Postprint of a Study on Timing and Influencing Factors of Non-steroidal Anti-inflammatory Drug Administration for Prevention of Post-ERCP Pancreatitis

Authors: Wu Xiangpeng, Li Enjun, Li Xiongwei, Wang Haihong, Cui Wei, Wu Xiangli, Qi Weihua, Hou Senlin, Wu Xiangpeng

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Abstract

Background Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for diagnosing and treating biliopancreatic diseases, but post-ERCP pancreatitis (PEP) is a serious complication. Non-steroidal anti-inflammatory drugs (NSAIDs) may play a role in preventing PEP due to their anti-inflammatory and analgesic effects. Exploring appropriate timing of medication administration and the effects of combination therapy can help reduce the risk of PEP occurrence. Objective This study aims to evaluate the timing of NSAID administration and influencing factors in PEP prevention, in order to determine its optimal application in clinical practice. Methods A total of 866 subjects who underwent ERCP treatment in the Department of General Surgery and Oncology at Handan Central Hospital from December 2021 to December 2023 were enrolled as study participants. They were divided into a preoperative medication group (431 cases) and a postoperative medication group (435 cases) according to the random number table method. Based on the type of NSAIDs used, they were further divided into preoperative monotherapy subgroup (210 cases), preoperative combination therapy subgroup (221 cases), postoperative monotherapy subgroup (247 cases), and postoperative combination therapy subgroup (188 cases). The preoperative monotherapy subgroup received an intramuscular injection of 75 mg diclofenac sodium 30 minutes before ERCP, while the preoperative combination therapy subgroup additionally received 100 mg indomethacin suppository per rectum at the same time. The postoperative monotherapy subgroup received an intramuscular injection of 75 mg diclofenac sodium immediately after ERCP, and the postoperative combination therapy subgroup received both 75 mg diclofenac sodium intramuscularly and 100 mg indomethacin suppository per rectum simultaneously. All interventions

were single-dose administrations. The primary observation indicators included the incidence and severity of PEP, as well as the incidence of postoperative perforation, bleeding, and cholangitis. Differences in the incidence, severity, and adverse reactions of post-ERCP pancreatitis were compared between groups. Multivariate Logistic regression analysis was used to analyze the influencing factors of PEP occurrence in subjects. Results Comparison of PEP incidence among the four subgroups showed a statistically significant difference (P<0.05). Specifically, the PEP incidence in the preoperative monotherapy subgroup was lower than that in the postoperative monotherapy subgroup and the postoperative combination therapy subgroup (P<0.05), and the PEP incidence in the preoperative combination therapy subgroup was lower than that in the postoperative monotherapy subgroup and the postoperative combination therapy subgroup (P<0.05). There was no statistically significant difference in PEP severity and adverse reaction incidence among the four groups (P>0.05). Multivariate Logistic regression analysis results showed that BMI$ $24 kg/m2 (OR=3.866, 95%CI=2.493~5.996), alcohol abuse (OR=2.624, 95%CI=1.520~4.529), diabetes mellitus (OR=2.687, 95%CI=1.559~4.634), cannulation time >10 min (OR=4.229, 95%CI=2.531~7.066), and use of double-wire technique (OR=3.542, 95%CI=2.159~5.809) were independent risk factors for PEP occurrence (P<0.05). B-ultrasound indicating extrahepatic bile duct dilation was a protective factor against PEP occurrence (OR=0.573, 95%CI=0.347~0.947). Conclusion BMI, alcohol abuse, diabetes mellitus, cannulation time >10 min, and use of double-wire technique are independent risk factors for PEP occurrence. Prophylactic combination use of indomethacin suppository and diclofenac sodium before ERCP can effectively reduce the risk and severity grade of PEP, and decrease the incidence of postoperative adverse reactions in subjects.

Full Text

Timing of Administration and Combination Therapy of Non-steroidal Anti-inflammatory Drugs for the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

WU Xiangpeng[1]*, LI Enjun[1], LI Xiongwei[1], WANG Haihong[1], CUI Wei[2], WU Xiangli[3], QI Weihua[4], HOU Senlin[5]

[1]Sixth Department of General Surgery, Handan Central Hospital, Handan 056008, China
[2]Department of Radiotherapy, Handan Central Hospital, Handan 056008, China
[3]Department of Pharmacy, Handan Central Hospital, Handan 056008, China
[4]Second Department of Oncology, Handan Central Hospital, Handan 056008, China
[5]The Second Hospital of Hebei Medical University, Shijiazhuang 050000, China

Corresponding author: WU Xiangpeng, Associate Chief Physician; E-mail: 86618251@qq.com

Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for diagnosing and treating biliary and pancreatic diseases, but post-ERCP pancreatitis (PEP) remains a serious complication. Non-steroidal anti-inflammatory drugs (NSAIDs), due to their anti-inflammatory and analgesic effects, may play a role in PEP prevention. Exploring optimal timing and combination therapy could help reduce PEP risk.

Objective: This study aimed to evaluate the administration timing and influencing factors of NSAIDs in PEP prevention to determine their optimal clinical application.

Methods: A total of 866 patients who underwent ERCP in the Department of General Surgery and Oncology at Handan Central Hospital between December 2021 and December 2023 were enrolled. Using a random number table, participants were assigned to a preoperative medication group (n=431) or a postoperative medication group (n=435). Based on NSAID type, they were further divided into four subgroups: preoperative monotherapy (n=210), preoperative combination therapy (n=221), postoperative monotherapy (n=247), and postoperative combination therapy (n=188). The preoperative monotherapy subgroup received 75 mg diclofenac sodium intramuscularly 30 minutes before ERCP, while the preoperative combination subgroup received additional 100 mg indomethacin suppository rectally at the same time. The postoperative monotherapy subgroup received 75 mg diclofenac sodium intramuscularly immediately after ERCP, and the postoperative combination subgroup received both 75 mg diclofenac sodium intramuscularly and 100 mg indomethacin suppository rectally. All interventions were single-dose. Primary outcomes included PEP incidence and severity, plus rates of postoperative perforation, bleeding, and cholangitis. Between-group differences in PEP incidence, severity, and adverse reactions were compared. Multivariate logistic regression was used to analyze PEP risk factors.

Results: PEP incidence differed significantly among the four subgroups (P<0.05). The preoperative monotherapy subgroup had lower PEP incidence than both the postoperative monotherapy and postoperative combination subgroups (P<0.05). The preoperative combination subgroup also showed lower PEP incidence than the postoperative monotherapy and postoperative combination subgroups (P<0.05). No significant differences were found in PEP severity or adverse reaction rates among the four groups (P>0.05). Multivariate logistic regression identified BMI $ 24kg/m^{2}$ (OR=3.866, 95%CI=2.493-5.996), alcohol abuse (OR=2.624, 95%CI=1.520-4.529), diabetes (OR=2.687, 95%CI=1.559-4.634), cannulation time >10

minutes (OR=4.229, 95%CI=2.531-7.066), and double guidewire technique use (OR=3.542, 95%CI=2.159-5.809) as independent risk factors for PEP (P<0.05). Ultrasonography-detected extrahepatic bile duct dilation was a protective factor (OR=0.573, 95%CI=0.347-0.947).

Conclusion: BMI $ 24kg/m^{2}$, alcohol abuse, diabetes, cannulation time >10 minutes, and double guidewire technique use are independent risk factors for PEP. Prophylactic combination therapy with indomethacin suppository and diclofenac sodium before ERCP effectively reduces PEP risk and severity while decreasing postoperative adverse reaction rates.

Keywords: Endoscopic retrograde cholangiopancreatography; Pancreatitis; Adverse reactions; Indomethacin suppositories; Diclofenac sodium

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Introduction

Since the 1960s, endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a diagnostic tool to the gold standard for therapeutic interventions in biliopancreatic diseases, playing an irreplaceable role in disease diagnosis, common bile duct stone extraction, and stent placement for malignant obstructive jaundice [1-2]. However, post-ERCP pancreatitis (PEP) remains one of the most common and serious complications, with an incidence ranging from 3% to 16% [3-4]. PEP not only prolongs hospital stays and increases healthcare costs but also significantly impairs patients' quality of life. Therefore, effective PEP prevention has become a major research priority in the ERCP field.

Non-steroidal anti-inflammatory drugs (NSAIDs), widely used for their anti-inflammatory and analgesic properties [5-6], have shown potential efficacy in PEP prevention [7-8]. NSAIDs exert their effects by inhibiting cyclooxygenase activity, thereby blocking the conversion of arachidonic acid to prostaglandins [9-10]. Consequently, NSAIDs have become one of the primary pharmacological approaches for PEP prevention. Both indomethacin and diclofenac sodium are NSAIDs that reduce prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), thereby decreasing inflammatory responses and pancreatic injury. Research suggests that combination therapy may enhance anti-inflammatory effects through multi-target action, complementary delivery routes, and reduced high-dose side effects of single agents, further lowering the risk of various acute inflammatory reactions [11]. This study evaluates the optimal timing, dosage, and route of NSAID administration for preventing PEP and other common post-ERCP adverse reactions, aiming to provide scientific evidence for NSAID use in ERCP complication prevention and clinical guidance on timing, dosage, and administration routes to further reduce PEP incidence and severity and improve patient outcomes.

Methods

1.1 Study Participants We enrolled 866 patients who underwent ERCP in the Department of General Surgery and Oncology at Handan Central Hospital between December 2021 and December 2023. Inclusion criteria were: (1) age >18 years; (2) ERCP indication; (3) no contraindications to NSAIDs before ERCP; (4) completed routine examinations including abdominal ultrasound, blood cell analysis, and biochemistry; (5) full civil capacity. Exclusion criteria included: (1) NSAID allergy or intolerance; (2) active upper gastrointestinal bleeding or bleeding tendency not effectively controlled; (3) severe hepatic or renal dysfunction including acute failure or decompensated cirrhosis; (4) pregnancy or lactation; (5) severe cardiac disease such as unstable angina, recent myocardial infarction, or severe heart failure; (6) severe infection or sepsis; (7) psychiatric or cognitive disorders preventing study cooperation; (8) incomplete clinical data; (9) participation in other clinical trials within one month; (10) other conditions deemed unsuitable by investigators. This study was approved by the Handan Central Hospital Medical Ethics Committee [Approval No.: (2024) Lun Shen Lun Wen No. (020)], and all participants and their families provided informed consent.

1.2 Study Design and Interventions **1.2.1 Grouping:** Participants were randomly assigned to preoperative or postoperative medication groups using a computer-generated random number table. A dedicated researcher performed the randomization while remaining blinded to patient data to reduce selection bias. Sample size calculation using PASS software with two-sample t-test (α=0.05, Power=90%, effect size d=0.5) determined a minimum of 86 participants per group. The final allocation yielded 431 patients in the preoperative group and 435 in the postoperative group. Based on NSAID type, participants were further divided into four subgroups: preoperative monotherapy (n=210), preoperative combination therapy (n=221), postoperative monotherapy (n=247), and postoperative combination therapy (n=188).

1.2.2 Data Collection: We collected baseline data, clinical characteristics, and examination indicators including sex, age, height, weight, alcohol abuse history (beer \$ $1000ml/dayorliquor > 100ml/day$), $smokinghistory$(\$1 pack/day), diabetes, hypertension, prior pancreatitis or cholelithiasis, bile duct dilation, ERCP technical details (cannulation attempts, precut sphincterotomy, double guidewire technique, balloon dilation), and pain scores.

1.2.3 ERCP Procedure: Senior physicians with >5 years of experience performed ERCP using an Olympus TJF-240 electronic duodenoscope with zebra guidewires and imported plastic biliary stents. For patient comfort and safety, 10 mg anisodamine, 10 mg diazepam, and 1 mg/kg pethidine were administered intramuscularly 30 minutes before the procedure. Prophylactic antibiotics were given to patients requiring biliary stent placement. The endoscope was advanced to the duodenum, and the papilla was cannulated with a catheter over a guidewire. After successful guidewire passage through the stricture, the catheter

was advanced and contrast was injected to visualize biliary anatomy. Cholangiography under fluoroscopy detailed biliary and pancreatic duct structures to identify stones, strictures, or tumors. The endoscope and catheter were withdrawn after completing all procedures.

1.2.4 NSAID Administration: The preoperative monotherapy subgroup received 75 mg diclofenac sodium intramuscularly 30 minutes before ERCP. The preoperative combination subgroup received the same diclofenac dose plus 100 mg indomethacin suppository rectally. The postoperative monotherapy subgroup received 75 mg diclofenac sodium intramuscularly immediately after ERCP. The postoperative combination subgroup received both 75 mg diclofenac sodium intramuscularly and 100 mg indomethacin suppository rectally. All interventions were single-dose.

1.2.5 Outcome Measures: (1) **PEP incidence and severity:** PEP was defined as new or worsened abdominal pain with serum amylase >3× normal within 24 hours post-procedure or imaging evidence of pancreatitis [12]. Severity was graded as: mild (transient abdominal pain with nausea/vomiting resolving within days without specific treatment), moderate (pain >3 days with fever, gastrointestinal dysfunction, ileus, or abdominal distension), or severe (prolonged pain with severe inflammation, organ dysfunction requiring ICU care, fluid resuscitation, antibiotics, and nutritional support). (2) **Adverse reactions:** Including perforation (abdominal pain, fever, peritoneal signs with free air on imaging), cholangitis (fever, chills, abdominal pain, jaundice with positive cultures), bleeding (hematemesis, melena, hematochezia, or hypotension), and pain scores assessed pre- and 24-hours post-procedure using a 10-cm visual analog scale (0=no pain, 10=worst pain) [13].

1.3 Statistical Analysis Data were analyzed using R 4.3.0 and PASS software. Continuous normally distributed data were expressed as mean±standard deviation and compared using one-way ANOVA. Categorical data were expressed as percentages and compared using chi-square or Fisher' s exact tests. Rank sum tests compared ordinal data across multiple groups. Univariate and multivariate logistic regression analyses identified PEP risk factors. P<0.05 was considered statistically significant.

Results

2.1 Baseline Characteristics Among 866 participants (442 men [51.04%], 424 women [48.96%]; mean age 51.3$±$7.1 years), 210 were in the preoperative monotherapy subgroup (24.25%), 221 in preoperative combination (25.52%), 247 in postoperative monotherapy (28.52%), and 188 in postoperative combination (21.71%). No significant differences existed among the four groups in sex, age, BMI, liver cirrhosis, diabetes, smoking, alcohol abuse, hypertension, pancreatitis history, cholelithiasis history, bile duct dilation, ERCP technical details

(cannulation attempts, precut, double guidewire technique, papillary balloon dilation), or pain scores (P>0.05) .

2.2 PEP Incidence and Severity PEP occurred in 96 of 866 patients (11.09%): 18 cases (8.57%) in preoperative monotherapy, 10 (4.52%) in preoperative combination, 41 (16.60%) in postoperative monotherapy, and 27 (14.36%) in postoperative combination. PEP incidence differed significantly among groups (P<0.001). Preoperative monotherapy showed lower PEP rates than postoperative monotherapy (^{2}=6.506, P=0.007) and postoperative combination (^{2}=3.316, P=0.048). Preoperative combination also had lower rates than postoperative monotherapy (^{2}=17.513, P<0.001) and postoperative combination (^{2}=11.946, P<0.001). No differences were found between preoperative monotherapy vs. preoperative combination (^{2}=2.903, P=0.065) or postoperative monotherapy vs. postoperative combination (^{2}=0.405, P=0.309) .

Of 96 PEP cases, 78 were mild (9.01%), 15 moderate (1.73%), and 3 severe (0.35%). Severity distribution did not differ significantly among groups (P=0.465) .

2.3 Adverse Reaction Rates Twenty bleeding events (2.309%), nine perforations (1.039%), and eleven cholangitis cases (1.270%) were reported. No significant differences existed among groups in bleeding, perforation, or cholangitis rates (P>0.05) .

2.4 Univariate and Multivariate Logistic Regression Analysis of PEP Risk Factors Univariate logistic regression with PEP occurrence as the dependent variable (no=0, yes=1) and sex (female=0, male=1), age (<60=0, $ $60=1), BMI (<24=0, $ $24=1), smoking, alcohol abuse, liver cirrhosis, diabetes, hypertension, cannulation time >10 minutes, cholelithiasis history, pancreatitis history, cannulation attempts >5, double guidewire technique, precut sphincterotomy, papillary balloon dilation, and ultrasonography-detected extrahepatic bile duct dilation as independent variables identified female sex (OR=2.163, 95%CI=1.387-3.373), BMI $ $24kg/m^{2}$ (OR=3.866, 95%CI=2.493-5.996), alcohol abuse (OR=3.060, 95%CI=1.982-4.723), diabetes (OR=3.250, 95%CI=2.109-5.010), prior pancreatitis (OR=3.882, 95%CI=1.440-10.465), cannulation time >10 minutes (OR=3.121, 95%CI=2.023-4.815), double guidewire technique (OR=3.527, 95%CI=2.272-5.473), and ultrasonography-detected extrahepatic bile duct dilation (OR=0.581, 95%CI=0.373-0.906) as significant factors .

Multivariate logistic regression of significant univariate variables revealed BMI $ $24kg/m^{2}$ (OR=3.751, 95%CI=2.293-6.136), alcohol abuse (OR=2.624, 95%CI=1.520-4.529), diabetes (OR=2.687, 95%CI=1.559-4.634), cannulation time >10 minutes (OR=4.229, 95%CI=2.531-7.066), and double guidewire technique use (OR=3.542, 95%CI=2.159-5.809) as independent risk factors,

while ultrasonography-detected extrahepatic bile duct dilation was protective (OR=0.573, 95%CI=0.347-0.947) .

Discussion

ERCP has evolved from a diagnostic modality to the therapeutic gold standard for biliopancreatic diseases, with indispensable roles in diagnosis, stone extraction, and malignant biliary obstruction stenting. PEP pathogenesis involves multifactorial interactions including mechanical injury, chemical irritation, and genetic susceptibility. Severe PEP increases healthcare costs and patient morbidity, limiting ERCP applications. This study compared preoperative versus postoperative NSAID administration and combination versus monotherapy, finding that preoperative indomethacin suppository and/or diclofenac sodium effectively reduced PEP incidence, demonstrating NSAIDs' preventive potential. Preoperative administration showed significantly lower adverse reaction risk than postoperative dosing, likely because NSAID anti-inflammatory effects begin during the procedure, reducing postoperative inflammatory responses.

PEP is ERCP' s most common complication with high incidence. Our study found 96 PEP cases (11.09%), consistent with literature reports of approximately 10% and up to 14.7% in high-risk populations [14-16]. PEP increases patient suffering, economic burden, and risks of severe complications including hemorrhagic pancreatitis, infection, and multi-organ failure, sometimes requiring ICU care and expensive treatments or causing death [17]. Our patients reported bleeding, perforation, and local inflammation, mostly mild, with no deaths. While most PEP cases improve with conservative management, mortality exceeds 0.7% in some reports [18-19], indicating life-threatening potential.

Previous studies show PEP incidence correlates with disease-related factors (acute pancreatitis history, bile duct stricture) and procedure-related factors (cannulation difficulty, contrast volume and injection rate) [17,20]. Preventing PEP is crucial for ERCP safety and feasibility. Our results demonstrate that preoperative prophylactic NSAIDs significantly reduce PEP occurrence. During ERCP, mechanical papillary stimulation and pancreatic cell injury induce local inflammation, activating pancreatic enzymes and triggering PEP. Preoperative NSAIDs inhibit inflammatory mediator synthesis before mechanical stimulation, effectively reducing local inflammation and pancreatic tissue injury [21]. NSAID timing depends on the inflammatory cascade initiation; blocking pancreatic zymogen activation and neutrophil infiltration requires pre-procedure administration to achieve effective plasma concentrations that inhibit COX-1/2 and reduce prostaglandin synthesis, thereby decreasing pancreatic duct permeability [22-23]. Postoperative administration misses this critical window, only partially mitigating later inflammation. Combining diclofenac sodium (rapid 15-30 minute onset covering the procedure) with indomethacin (maintaining postoperative anti-inflammatory levels) creates pharmacokinetic synergy, while dual COX-2

selective and COX-1/2 blockade inhibits 90% of prostaglandin production and synergistically inhibits phospholipase A2 for multi-target anti-inflammatory effects [24].

Our study found that diclofenac sodium injection combined with indomethacin suppository significantly reduced PEP risk compared to diclofenac alone, suggesting different NSAIDs may synergistically enhance prevention through distinct mechanisms. This combination strategy likely reduces inflammatory mediator release through multiple pathways. Beyond irreversible COX-1/2 inhibition blocking arachidonic acid conversion to prostaglandins, NSAIDs also inhibit neutrophil-endothelial adhesion, blocking inflammatory cascade amplification [25-26], which aligns with our observed PEP reduction. In contrast, postoperative combination therapy showed minimal effect, possibly because the inflammatory response had already initiated, making it difficult for NSAIDs to suppress the established process. Regarding other common post-ERCP complications (perforation, bleeding, cholangitis), prophylactic medication showed no significant reduction.

Our results identified BMI $ 24kg/m^{2}, alcohol abuse, diabetes, cannulation time > 10 minutes, and double guidewire technique as independent PEP risk factors. The mechanisms in overweight, alcohol grade inflammation and insulin resistance through adipose−derived free fatty acids and pro−inflammatory cytokines, worsening pancreatic microcirculation while peripancreatic fatin filtration increases [29]. Diabetic patients often have vascular disease and autonomic dysfunction causing abnormal pancreatic secretion reperfusion injury repair [30−31]. These conditions collectively cause sphincter of Oddi dysfunction, pancreatic prolonged cannulation and double guidewire technique cause papillary injury→pancreatic duct outflow obstructio hypertension, while impacted stones/chronic cholangitis cause papillary edema, increasing cannulation difficulty and promoting bile reflux-induced enzyme activation. Small-diameter bile ducts (<5 mm) require guidewire exploration, increasing accidental pancreatic duct cannulation risk. Excessive contrast injection directly aggravates acinar cell injury. These findings help clinicians perform comprehensive preoperative risk assessment and implement appropriate preventive measures.

For high-risk patients, clinicians may consider preoperative prophylactic NSAIDs or more cautious cannulation strategies to reduce PEP risk [33-34]. These identified risk factors also facilitate better patient communication about potential complications, improving compliance and optimizing postoperative management. Individualized monitoring for high-risk patients can reduce PEP incidence and improve outcomes, with important implications for precision prevention, though the synergistic mechanisms between microcirculatory dysfunction and metabolic toxicity require further investigation.

Our findings have important clinical implications for ERCP perioperative management. First, they confirm NSAIDs' key role in PEP primary prevention through anti-inflammatory mechanisms, providing new evidence for clinical guidelines. Second, the proposed multimodal prevention strategy integrating pharmacological and non-pharmacological interventions demonstrates synergistic potential. Third, identifying independent risk factors enables better

individual risk assessment and targeted prevention. For high-risk patients, clinicians can implement enhanced monitoring and individualized prevention strategies, potentially reducing PEP incidence and improving outcomes.

Limitations: (1) Sample size constraints may limit statistical power to detect small effect sizes, requiring cautious generalization. (2) Single-center selection bias: participants from one regional medical center may not represent national populations, potentially causing ecological fallacy. (3) Observational design: non-randomization cannot fully control confounders (operator experience, equipment choice); multicenter RCTs or Mendelian randomization studies are needed for causal validation. (4) Safety monitoring: despite excluding some non-significant risk factors, potential adverse effects require consideration, especially regarding absolute risk reduction for severe complications. Although bleeding and perforation were recorded, limited sample size may reduce detection power for rare adverse events, and delayed events may be missed due to fixed follow-up or incomplete post-discharge reporting. Future studies should employ multicenter, large-sample designs to enhance representativeness and generalizability.

In summary, prophylactic combination therapy with indomethacin suppository and diclofenac sodium before ERCP effectively reduces postoperative pancreatitis risk and severity while decreasing perforation, bleeding, cholangitis rates, and pain scores. This strategy may become the standard for PEP prevention. Future research should explore optimal NSAID dosing, administration routes, and combination regimens to maximize preventive efficacy.

Author Contributions

WU Xiangpeng: Study conception, protocol development, project management, resource coordination. LI Enjun: Data collection and verification. LI Xiongwei: Protocol development, data analysis, results verification. WANG Haihong: Data collation and collection. CUI Wei: Data collation, manuscript writing and revision. WU Xiangli: Data analysis, study supervision. QI Weihua: Data collation and analysis. HOU Senlin: Study supervision and project management.

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Note: Figure translations are in progress. See original paper for figures.