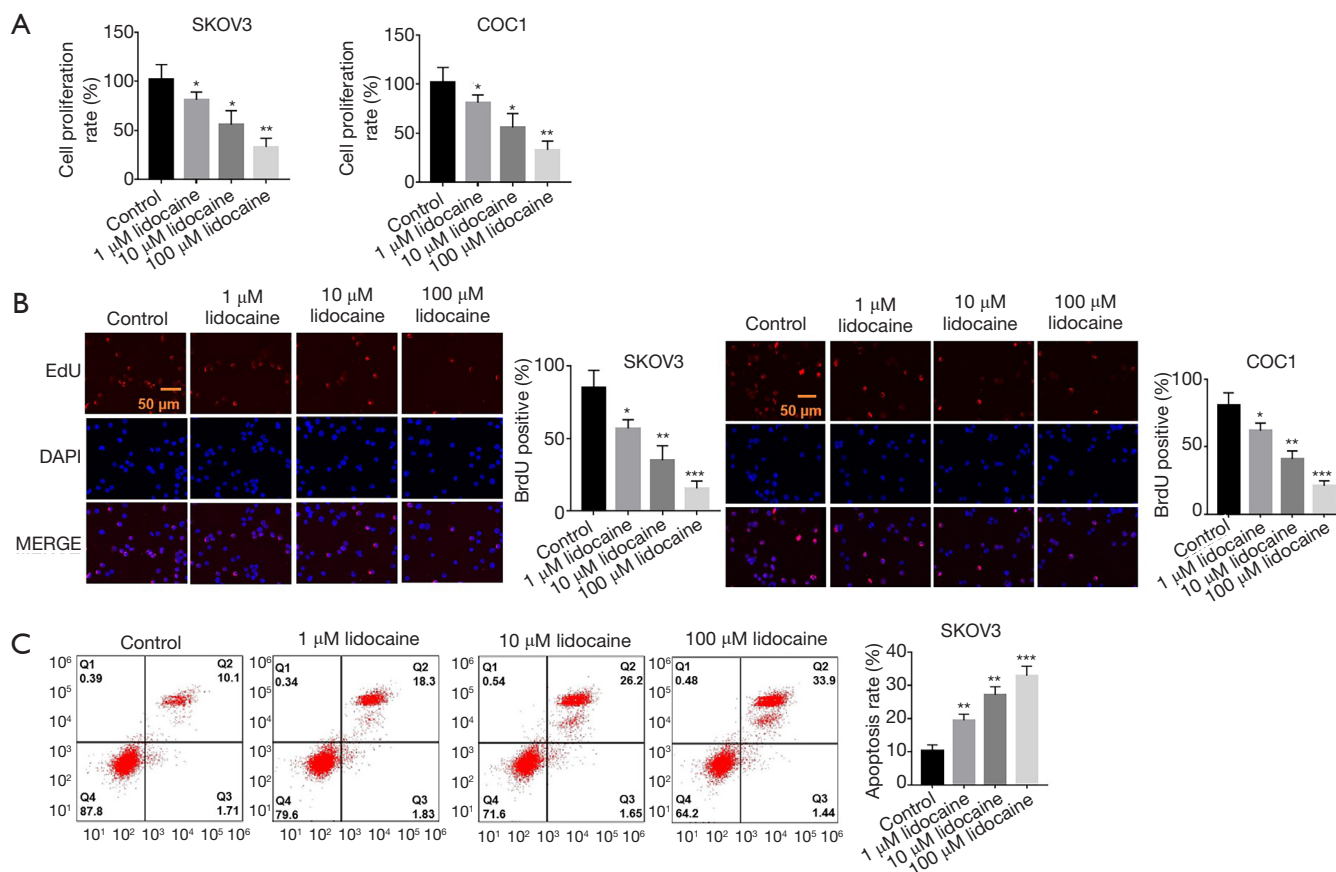


Figure 1 Lidocaine inhibits the proliferation and promote apoptosis of ovarian cancer cell lines. (A) Lidocaine inhibits the proliferation of ovarian cancer cell lines in a dose-dependent manner. (B) Cell proliferation assay for ovarian cancer cells with different doses of lidocaine by BrdU test (scale bar =50 μ m). (C) Lidocaine promotes apoptosis of ovarian cancer cell line in a dose-dependent manner. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$: other groups compared with control group.

control group. The migration rate was reduced by 2-fold in the 10 μ M lidocaine group, while it was reduced by 4-fold in the 100 μ M lidocaine group compared with the control group. We then carried out a Transwell assay to examine cell invasion with different concentrations of lidocaine. These findings demonstrated that lidocaine inhibits the invasion of ovarian cancer cells lines SKOV3 and COC1 in a dose-dependent manner (Figure 2B). As MMP-7, MMP-9, and VEGF were key determinants for cell migration and invasion, we detected their changes in mRNA expression levels by quantitative reverse transcription-PCR (qRT-PCR). The findings revealed that the expression levels of MMP-7, MMP-9, and VEGF were also inhibited in ovarian cancer cells lines SKOV3 and COC1 in a dose-dependent manner (Figure 2C,D,E). These data indicated that lidocaine can suppress the migration and invasion of ovarian cancer

cells via inhibiting the expression of MMP-7, MMP-9, and VEGF.

Lidocaine inhibits EMT in ovarian cancer cells

EMT has been shown to be a critical process for the migration, invasion, and metastasis of cancer cells. Therefore, in the present study, we treated ovarian cancer cells with different concentrations of lidocaine to investigate the changes of EMT-associated genes of ovarian cancer cells lines SKOV3 and COC1. Snail, an important transcription factor to determine EMT, was inhibited by lidocaine, and the inhibiting effect was more significant as the lidocaine concentration increased (Figure 3A). Because Wnt and β -catenin is involved in the EMT process, qRT-PCR analysis revealed that the expression level of Wnt and

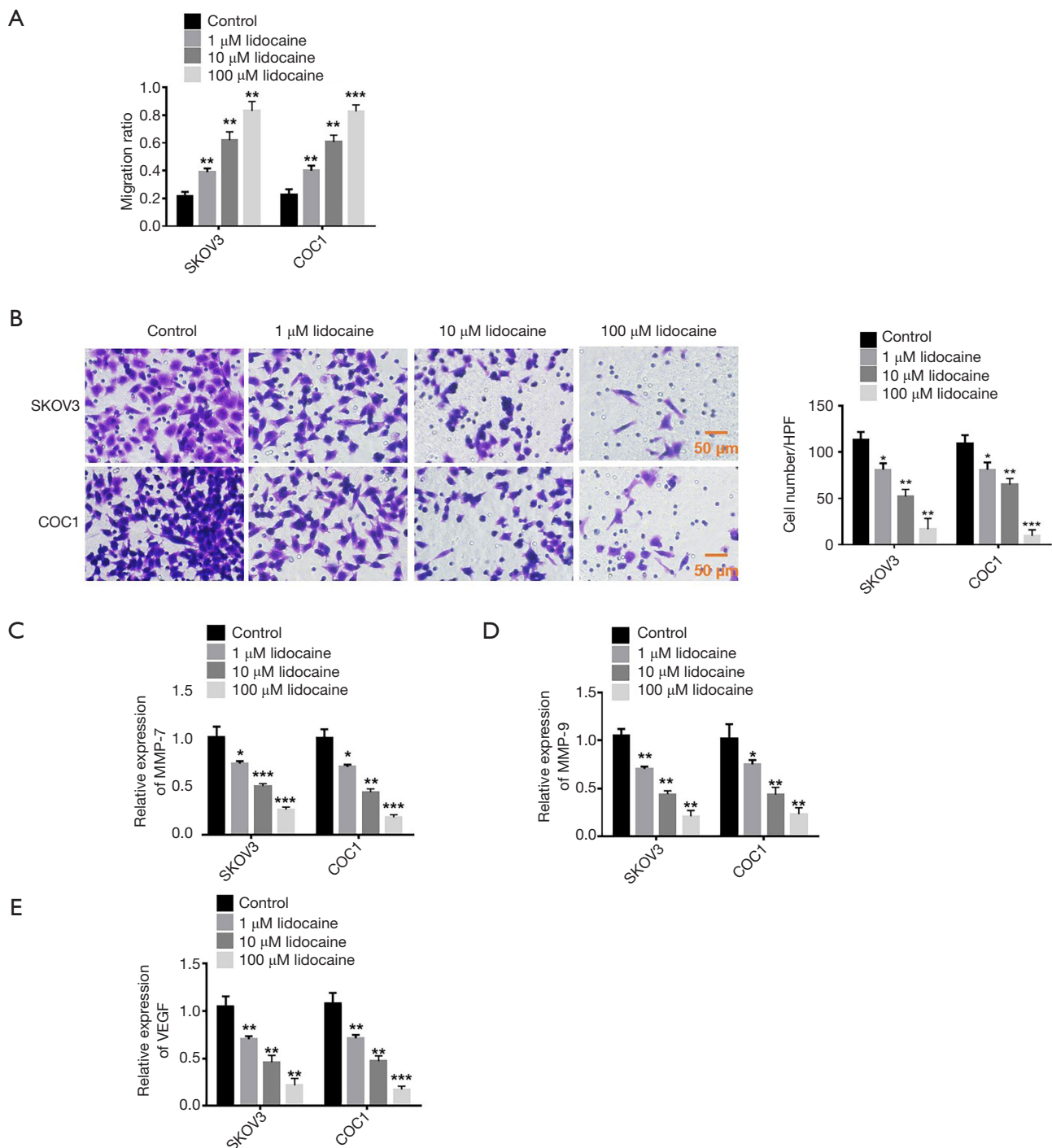


Figure 2 Lidocaine inhibits the migration of ovarian cancer cells lines. (A) Lidocaine inhibits the migration of ovarian cancer cells lines SKOV3 and COC1 in a dose-dependent manner. (B) Lidocaine inhibits the invasion of ovarian cancer cells lines SKOV3 and COC1 in a dose-dependent manner. (C) Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to analyze matrix metalloproteinase (MMP)-7 expression of ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine. (D) qRT-PCR was used to analyze MMP-9 expression of ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine. (E) qRT-PCR was used to analyze vascular endothelial growth factor (VEGF) expression of ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$: other groups compared with control group.

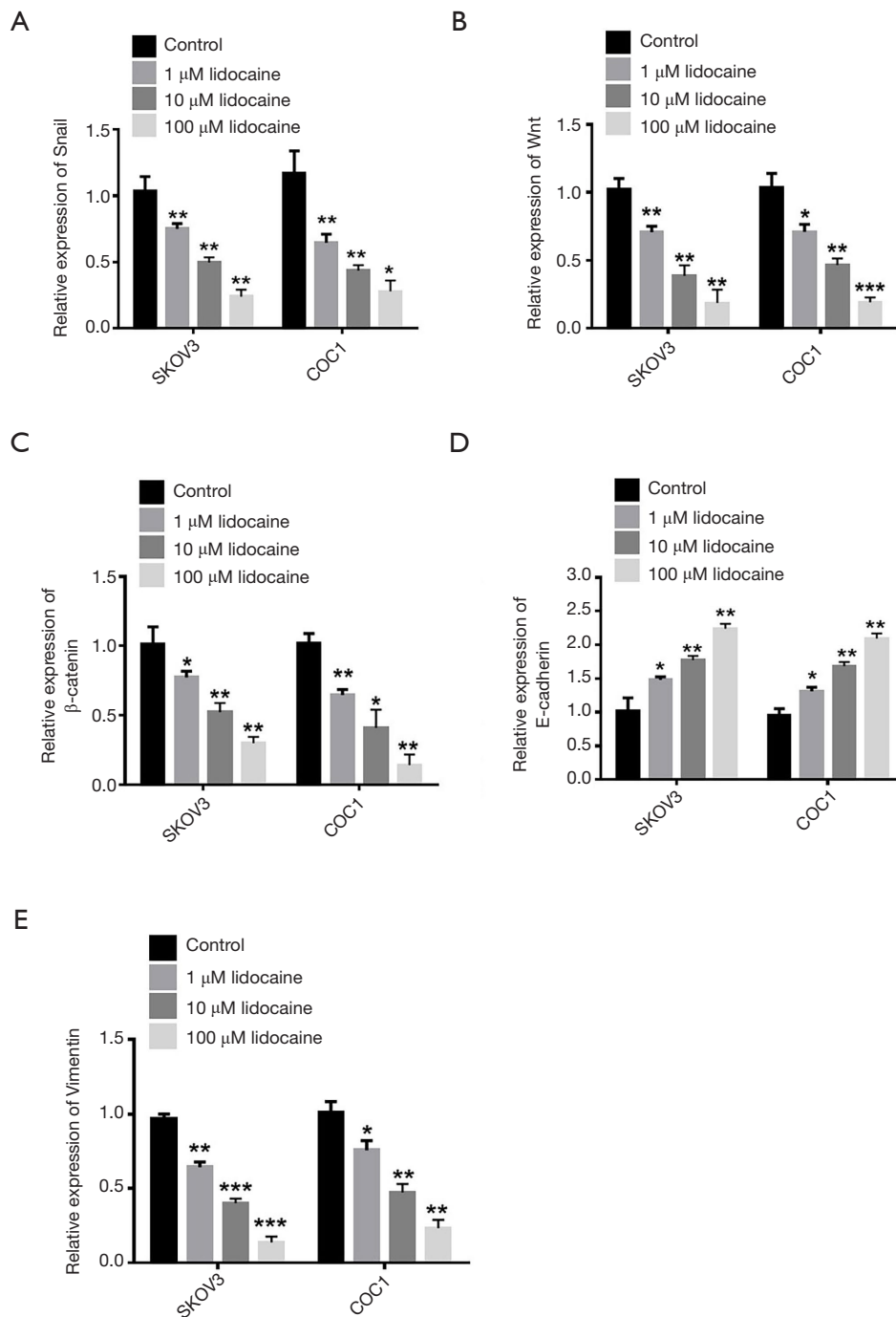


Figure 3 Lidocaine inhibits EMT in ovarian cancer cells. (A) Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to analyze the expression of Snail in ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine. (B) qRT-PCR was used to analyze the expression of Wnt in ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine. (C) qRT-PCR was used to analyze the expression of β -catenin in ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine. (D) Lidocaine enhanced the expression of E-cadherin in ovarian cancer cells lines SKOV3 and COC1 in a dose-dependent manner. (E) Lidocaine inhibited the expression of vimentin in ovarian cancer cells lines SKOV3 and COC1 in a dose-dependent manner. *P<0.05, **P<0.01, ***P<0.001: other groups compared with control group.

-catenin mRNA was repressed in ovarian cancer cells lines SKOV3 and COC1 with different doses of lidocaine (Figure 3B,C). In addition, E-cadherin and vimentin, markers of the EMT process, were more significantly inhibited and increased, respectively, as the lidocaine concentration increased compared with the control group (Figure 3D,E). These data indicated that lidocaine dose dependently inhibits EMT progression in ovarian cancer cells.

Overexpression of Wnt reverses the carcinostatic effect of lidocaine

To further investigate the function of the Wnt/ β -catenin pathway in the carcinostatic effect of lidocaine, we constructed the Wnt overexpression plasmid and treated SKOV3 cells with blank plasmid, Wnt recombinant plasmid, 100 μ M lidocaine, and Wnt recombinant plasmid + 100 μ M lidocaine. Cell scratch test results found that overexpressed Wnt could significantly enhance SKOV3 cell migration ability, while the lidocaine-treated group remarkably suppressed migration ability compared with the control group. The migration ability was obviously reversed in Wnt recombinant plasmid + 100 μ M lidocaine-treated group compared with that in the 100 μ M lidocaine-treated group (Figure 4A). Similarly, Transwell assay results showed that overexpressed Wnt substantially promoted cell invasion capacity, while the lidocaine-treated group considerably inhibited cell invasion capacity compared with the control group. Cell invasion capacity was significantly reversed in Wnt recombinant plasmid + 100 μ M lidocaine-treated group compared with that in the 100 μ M lidocaine-treated group (Figure 4B). We also examined the expression level of Wnt and β -catenin mRNA and found that Wnt recombinant plasmid reversed the inhibition of lidocaine for Wnt and β -catenin mRNA expression (Figure 4C,D). Moreover, Wnt recombinant plasmid reversed the promotion of lidocaine for E-cadherin and the inhibition of lidocaine for vimentin mRNA expression (Figure 4E,F). These data indicated that Wnt overexpression reversed the carcinostatic effect of lidocaine.

Wnt inhibitor XAV-939 enhances the carcinostatic effect of lidocaine

XAV-939, a selective inhibitor for the Wnt/ β -catenin pathway, was used to investigate the role of Wnt/ β -catenin signaling in the carcinostatic effect of lidocaine. We found

that XAV-939 could inhibit cell migration compared with the control group. Moreover, cell migration was remarkably reduced in XAV-939 + 100 μ M lidocaine-treated group compared with that in the 100 μ M lidocaine-treated group (Figure 5A). Transwell assay showed that XAV-939 could significantly inhibit the cell invasion capacity, while the cell invasion capacity in XAV-939 + 100 μ M lidocaine-treated group was substantially suppressed compared with that in the 100 μ M lidocaine-treated group (Figure 5B). The qRT-PCR data demonstrated that XAV-939 could obviously downregulate the expression level of Wnt and β -catenin mRNA compared with the control group, while the expression level of Wnt and β -catenin mRNA in XAV-939 + 100 μ M lidocaine-treated group, was considerably downregulated compared with that in the 100 μ M lidocaine-treated group (Figure 5C,D). In addition, XAV-939 could increase the expression of E-cadherin mRNA. When ovarian cancer cells were treated by XAV-939 + 100 μ M lidocaine, the expression level of E-cadherin mRNA was remarkably upregulated compared with that in the 100 μ M lidocaine-treated group (Figure 5E). XAV-939 also decreased the expression level of vimentin mRNA. XAV-939 + 100 μ M lidocaine-treated ovarian cancer cells significantly downregulated the expression level of vimentin mRNA compared with that in the 100 μ M lidocaine-treated group (Figure 5F). These data indicated that Wnt/ β -catenin inhibitor XAV-939 could enhance the carcinostatic effect of lidocaine.

Discussion

The present study demonstrated that lidocaine could regulate the progression of ovarian cancer through inhibiting proliferation, migration, and invasion and inducing apoptosis of ovarian cancer cells in a dose-dependent manner. Wnt/ β -catenin signaling was involved in the suppression of EMT progression of ovarian cancer cells, which resulted in the downregulation of Snail and vimentin, as well as the upregulation of E-cadherin. Furthermore, overexpressed Wnt could reverse the carcinostatic effect of lidocaine, while Wnt inhibitor XAV-939 enhanced the carcinostatic effect of lidocaine. These data indicated that lidocaine could inhibit proliferation and metastasis EOC by the Wnt/ β -catenin pathway.

Lidocaine, as a local anesthetic, has been found to have anticancer actions in a wide range of cancer cells. It does not only inhibit tumor cell growth in colon adenocarcinoma, bladder cancer, and gastric cancer, but also represses

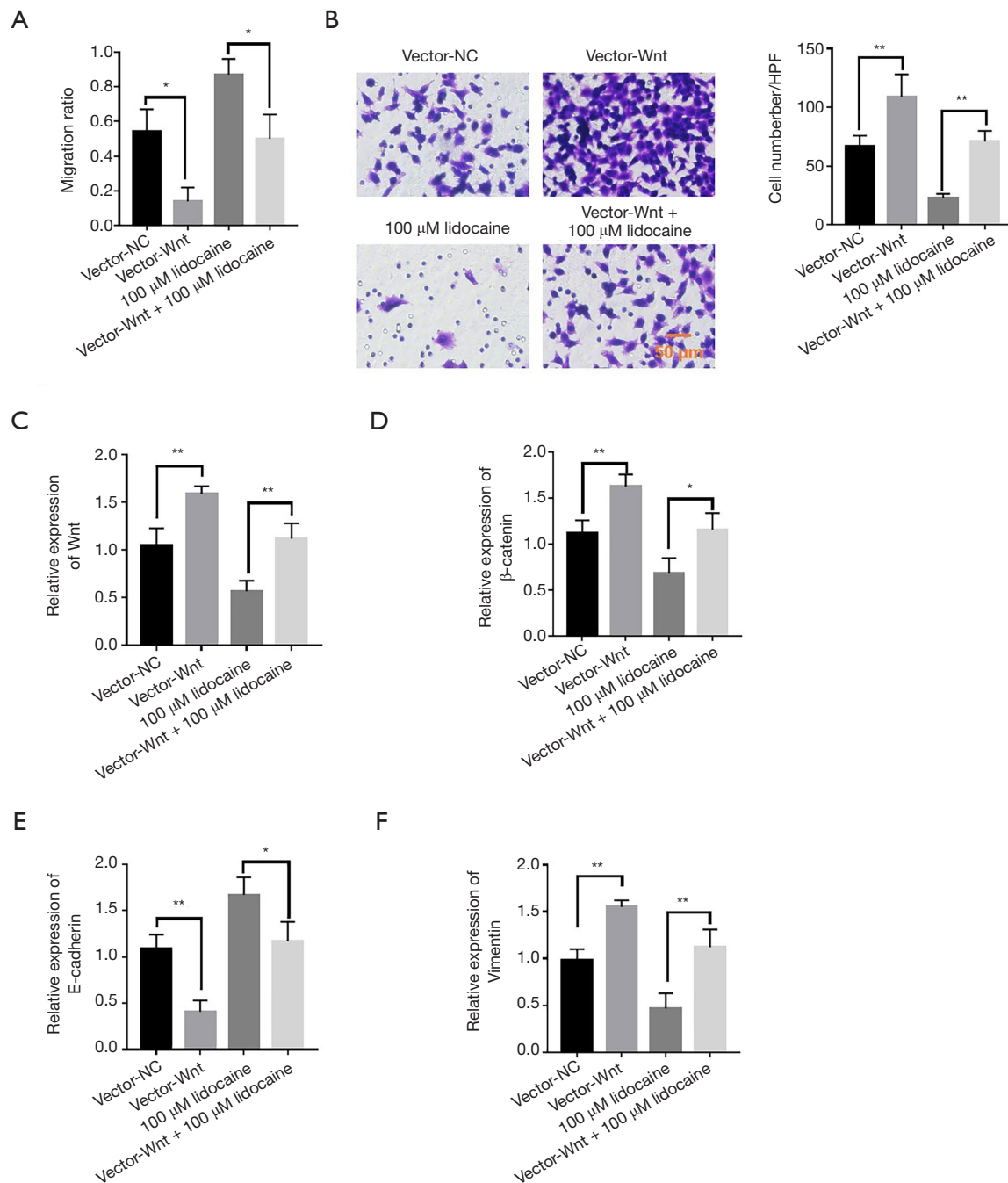


Figure 4 Overexpression of Wnt reduced the antitumor effect of lidocaine. (A) Migration distance was measured in Wnt recombinant plasmid, blank plasmid, 100 μ M lidocaine, and Wnt recombinant plasmid + 100 μ M lidocaine-treated group, by cell scratch test. (B) Cell invasion was detected in Wnt recombinant plasmid, blank plasmid, 100 μ M lidocaine, and Wnt recombinant plasmid + 100M lidocaine-treated group by Transwell assay. (C,D,E,F) Expression of Wnt, β -catenin, E-cadherin, and vimentin was examined in Wnt recombinant plasmid, blank plasmid, 100 μ M lidocaine, and Wnt recombinant plasmid + 100 μ M lidocaine-treated group by quantitative reverse transcription polymerase chain reaction test. * $P < 0.05$, ** $P < 0.01$: other groups compared with vector-NC group.

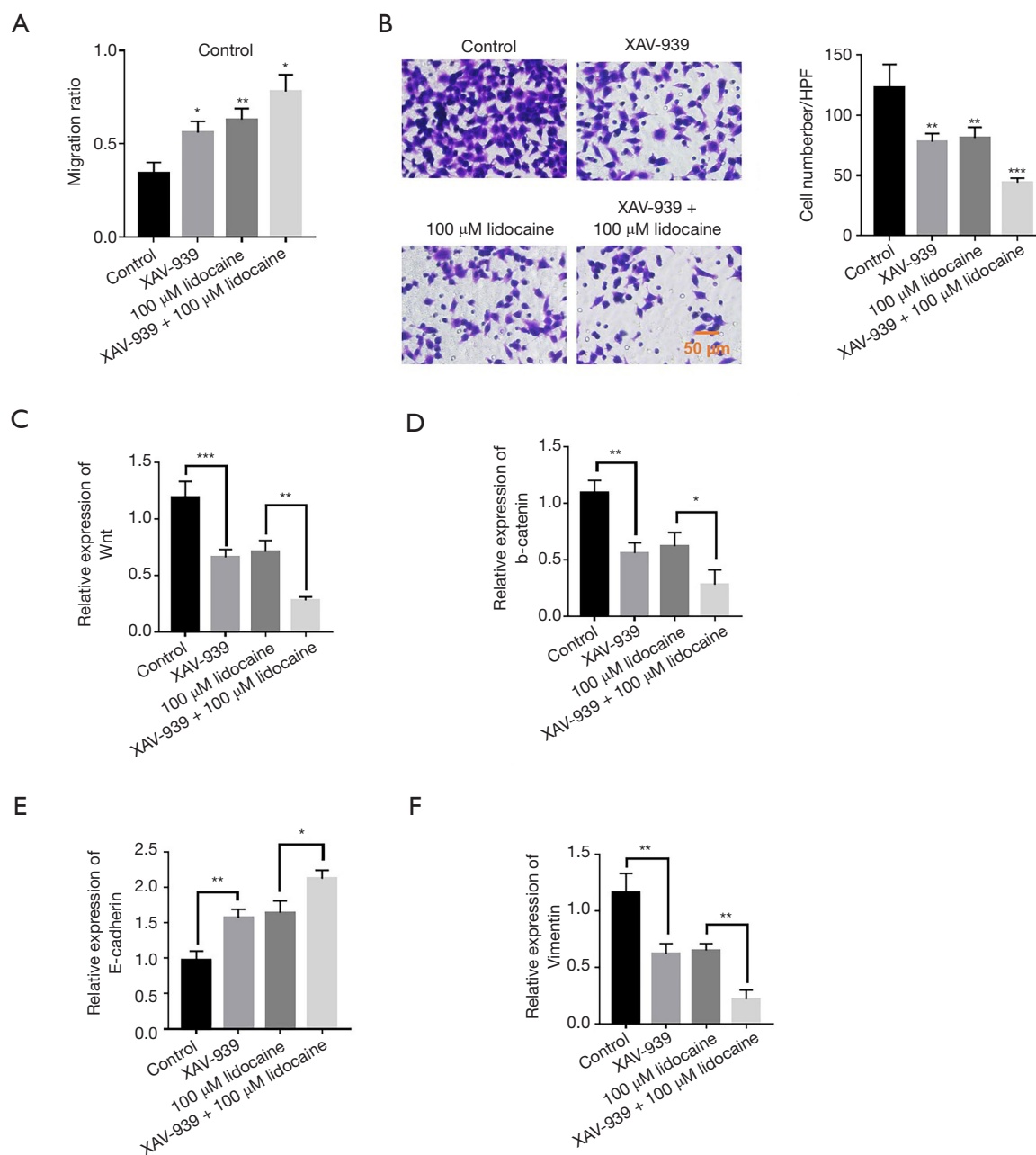


Figure 5 Wnt inhibitor XAV-939 enhanced the antitumor effect of lidocaine. (A) Migration distance was measured in PBS, XAV-939, 100 M lidocaine, and XAV-939 + 100 μM lidocaine-treated group by cell scratch test. (B) Cell invasion was detected in PBS, XAV-939, 100 μM lidocaine, and XAV-939 + 100 μM lidocaine + treated group by Transwell assay. (C) Expression of Wnt was examined in PBS, XAV-939, 100 μM lidocaine, and XAV-939 + 100 μM lidocaine-treated group by quantitative reverse transcription polymerase chain reaction (qRT-PCR) test. (D) Expression of β-catenin was examined in PBS, XAV-939, 100 μM lidocaine, and XAV-939 + 100 μM lidocaine-treated group by qRT-PCR test. (E) Expression of E-cadherin was examined in PBS, XAV-939, 100 μM lidocaine, and XAV-939 + 100 μM lidocaine-treated group by qRT-PCR test. (F) Expression of Wnt was examined in PBS, XAV-939, 100 μM lidocaine, and XAV-939 + 100 μM lidocaine-treated group by qRT-PCR test. *P<0.05, **P<0.01, ***P<0.001: other groups compared with control group. PBS: phosphate buffer saline.

tumor metastasis by inhibiting migration and invasion (12-15). We also found that lidocaine inhibits proliferation, migration, and invasion, and induces apoptosis in ovarian cancer cells in a dose-dependent manner. In addition, Snail, E-cadherin, and vimentin, markers of the EMT process, were more significantly regulated as the lidocaine concentration increased compared with the control group, and EMT-associated genes matrix metalloprotein (MMP)-7 and matrix metalloprotein (MMP)-9 were downregulated by lidocaine. These findings in EOC are similar to those of lung cancer, in which lidocaine was found to upregulate the cleavage of pro-apoptotic protein caspase-3, as well as altering EMT-related proteins MMP-9 and vimentin (23). Further, lidocaine is safe drug with little side effects. In one study of intravenous lidocaine for cancer pain, the most common side effects of lidocaine were drowsiness, perioral numbness, nausea, and slight fluctuations in blood pressure. It is safe and effective in cancer patients (24).

Wnt signaling is one of the key cascades regulating carcinogenesis (21,25). The canonical Wnt pathway is commonly β -catenin-dependent signaling (26,27). We found that lidocaine dose dependently inhibits the expression level of Wnt mRNA in ovarian cancer cells. β -Catenin is a crucial signaling transducer in Wnt signaling (28,29); therefore, we further examined the expression level of β -catenin mRNA by qRT-PCR and found that β -catenin mRNA also had a low expression in ovarian cancer cells in the lidocaine-treated group compared with the control group. Moreover, overexpressed Wnt reduced the antitumor effect of lidocaine by Wnt recombinant plasmid. In human cancers, Wnt/ β -catenin signaling is highly activated, which has led to the development of various Wnt signaling inhibitors for cancer therapies (30). We also found that Wnt inhibitor XAV-939 could enhance the antitumor effect of lidocaine, which decreased EMT progression and ovarian cancer. We demonstrated that lidocaine could inhibit the proliferation and metastasis of EOC through the Wnt/ β -catenin pathway. Further, lidocaine has been reported to promote ovarian and breast cancer cell ferroptosis via miR-382-5p/SLC7A11 axis (31). Lidocaine could promote thyroid cancer cells apoptosis via MAPK pathway (32). The invasion and migration of breast cancer, prostatic cancer and ovarian cancer cells with TRPV6-expressing could be inhibited by lidocaine, while this inhibition was associated with calcium influx reduction (12). In addition, lidocaine was also found to significantly inhibit C-X-C motif chemokine receptor 4 (CXCR4) signaling, EGFR signaling, and the MAP kinase kinase 1 (MEK)/extracellular regulated protein kinases

(ERK) and nuclear factor kappa-B (NF- κ B) pathways, as well as activate the phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (Akt) pathway (6,15,16,23). Thus, lidocaine could exert anti-EOC effect via multi signal pathways.

Conclusions

We demonstrated that lidocaine could inhibit proliferation, migration, and invasion, and induce apoptosis in ovarian cancer cells in a dose-dependent manner to regulate the progression of ovarian cancer. It also could suppress the EMT progression of ovarian cancer through the Wnt/ β -catenin pathway. Wnt inhibitor XAV-939 further enhanced the antitumor effect of lidocaine.

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Footnote

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Data Sharing Statement: Available at <https://dx.doi.org/10.21037/tcr-21-1047>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/tcr-21-1047>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and informed consent were waived.

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