Clinical Case Report

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Sepsis as an important risk factor for gastrointestinal bleeding in acute coronary syndrome patients

Two case reports

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Abstract

Rationale: Sepsis is a common stressor that may decrease microcirculation in the gastrointestinal tract in patients and increase the gastrointestinal bleeding risk of stress-related mucosal disease. However, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) bleeding risk score, recommended by authoritative guidelines for acute coronary syndrome (ACS), does not include sepsis as a bleeding risk factor.

Patient concerns: The 2 cases were about ACS with hemorrhagic complications. The first patient was an 88-year-old man with hypertension, gallstones, hepatic cysts, and chest pain; the second one was a 79-year-old man with chest pain and hypertension. These 2 ACS patients had no bleeding on admission; however, both patients suffered apparent gastrointestinal bleeding immediately after the development of sepsis or severe sepsis.

Diagnoses: Both patients were diagnosed as ACS with sepsis.

Interventions: The first ACS patient had no use of proton pump inhibitors (PPIs) for prophylaxis prior to the diagnosis of sepsis. The second one was administered PPIs at standard oral doses.

Outcomes: The first patient suffered from gastrointestinal bleeding immediately after the onset of sepsis. And oral PPIs failed to prevent upper gastrointestinal bleeding for the second patient, when severe sepsis developed. However, the second patient's gastrointestinal hemorrhage gradually stopped immediately after high doses of PPIs were administered intravenously, rather than orally. When sepsis developed again, the second patient also had no recurrent gastrointestinal bleeding under the protection of PPIs at standard oral doses.

Lessons: Our report suggests that sepsis may be an important bleeding risk factor for ACS patients, and the reasonable use of PPIs to prevent gastrointestinal bleeding could be vital for ACS patients complicated with sepsis.

Abbreviations: ACS = acute coronary syndrome, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK-MB = creatine kinase-muscle/brain isoenzyme, CRP = C-reactive protein, CRUSADE = can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines, H2RAs = histamine 2 receptor antagonists, Hb = hemoglobin, Hct = hematocrit, LDH = lactic dehydrogenase, LDL-C = low-density lipoprotein cholesterol, NT-proBNP = N-terminal pro brain natriuretic peptide, PCI = percutaneous coronary intervention, PCT = procalcitonin, PPI = proton pump inhibitor, STEMI = ST segment elevated myocardial infarction, TIMI = thrombolysis in myocardial infarction, WBC = white blood cell count.

Keywords: acute coronary syndrome, CRUSADE bleeding risk score, gastrointestinal bleeding, proton pump inhibitor, sepsis

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1. Introduction

Antithrombotic therapy has increasingly been used worldwide for the prevention and treatment of primary and recurrent ischemic events in acute coronary syndrome (ACS); however, this therapy is also associated with gastrointestinal bleeding complications.[1] Gastrointestinal bleeding events are accompanied by increased expenditures, as well as worse outcomes and prognosis.[2] Therefore, the minimization of gastrointestinal bleeding complications is an overarching goal in the management of ACS patients.

The European Society of Cardiology guidelines encourage clinicians to apply the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) bleeding risk score to manage the in-hospital bleeding risks of patients. When calculating the scores, baseline patient characteristics (sex, history of diabetes, and peripheral vascular disease), admission clinical variables (heart rate, systolic blood pressure, and signs of congestive heart failure), and admission laboratory values (hematocrit and calculated creatinine clearance) are key components of the CRUSADE bleeding scores.[3] In clinical practice, however, the ability of these scores to distinguish ACS patients is only moderate at different bleeding risks,[4] and the applicability of bleeding risk scores to the management of the patient remains uncertain.

Our clinical experiences suggested that patients with comorbid ACS and sepsis were more likely to exhibit gastrointestinal hemorrhage, indicating sepsis may be an important part of the risk factors for bleeding. Thus, we report 2 cases of gastrointestinal bleeding in ACS patients with sepsis, so as to provide clinical reference.

2. Case report one

An 88-year-old man with hypertension, gallstones, hepatic cysts, and chest pain was admitted to our hospital on November 4, 2015. On admission, the patient complained of frequent chest pain during the previous 2 years and aggravation in the previous 2 hours. The electrocardiogram results indicated that the patient had myocardial ischemia. The chest pain was gradually relieved after nitroglycerin administration. Coronary angiography verified that the patient was suffering from coronary atherosclerotic heart disease, with a left main coronary stenosis of 50%, an anterior descending branch stenosis of 50 to 75%, circumflex branch mild stenosis and complete occlusion of the right coronary artery. To treat ACS, the patient began to take drugs from the first day of admission, including isosorbide mononitrate, metoprolol, benazepril, aspirin, clopidogrel, atorvastatin, low-molecular-weight heparin, and nifedipine.

We calculated the first CRUSADE bleeding risk score for the patient immediately after his admission. He was 173 cm tall and weighed 70 kg. His blood pressure was 145/86 mm Hg, with a heart rate at 80 beats/min, and body temperature at 36.5°C. The patient did not have a history of diabetes, vascular diseases or infectious diseases, and there were no signs of bleeding, hepatosplenomegaly, or heart failure on admission. Blood biochemical examination on admission indicated leukocytosis due to stress effect of ACS. And the laboratory results revealed, white blood cell count (WBC): 9630/μL (Fig. 1A), neutrophil count: 8380/μL, percentage of neutrophil granulocytes: 87%, hemoglobin: 130 g/L (Fig. 1A), hematocrit (Hct): 36.90%, and the platelet level remained within the normal range. Besides, alanine aminotransferase (ALT: 24 U/L) and procalcitonin (PCT < 0.05 ng/mL) were also within the normal ranges, whereas increases were observed in the random blood glucose (10.7 mmol/L), low-density lipoprotein cholesterol (LDL-C: 3.13 mmol/L), and aspartate aminotransferase (AST: 78U/L). The renal function (serum creatinine: 100 μmol/L) and N-terminal probrain natriuretic peptide (NT-proBNP: 358 ng/L) were normal. The CRUSADE bleeding risk score was 33 points on admission, indicating a moderate risk. The patient did not take any drugs, including proton pump inhibitors (PPIs), to prevent gastrointestinal bleeding. On the 3rd day, the fecal occult blood test result was negative. On the 4th day, the patient developed symptoms of fever, cough, and sputum, which were accompanied by debilitation and dizziness. On the 6th day, the patient was treated with moxifloxacin. On the 4 to 8th days, his body temperature remained abnormal with a maximum point of 38.4°C; substantial increases in the WBC (13,800/μL, Fig. 1A), neutrophils (12,390/μL), percentage of neutrophil granulocytes (89.8%), and PCT (0.38 ng/mL) were noted. The patient's condition was consistent with the diagnostic criteria of sepsis. On the 8th day, the patient presented with fresh blood stool for the first time with a 65 beats/min heart rate, 110/50 mm Hg blood pressure and a substantial decrease in hemoglobin (102 g/L, Fig. 1A), without petechiae or bruising in the skin-mucosa or subcutaneous hemorrhage. Aspirin, clopidogrel, and low-molecular-weight heparin were subsequently discontinued. A bismuth mixture, esomeprazole, thrombin, and noradrenaline were administered later; however, the stool remained black. Following termination of anticlotting drugs, on the 9th day, the patient complained of worsening chest pain, along with an observed increase in serum cardiac markers, and an emerging and complete right bundle branch block. Low doses of clopidogrel (50 mg/d) and fondaparinux sodium were administered, considering possibility of recurrent myocardial infarction. On the 11th day, the patient was referred to the cardiovascular care unit, where the anti-infective drug was substituted with imipenem. On the 13th day, the patient had a sudden loss of consciousness and limb twitching. His X-rays indicated sheet-like images in the lower field of both lungs, patchy shadows in the middle field of the right lung and suspicious patchy shadows in the left upper lung. His clinical status simultaneously worsened, with a significant increase in the WBC (16,640/μL, Fig. 1A) and PCT (6.08 ng/mL), a sharp decrease in hemoglobin (95 g/L, Fig. 1A), deterioration of cardiac function and damage of liver and kidney functions. The fecal occult blood tests remained positive since the first bloody stool during his hospitalization. At 3:12 AM of the 16th day, the patient appeared: loss of consciousness, limb twitching, and frequent paroxysmal ventricular tachycardia. His blood pressure was quite low, at 73/46 mm Hg. Ventricular tachycardia was terminated by defibrillation; however, the restoration of the sinus rhythm could not be maintained. His family members refused all rescue measures, and at 4:25 AM, the patient was considered clinical death. No autopsy was carried out afterward.

3. Case report two

A 79-year-old man with chest pain and hypertension was admitted to our hospital on November 2, 2015. On admission, the patient complained of chest pain that had occurred 5 hours earlier; he could not bear aggravation of the pain and exhibited symptoms of mild cough, sputum, and asthma. The electrocardiogram results showed a sinus tachycardia, and ST segment elevation in the inferior wall as well as V1-V5 leads, which

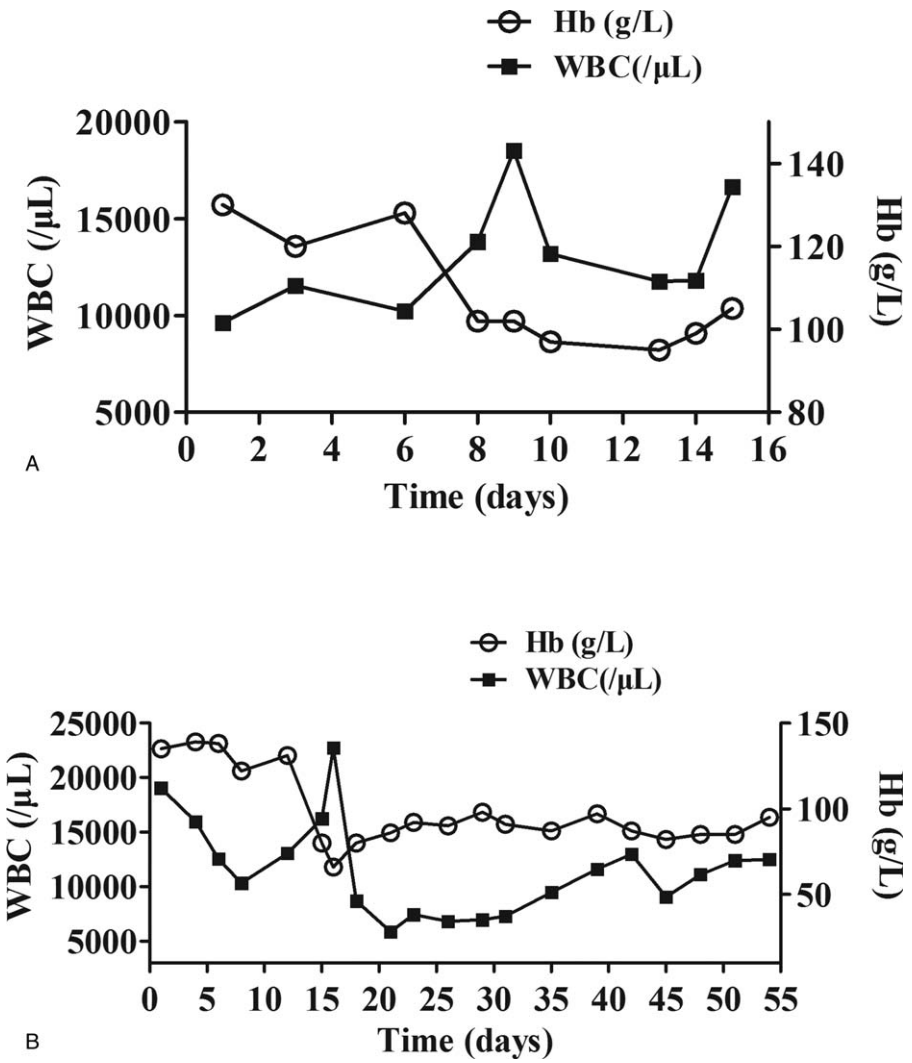

Figure 1. Curves of the levels of WBC and Hb. (A) case report one; (B) case report two. Hb = hemoglobin, WBC = white blood cell count.

suggested the potential for acute ST segment elevated myocardial infarction (STEMI) in the inferior wall and extensive anterior wall. A combination regimen of ticagrelor and aspirin was used. Coronary angiography verified that the patient was suffering from STEMI, with complete occlusion of the left main coronary and mild stenosis in the right coronary artery. A percutaneous coronary intervention (PCI) operation was immediately conducted, and a drug-eluting stent was placed in the left anterior descending branch, followed by grade-III thrombolysis in myocardial infarction (TIMI) coronary blood flow. The patient was administered drugs from the first postoperative day, including isosorbide dinitrate, aspirin, ticagrelor, atorvastatin, fondaparinux sodium, acetylcysteine, ambroxol, and furosemide.

We calculated the CRUSADE bleeding risk score as 36 points, which indicated a moderate risk, the first time immediately after his admission. The patient was 160 cm in height and 65 kg in weight. His blood pressure was 122/65 mm Hg, heart rate was 65 beats/min, and body temperature was 36.3°C. This patient had a history of chronic obstructive pulmonary disease for over 20 years, and showed signs of heart failure; however, there was no evidence of bleeding or hepatosplenomegaly, and he had no previous history of diabetes, vascular diseases, or infectious diseases either. After the PCI operation, his blood pressure rapidly decreased to 64/40 mm Hg, and dopamine was immediately administered via a microinfusion pump to maintain his blood pressure. Blood examination on admission indicated leukocytosis on account of stress effect of ACS. And the results showed, the WBC: 19,030/μL (Fig. 1B), neutrophils count: 17,810/μL, percentage of neutrophil granulocytes: 93.6%, hemoglobin: 135 g/L (Fig. 1B), Hct: 40.50%, and the platelet level was within normal limits. For blood biochemical indexes, increases occurred in high sensitive C-reactive protein (CRP > 20 mg/L), PCT (45.34 ng/ml), ALT (65 U/L), AST (467 U/L), lactic dehydrogenase (LDH: 1074 U/L), LDL-C (2.03 mmol/L), and serum creatinine (115 μmol/L), whereas decreases occurred in the total protein (61 g/L), prealbumin (132 mg/L), and serum albumin (34 g/L). Increases in myoglobin (528.1 μg/L), creatine kinase-MB (CK-MB > 300 μg/L), troponin (9.290 μg/L), and NT-proBNP (20856 ng/L) were also noticed. The patient underwent a series of treatments for asthma, cough, and phlegm. On the 5th day, piperacillin/tazobactam was added, and standard oral doses of PPI (esomeprazole magnesium enteric-coated tablet, 40 mg qd po) were also administered to prevent gastrointestinal bleeding. Rosuvastatin, instead of atorvastatin, was administered to lower lipids. Meanwhile, both of spironolactone and digoxin were administered for chronic heart failure. Then, the serum

markers gradually improved after admission. The levels of several biochemical indicators, such as ALT (51U/L), AST (120U/L), serum creatinine (97 μmol/L), and PCT (17.76 ng/ml), were much lower. And his blood pressure and heart rate returned to the normal level. On the 7th day, the fecal occult blood test was negative. On the 9th day, ivabradine was added. On the 10th day, serum transaminases of ALT (24U/L) and AST (36U/L), which were the representative items of liver function test, returned to the normal level. On the 11th day, benazepril was added as well.

However, at 7:00 AM of the 15th day, the infection aggravated, and the patient showed symptoms of cough, phlegm, and exacerbation of asthma, with the body temperature at 38.4°C, heart rate at 78 beats/min, breaths at 20/min and blood pressure at 88/57 mm Hg. The patient began to repeatedly spit out blood from 8:10 AM of the 15th day, with a daily volume of approximately 800 mL. An emergency gastroscopy indicated erosive esophagitis and diffuse bleeding (Fig. 2). At 10:03 AM of the same day, the routine blood examination indicated a substantial increase in the WBC (17,210/μL), neutrophils (14,380/μL), and percentage of neutrophil granulocytes (83.5%), as well as a substantial decrease in hemoglobin (126 g/L). At 23:52 PM of the day, another routine blood examination was performed again, and the hemoglobin (80 g/L, Fig. 1B) exhibited a further decrease. The patient's conditions fulfilled the diagnostic criteria for severe sepsis with apparent gastrointestinal bleeding. A series of treatments were immediately initiated, and dopamine was administered via a micro infusion pump to maintain the blood pressure. To terminate the gastrointestinal bleeding, all antithrombotic drugs were stopped, and instead thrombin and noradrenaline were administered; somatostatin was administered via a micro infusion pump, and proton pump inhibitor (PPI, esomeprazole) was instantly adjusted to an intravenous, rather than oral, administration. The PPI therapy strategy during hospitalization was as follows: PPI was initially administered via intravenous pumping from high doses to low doses gradually, followed by a transition to intravenous drip, and subsequently oral maintenance treatment. Hydroxyethyl starch, succinylated gelatin and a blood transfusion were given, and the antibiotic drug was adjusted to ceftizoxime.

The fecal occult blood tests were still positive on both the 16th and 20th days after hematemesis. On the 23rd day, the patient's infection improved greatly, with a negative fecal occult blood test and a gradual increase in hemoglobin (Fig. 1B). He was then administered a single, low dose of clopidogrel (50 mg qd po) for antithrombotic therapy. On the 27th day, the single dose of clopidogrel was reverted to a standard dose (75 mg qd po). The PPI was finally adjusted to oral administration on the 33rd day. It was worth noting that the blood examination again indicated leukocytosis on the 39th day. On the 42nd day, at 7:00 AM, his body temperature was at 38.4°C, heart rate at 79 beates/min, and blood pressure at 123/59 mm Hg; an obvious increase was also noted in the WBC (12,960/μL, Fig. 1B) and neutrophils (6780/μL). The patient's conditions indicated that sepsis had developed again. Yet there were no signs or symptoms of gastrointestinal bleeding with the protection usage of standard oral PPI. *Acinetobacter baumannii* was identified from the deep sputum culture, together with renal insufficiency; thus, a series of adjustments in the anti-infective therapy were implemented. Meropenem, followed by levofloxacin, and subsequently levofloxacin and minocycline were administered. The fecal occult blood tests remained negative since the 23rd day. Finally, on the 53rd day, the patient was discharged from hospital in an improved health condition.

4. Discussion

ACS comprises a group of cardiovascular disorders, including angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. The common theme that underlies these disorders is the rupture of a vulnerable atherosclerotic plaque, followed by partial or complete thrombotic occlusion of an artery. A combination of antiplatelets and anticoagulants remains the standard treatment of antithrombotic therapy for ACS; however, this therapy has been demonstrated to increase the incidence of upper gastrointestinal bleeding, possibly because of the cumulative effects of these drugs.[5,6] For ACS patients, gastrointestinal hemorrhagic complications have become an independent risk factor for subsequent mortality, which represents a hazard equivalent to or even greater than that for myocardial infarction.[7,8]

Sepsis is a common stressor that has been demonstrated to decrease microcirculation in the gastrointestinal tract.[9,10] Sepsis has also been reported to be associated with an increased risk for stress ulcer related gastrointestinal bleeding during the last 20 years.[11–15] Furthermore, a simple regression analysis has also identified sepsis as a risk factor for stress ulcer related gastrointestinal bleeding.[10] For ACS patients, sepsis may increase the gastrointestinal bleeding risk, and once gastrointestinal bleeding occurs, it is easy to cause bacterial infection. Moreover, both sepsis and bleeding may reinforce each other, which may aggravate the situation and may even cause death in serious cases.[16] Thus, the assessment of the bleeding risk and prevention of bleeding are important objectives in the management of patients with ACS or ACS accompanied by sepsis. The CRUSADE bleeding risk score for ACS is recommended as an acknowledged and common scoring system by authoritative

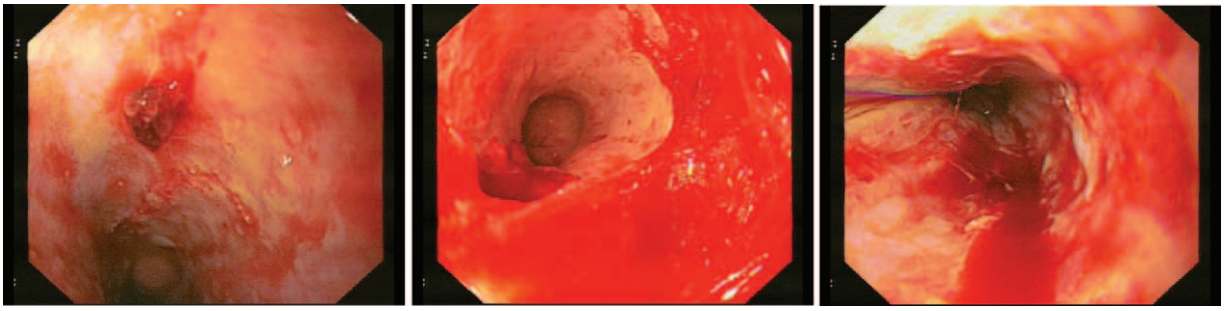

Figure 2. Erosive esophagitis and diffuse bleeding observed by gastroscopy.

guidelines;[17] however, sepsis is not included. Moreover, up to date, no relative research has examined the link between sepsis and ACS bleeding risk factors.

In the 2 presented cases, the ACS patients had no bleeding on admission; however, both patients suffered apparent gastrointestinal bleeding immediately after the development of sepsis or severe sepsis. The gastrointestinal bleeding might be induced by various factors, such as aspirin, clopidogrel, ticagrelor, low-molecular-weight heparin, fondaparinux sodium, sepsis, or the cumulative effects of these factors. However, considering the characteristics of sepsis and the time point of gastrointestinal bleeding, sepsis should be at least one of the bleeding factors for both ACS patients. Does sepsis have a clinical significance as a bleeding risk factor for ACS patients? Should sepsis be included in the bleeding risk score to manage the bleeding risks for patients? How should the score be determined? More research is required to solve these problems.

In clinical practice, there is a time window for ACS patients between the onset of sepsis and gastrointestinal bleeding; thus, an early diagnosis of sepsis, an accurate assessment of bleeding risk, and timely and effective preventive measures are critical. PPIs make up the primary prevention measure that protects the alimentary tract from injury induced by antiplatelet medicines for ACS patients.[18] PPIs are also the basic precautions for stress ulceration gastrointestinal bleeding.[19] The Surviving Sepsis Campaign guidelines in 2013 favored the use of PPIs, compared with Histamine 2 Receptor Antagonists (H2RAs), for stress-related mucosal disease prophylaxis.[20] Thus, PPIs are the preferred drugs to prevent gastrointestinal bleeding induced by sepsis in ACS patients.

Effective prophylaxis requires the correct timing and appropriate dosage of proper medication, as well as the appropriate method of administration. In the first case, the patient did not use PPIs for prophylaxis prior to the diagnosis of sepsis, and ultimately he died because of multiple organ dysfunction, which was induced by ACS, sepsis, gastrointestinal bleeding, and other risk factors. In the second case, the ACS patient was administered PPIs at standard oral doses, but it failed to prevent upper gastrointestinal bleeding when severe sepsis developed. However, the hemorrhage gradually stopped when the PPI was immediately administered at high doses intravenously, rather than orally, and the PPI was gradually adjusted to standard oral doses. When sepsis developed again, the patient had no recurrent gastrointestinal bleeding. These 2 cases suggested that ACS patients should be immediately administered PPIs to prevent gastrointestinal bleeding when sepsis occurred, and intravenous PPIs at high doses were required once severe sepsis or septic shock happened.

5. Conclusion

These 2 cases suggest that sepsis may be an important risk factor for gastrointestinal bleeding in ACS patients, but it is lack of direct evidence for the correlation between sepsis and gastrointestinal bleeding, so we still need large-sample clinical trials to verify the relevance and explore the mechanism. Moreover, our report indicates that PPIs could prevent gastrointestinal bleeding effectively in ACS patients complicated with sepsis, but the starting time and dosage of PPIs remain further research.

Author contributions

Conceptualization: Qi-Yu Yang, Jing Ouyang, Jia-Dan Yang.
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Methodology: Qi-Yu Yang, Jing Ouyang.
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Validation: Jiadan Yang.
Writing – original draft: Qi-Yu Yang, Jing Ouyang.
Writing – review & editing: Jia-Dan Yang.

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