

## Diagnostic Value of Signal Peptide-CUB-EGF Domain-Containing Protein 1 (SCUBE-1), Intestinal Fatty Acid Binding Protein (iFABP), and Ischemia-Modified Albumin (IMA) in Mechanical Bowel Obstruction

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### Abstract

**Objective:** Mechanical bowel obstruction (MBO) is a common surgical pathology among patients presenting to the emergency department with abdominal pain worldwide and is associated with high morbidity rates. Delays in diagnosis and surgical intervention decisions can lead to severe complications such as bowel ischemia, adversely affecting patient survival rates. Therefore, reliable biomarkers are needed for the early diagnosis of MBO and in the surgical decision-making process. This study aimed to evaluate the diagnostic value of i-FABP, SCUBE-1, and IMA in predicting strangulation and bowel ischemia.

**Method:** This prospective study was conducted at a tertiary hospital between January 2020 and January 2022. The study included 44 patients diagnosed with mechanical bowel obstruction who presented to the emergency department with abdominal pain, along with a control group of 40 healthy individuals. Patients were classified into two groups based on the need for surgical intervention: those who underwent surgery (Group B) and those who did not (Group A). Venous blood samples were collected, and the levels of i-FABP, SCUBE-1, and IMA were measured using the ELISA method. Data were analyzed using SPSS software.

**Results:** The mean i-FABP levels were 56.4±11.5 ng/mL in Group A, 62.3±10.1 ng/mL in Group B, and 41.9±12.2 ng/mL in the control group, with a statistically significant difference observed between the groups ( $p<0.001$ ). SCUBE-1 levels were measured as 80.3±84.9 ng/mL in Group A and 132.4±124.7 ng/mL in Group B, and this difference was found to be statistically significant ( $p=0.001$ ). The IMA values were 88.8±14.3 ng/mL in Group A, 106.1±29.9 ng/mL in Group B, and 90.1±14.1 ng/mL in the control group, with a significant difference observed between the groups ( $p<0.001$ ).

**Conclusion:** This study evaluated the diagnostic value of SCUBE-1, i-FABP, and IMA biomarkers in patients diagnosed with MBO and demonstrated that these biomarkers could serve as important tools in determining the need for surgical intervention. SCUBE-1, i-FABP, and IMA levels were found to show a significant difference in predicting bowel ischemia and strangulation.

**Keyword:** Bowel obstruction; iFABP; IMA; Ischemia; SCUBE 1

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**INTRODUCTION**

Mechanical bowel obstruction (MBO) is one of the most commonly encountered surgical pathologies in patients presenting to the emergency department with abdominal pain and is a significant cause of morbidity worldwide, being associated with high healthcare costs (1,2). MBO is characterized by the localized obstruction of intestinal content passage and may arise due to intramural, mural, or extramural factors (3). Following obstruction, the accumulation of gas and fluid within the intestinal lumen leads to an increase in intraluminal pressure. If the obstruction is not relieved, regardless of its etiology, bowel wall edema progresses, ultimately resulting in

impaired intestinal circulation and bowel wall ischemia (4).

The primary challenge in MBO management is determining the necessity for surgical intervention. Delays in diagnosis and surgery may lead to ischemia, thereby increasing morbidity and mortality (5,6). In patients without signs of strangulation, the current approach is conservative treatment, from which most patients benefit. However, in a subset of patients, surgical treatment becomes necessary (7). Nevertheless, debates continue regarding the type of MBO treatment and the timing of surgery (8). The potential devastating consequences of delayed treatment of bowel ischemia and diagnostic challenges have led researchers to focus on predictors of bowel ischemia. Clinically, ischemia is associated with findings such as fever, localized abdominal pain, leukocytosis, and increased lactate levels, though none of these parameters have high predictive value (7). Although computed tomography (CT) is a valuable diagnostic tool for assessing bowel ischemia, it

may fail to detect ischemia. Additionally, most MBO cases occur secondary to previous adhesions, leading to repeated CT imaging and an increased cumulative radiation risk (9,10).

Intestinal fatty acid-binding protein (i-FABP) is a cytosolic protein found in the intestinal mucosa. Recent studies have suggested that i-FABP could serve as a biomarker for bowel ischemia (9,11,12). In an experimental rat study, Tyagunov et al. demonstrated that i-FABP levels increased in strangulated small bowel obstruction (13). Signal peptide-CUB-EGF domain-containing protein 1 (SCUBE-1) is a cell surface protein expressed by vascular endothelial cells and platelets, playing a role in thrombotic events (14,15). Ischemia-modified albumin (IMA) refers to structurally altered albumin due to ischemia (16). It was first identified in patients with myocardial infarction. IMA constitutes 1–2% of serum albumin levels, which can increase up to 8% in ischemic conditions (17).

The potential negative effects of delays in diagnosing MBO and determining the timing of surgical intervention on morbidity and mortality highlight the importance of reliable biomarkers for early detection of bowel ischemia (5–7). Therefore, the primary objective of this study was to comprehensively investigate and determine the diagnostic utility and predictive accuracy of serum i-FABP, SCUBE-1, and IMA levels for identifying

bowel ischemia and predicting the necessity for surgical intervention in patients with MBO.

## METHODS

### *Study Design and Participants*

This study was conducted between January 2020 and January 2022 after obtaining approval from the Acıbadem Mehmet Ali Aydınlar University Medical Research Ethics Committee (decision number 2019-9/15). The study included adult patients ( $\geq 18$  years old) who presented to the emergency department of a tertiary hospital with abdominal pain and were diagnosed with MBO, provided they read and signed the written informed consent form.

Patients were excluded if they were pregnant, younger than 18 years, had missing data in their medical records, withdrew their written consent, or were diagnosed with acute coronary syndrome, hemorrhagic stroke, cerebrovascular disease, liver failure, acute pulmonary edema, cardiopulmonary arrest, acute mesenteric ischemia, pulmonary thromboembolism, or an infection focus unrelated to MBO.

MBO diagnosis was established based on the following criteria:

1. Presence of bowel obstruction symptoms and signs (e.g., abdominal pain, nausea, vomiting, absence of gas and stool passage)
2. Radiological findings of MBO (direct X-ray, CT)

3. Hospital admission following a general surgery consultation confirming MBO

The clinical and demographic characteristics of the patients included in the study, onset time of abdominal pain, symptoms and physical examination findings, laboratory parameters, direct X-ray, abdominal ultrasound, and CT findings, discharge status, and pathology results of surgically treated patients were recorded in the study form.

Patients were classified into two groups: those who did not undergo surgery due to MBO (Group A) and those who required surgical intervention (Group B). Additionally, 18-year-old or older healthy volunteers who presented to the hospital for check-ups and provided informed consent were included as the control group.

#### ***Analysis of Laboratory Parameters***

Venous blood samples were collected from the patients at the time of presentation. Blood samples were obtained in serum separator tubes under vacuum. Gel separator tubes were used for serum isolation, while potassium-EDTA tubes were used for complete blood counts. Samples were centrifuged at 3000 rpm for 10 minutes, and plasma was separated and stored at -80°C. Serum glucose, C-reactive protein (CRP), urea, creatinine, and albumin levels were measured spectrophotometrically using a closed system on the Cobas 600 series c501 modular analyzer in the hospital laboratory.

White blood cell (WBC), neutrophil, lymphocyte, and platelet counts were obtained using the XN-1000 analyzer in the hospital laboratory. SCUBE-1, i-FABP, and IMA levels in human serum samples were measured using enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's recommendations. SCUBE-1, i-FABP, and IMA levels in the samples were calculated in ng/mL.

#### ***Outcomes***

The primary outcome of this study was to evaluate the diagnostic value of SCUBE-1, i-FABP, and IMA in predicting the need for surgical intervention and the presence of bowel ischemia and/or strangulation in patients presenting with MBO.

#### ***Statistical Analysis***

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) statistical software package was used for data analysis. Descriptive statistics were presented as mean  $\pm$  standard deviation or median (25th and 75th percentiles) for continuous variables and as frequency and percentage (%) for categorical variables. The normal distribution of variables was assessed using visual and analytical methods (Shapiro-Wilk Test). For categorical and continuous variables conforming to normal distribution, comparisons were performed using parametric tests: Independent Samples t-Test for variables

with two subgroups, One-Way ANOVA for variables with more than two subgroups. For categorical and continuous variables not conforming to normal distribution, comparisons were performed using nonparametric tests: Mann-Whitney U Test for variables with two subgroups, Kruskal-Wallis H-Test (Nonparametric ANOVA) for variables with more than two subgroups. For correlation analyses between continuous variables, Pearson or Spearman correlation analyses were used depending on the normality of the distribution. A statistical significance level (Type 1 error level) of  $p < 0.05$  was considered significant.

## RESULTS

A total of 44 patients aged 18 years and older, who presented to the emergency department

with abdominal pain and were diagnosed with MBO, along with 40 healthy volunteers as the control group, were included in the study. Among the 27 patients in Group A (non-operated patients under clinical follow-up), 29.6% were male and 70.4% were female. Among the 17 patients in Group B (operated patients), 47.1% were male and 52.9% were female. In the control group, 40% were male and 60% were female. The mean ages of the groups were as follows: Group A:  $57.5 \pm 21.7$  years, Group B:  $72.8 \pm 15$  years, Control group:  $56.5 \pm 23.1$  years. The mean age of patients who underwent surgery for MBO was higher than that of the non-operated patient group. However, there was no statistically significant

**Table 1.** Comparison of patient groups in terms of socio-demographic and laboratory variables

	<b>Group A (Mean± SD) n=27</b>	<b>Group B (Mean± SD) n=17</b>	<b>Control Group (Mean± SD) n=40</b>	<b>P Value</b>
<b>Gender</b>				
Male (n=32)	8 (29.6%)	8 (47.1%)	16 (40%)	0.482
Female (n=52)	19 (70.4%)	9 (52.9%)	24 (60%)	
<b>Age (min-max)</b>	$57.5 \pm 21.7$ (29-90)	$72.8 \pm 15$ (45-96)	$56.5 \pm 23.1$ (29-94)	>0.05
<b>Symptom Time (hour, min-max)</b>	$56.8 \pm 83.3$ (3-360)	$69.9 \pm 80.9$ (4-240)	---	0.799
<b>Abdominal pain</b>				
No	1 (3.7%)	0 (0%)	---	>0.05
Yes	26 (96.3%)	17 (100%)	---	
<b>Glucose (mg/dL)</b>	$144.5 \pm 46.2$	$165.6 \pm 71.2$	$109.9 \pm 35.4$	<0.001
<b>Urea (mg/dL)</b>	$17.6 \pm 9.6$	$24.5 \pm 21$	$11.4 \pm 4$	<0.001
<b>Creatine (mg/dL)</b>	$0.9 \pm 0.3$	$1 \pm 0.4$	$0.7 \pm 0.1$	0.028
<b>Albumin (g/dL)</b>	$4 \pm 0.6$	$3.8 \pm 0.7$	$4.6 \pm 0.4$	<0.001
<b>WBC (cells/mm<sup>3</sup>)</b>	$11056.7 \pm 3305.7$	$10415.7 \pm 3220.8$	$7300.5 \pm 1599.3$	<0.001
<b>Neutrophil (cells/mm<sup>3</sup>)</b>	$8384.4 \pm 2924.3$	$7664.4 \pm 2214.1$	$4428.3 \pm 1445.1$	<0.001
<b>Lymphocyte (cells/mm<sup>3</sup>)</b>	$1833.3 \pm 1266.8$	$1614.1 \pm 679.4$	$2182.8 \pm 688.7$	0.006
<b>Thrombocyte (cells/mm<sup>3</sup>)</b>	$266666.7 \pm 100485.7$	$287882.4 \pm 143402.4$	$261625 \pm 69837.1$	0.999
<b>CRP (mg/L)</b>	$3 \pm 4$	$3.4 \pm 5$	$0.2 \pm 0.2$	<0.001

$\chi^2$ : Chi-square test statistic, F: Fisher's Exact test statistic, SD: Standard Deviation, min: minimum, max: maximum, CRP: C-Reactive Protein, SD: Standard deviation, WBC: White blood cells.

**Table 2.** Comparison of categorical variables by groups

	Group A (%)	Group B (%)	Total (%)	Test Statistic	P Value
<b>Nausea</b>					
No	2 (7.4)	1 (5.9)	3 (6.8)	---	1.000 <sup>F</sup>
Yes	25 (92.6)	16 (94.1)	41 (93.2)		
<b>Vomiting</b>					
No	9 (33.3)	7 (41.2)	16 (36.4)	$\chi^2=0.277$	0.598
Yes	18 (66.7)	10 (58.8)	28 (63.6)		
<b>Anorexia</b>					
No	17 (63)	7 (41.2)	24 (54.5)	$\chi^2=1.997$	0.158
Yes	10 (37)	10 (58.8)	20 (45.5)		
<b>Tenderness</b>					
No	2 (7.4)	3 (17.6)	5 (11.4)	---	0.359 <sup>F</sup>
Yes	25 (92.6)	14 (82.4)	39 (88.6)		
<b>Defense</b>					
No	18 (66.7)	13 (76.5)	31 (70.5)	$\chi^2=0.482$	0.488
Yes	9 (33.3)	4 (23.5)	13 (29.5)		
<b>Rebound</b>					
No	23 (85.2)	17 (100)	40 (90.9)	---	0.147 <sup>F</sup>
Yes	4 (14.8)	0 (0)	4 (9.1)		
<b>Other Physical Examination Findings</b>					
Normal	25 (92.6)	14 (82.4)	39 (88.6)		
Distension	1 (3.7)	1 (5.9)	2 (4.5)	$\chi^2=4.038$	0.401
Inguinal hernia	0 (0)	1 (5.9)	1 (2.3)		
Umbilical hernia	0 (0)	1 (5.9)	1 (2.3)		
Hyperactive bowel sounds	1 (3.7)	0 (0)	1 (2.3)		
<b>Direct Abdominal Radiography Findings</b>					
Normal	4 (14.8)	4 (23.5)	8 (18.2)		
Air-fluid level	20 (74.1)	12 (70.6)	32 (72.7)	$\chi^2=0.767$	0.682
Dilated colon gas	3 (11.1)	1 (5.9)	4 (9.1)		
<b>Abdominal Ultrasound (USG) Findings</b>					
No findings	27 (100)	16 (94.1)	43 (97.7)	---	---
Inguinal hernia	0 (0)	1 (5.9)	1 (2.3)		
<b>Discharge Status</b>					
No	0 (0)	2 (11.8)	2 (4.5)	---	0.144 <sup>F</sup>
Yes	27 (100)	15 (88.2)	42 (95.5)		
<b>Additional Diseases</b>					
None	8 (29.6)	7 (41.2)	15 (34.1)		
Appendectomy	4 (14.8)	1 (5.9)	5 (11.4)		
Colon Cancer	5 (18.5)	1 (5.9)	6 (13.6)		
Ovarian Cancer	4 (14.8)	0 (0)	4 (9.1)		
Inguinal Hernia	2 (7.4)	0 (0)	2 (4.5)		
Cesarean Section	3 (11.1)	0 (0)	3 (6.8)	$\chi^2=14.045$	0.298
SMA Syndrome	1 (3.7)	0 (0)	1 (2.3)		
Operated Hernia	1 (3.7)	1 (5.9)	2 (4.5)		
HT	4 (14.8)	4 (23.5)	8 (18.2)		
DM	2 (7.4)	3 (17.6)	5 (11.4)		
Cholecystectomy	0 (0)	1 (5.9)	1 (2.3)		
Operated Gastric Ulcer	1 (3.7)	2 (11.8)	3 (6.8)		
<b>Abdominal CT Findings*</b>					
No findings	2 (7.4)	1 (5.9)	3 (6.8)		
Ileus	21 (77.8)	16 (94.1)	37 (84.1)		
Fecalith	2 (7.4)	1 (5.9)	3 (6.8)		
Inguinal hernia	4 (14.8)	1 (5.9)	5 (11.4)	$\chi^2=7.281$	0.400
Volvulus	1 (3.7)	0 (0)	1 (2.3)		
Umbilical Hernia	0 (0)	1 (5.9)	1 (2.3)		
Dilated Colon	3 (11.1)	0 (0)	3 (6.8)		

$\chi^2$ : Chi-square test statistic, F: Fisher's Exact test statistic, \* preliminary diagnosis based on abdominal CT result, \*\* Final diagnosis after clinical ward hospitalization

difference between the groups regarding mean age values ( $p > 0.05$ ). Upon evaluating the symptom onset durations at emergency department admission, the mean symptom onset duration in the operated patient group was found to be longer than in the non-operated group; however, the difference was not statistically significant ( $p > 0.05$ ). There was no statistically significant difference between Group A and Group B regarding comorbidities, preliminary diagnoses based on abdominal CT findings, or final diagnoses after hospitalization in the clinical ward ( $p > 0.05$ ). The sociodemographic characteristics, clinical features, comorbidities, laboratory parameters, and radiological findings—including plain radiography, ultrasonography, and abdominal CT—are summarized in Tables 1 and 2.

The IMA levels measured from blood samples were as follows: Group A:  $88.8 \pm 14.3$  ng/mL, Group B:  $106.1 \pm 29.9$  ng/mL, Control group:  $90.1 \pm 14.1$  ng/mL, A statistically significant difference was observed between the groups ( $p < 0.001$ ). The SCUBE-1 levels were as follows: Group A:  $80.3 \pm 84.9$  ng/mL, Group B:  $132.4 \pm 124.7$  ng/mL, A statistically significant difference was found between the groups ( $p = 0.001$ ). The i-FABP levels were as follows: Group A:  $56.4 \pm 11.5$  ng/mL, Group B:  $62.3 \pm 10.1$  ng/mL, Control group:  $41.9 \pm 12.2$  ng/mL, A statistically significant difference was found between the groups ( $p < 0.001$ ). The intergroup comparisons of IMA, SCUBE-1, and i-FABP levels are presented in Table 3.

**Table 3.** Comparison of IMA, SCUBE1, I-FABP values according to groups

		Group A n=27	Group B n=17	Control Group n=40	p value
IMA	Mean±SD	$88.8 \pm 14.3^b$	$106.1 \pm 29.9^a$	$90.1 \pm 14.1^b$	<b>&lt;0.001</b>
	(min-max)	(54.6–115.3)	(74.4–194.5)	(63.1–124.1)	
SCUBE1	Mean±SD	$80.3 \pm 84.9^b$	$132.4 \pm 124.7^a$	$76.4 \pm 11.8^b$	<b>0.001</b>
	(min-max)	(33.5–392.9)	(27.1–454.3)	(50.2–105)	
I-FABP	Mean±SD	$56.4 \pm 11.5^{a,b}$	$62.3 \pm 10.1^a$	$41.9 \pm 12.2^b$	<b>&lt;0.001</b>
	(min-max)	(28.7–79.3)	(45.8–79.2)	(18.3–77.3)	

<sup>a-b</sup>: No difference between groups with the same letter, min: minimum, max: maximum, SD: Standard Deviation

## DISCUSSION

In the present study, IMA, i-FABP, and SCUBE-1 levels measured at the time of emergency department presentation successfully differentiated patients in the surgical group from those in the non-surgical and control groups. The study found that

patients with higher IMA, i-FABP, and SCUBE-1 levels at presentation required surgical intervention more frequently.

Although different pathologies contribute to MBO, failure to resolve the obstruction results in intestinal ischemia, which in turn increases morbidity and mortality rates (4). The decision

for surgical intervention in the management of MBO is crucial, as a delayed surgical decision may lead to ischemia and bowel necrosis (5,6). Clinicians rely on fever, peritoneal irritation findings, leukocytosis, increased lactate levels, and CT imaging to predict bowel ischemia and decide on surgical intervention. However, these methods have low predictive value and pose risks such as radiation exposure (4,7,9,10). Thus, there is a need for early diagnostic tools to identify bowel ischemia (9,18).

i-FABP is a cytosolic protein found in intestinal mucosal villi. Following enterocyte damage, i-FABP is rapidly released into circulation. (11,12). Hypoperfusion due to MBO leads to intestinal ischemia, causing enterocyte membrane disruption and a rapid increase in i-FABP plasma concentration (18). Several studies have demonstrated the diagnostic value of i-FABP in detecting bowel ischemia and strangulation (9,12,18,19). Tyagunov et al. examined rats with strangulated and non-strangulated bowel obstruction and found that i-FABP levels were significantly higher in the strangulated group. They also observed that i-FABP peaked at the 4th hour (13). Similarly, Kittaka et al., in a study on 37 patients, reported that serum i-FABP levels successfully differentiated strangulated obstruction cases (18). Another study found that i-FABP concentrations were significantly higher in ischemic acute abdomen patients compared to both non-ischemic acute abdomen patients and

healthy individuals (19). The present study demonstrated that serum i-FABP levels were significantly higher in surgically treated patients with strangulation findings compared to both simple MBO patients and the control group.

SCUBE-1 is a novel cell surface protein stored in alpha granules of inactivated platelets and translocated to the platelet surface upon thrombin activation (20). SCUBE-1 accumulation has been demonstrated in the subendothelial regions of atherosclerotic plaques. It functions as an adhesion molecule between platelets and endothelial cells. SCUBE-1, released from activated platelets, binds to the subendothelial matrix, playing a role in adhesion (21,22). Studies suggest that SCUBE-1 may serve as a useful biomarker in ischemic pathologies, such as acute coronary syndrome and ischemic stroke (20,23). Türkmen et al., in an experimental study on rats, demonstrated that SCUBE-1 levels increased rapidly within 2 hours in acute mesenteric ischemia. Moreover, the study showed that SCUBE-1 levels continued to rise even after the 2-hour mark (22). Similarly, Aköz et al., in an experimental study on rats with induced acute mesenteric ischemia, proposed that elevated SCUBE-1 levels could be an early marker of mesenteric ischemia (20). In another animal study investigating the relationship between SCUBE-1 and strangulated bowel obstruction, an increase in

SCUBE-1 levels was detected as early as the 1st hour of strangulation, which persisted up to 6 hours (4). In the present study, SCUBE-1 levels measured at admission were significantly higher in the surgical MBO group.

Human serum albumin undergoes structural modifications due to oxidative stress, free oxygen radicals, and acidosis triggered by ischemia, leading to a decrease in its affinity for heavy metals such as cobalt, copper, and nickel. This modified albumin form, resulting from ischemic alterations, is termed ischemia-modified albumin (IMA) (24). The literature suggests that IMA can serve as a diagnostic biomarker for ischemic conditions, including myocardial ischemia, pulmonary embolism, and ischemic stroke (25–27). Gündüz et al., in a study on patients with acute mesenteric ischemia, reported that IMA levels were significantly higher in the ischemic group compared to the control group (28). Similarly, Cekic et al. found that IMA levels were significantly elevated in rats with strangulated bowel obstruction compared to those without strangulation (4). Tomandlova et al. investigated the efficacy of IMA in predicting intestinal ischemia in patients undergoing abdominal aortic surgery and reported a significant increase in IMA levels 1 hour after aortic cross-clamping in patients with intestinal ischemia (29). In the present study, serum IMA levels were significantly higher in surgically treated MBO patients compared to other

groups. However, serum IMA levels did not differ significantly between healthy volunteers and non-operated MBO patients.

### **Limitations**

This study has certain limitations due to its single-center design and relatively small sample size. The limited study population may reduce the generalizability of the obtained results. Additionally, as this study only evaluated biomarker levels at the time of admission and did not assess long-term outcomes, the inability to determine changes over time through serial measurements is considered another limitation. Future studies with larger sample sizes, multi-center participation, and long-term follow-up are needed.

### **CONCLUSION**

This study evaluated the diagnostic value of SCUBE-1, i-FABP, and IMA biomarkers in patients diagnosed with MBO and it was thought that these biomarkers could serve as important tools in determining the need for surgical intervention. SCUBE-1, i-FABP, and IMA levels were found to show a significant difference in predicting bowel ischemia and strangulation. The findings suggest that these biomarkers may support early clinical decision-making and assist in the early diagnosis of bowel ischemia. However, to enhance the accuracy of these biomarkers in routine clinical practice and to evaluate their efficacy in larger

populations, more comprehensive, multi-center, and prospective studies are required.

**Ethics Committee Approval:** Approval for this study was obtained from the Acibadem Mehmet Ali Aydınlar University Medical Research Evaluation Committee (Decision No: 2019-9/15).

We state that the parents have given their written informed consent to be involved in the study, in accordance with the Declaration of Helsinki.

**Peer-review:** Externally peer-reviewed

**Author Contributions:** Concept: AA, ST, SY, AO Design: AA, ST, SY, KDB; Data Collection and Processing: AA, ST; Analysis and Interpretation: AA, TN, MSS; Writing: AA, ST, MSS, AO;

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