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Signa Vitae

ORIGINAL RESEARCH

Comparison of clinical characteristics in acute pancreatitis with and without diabetes mellitus: a retrospective study

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Abstract

Background: Current research shows a cause-and-effect relationship between acute pancreatitis (AP) and diabetes mellitus (DM). In this study the difference in clinical features between AP with DM and AP without DM was analyzed to explore implications for the treatment of these two conditions. **Methods**: From January 2016 to December 2018 all patients with AP admitted to the Changsha Central Hospital were included in a retrospective study. Clinical and laboratory variables obtained from AP patients were analyzed and compared with a DM group and a non-DM group. **Results**: A total of 869 patients with AP including 139 patients in DM the group and 730 patients in the non-DM group were analyzed. Hypertension ($P = 0.002$), coronary heart disease (CHD, $P = 0.003$) and hypertriglyceridemia ($P = 0.045$) were more common in the DM than the non-DM group, while BISAP ($P < 0.001$) and Ranson ($P < 0.001$), the incidence of AP recurrence ($P = 0.034$) and length of hospital stay ($P = 0.045$) were significantly higher for the DM group as were levels of blood sugar ($P < 0.001$), glycated hemoglobin ($P < 0.001$), ALT ($P = 0.003$), AST ($P = 0.032$), BUN ($P = 0.017$), creatinine ($P = 0.003$), cholesterol ($P < 0.001$), LDL ($P < 0.001$) and TG ($P < 0.001$). **Conclusion**: AP patients with DM were prone to comorbidities with higher levels of organ function indicators and higher incidence of dyslipidemia and recurrence of AP.

Keywords

Acute pancreatitis; Diabetes mellitus; Comorbidity; Dyslipidemia

1. Introduction

AP is still a disease with different clinical outcomes that vary from mild to severe depending on different clinical features such as comorbidities [1]. DM is a metabolic disorder with a chronically progressive evolution. It has a detrimental impact on multiple organs with both local and system complications and an incidence that has increased significantly over the last two decades [2]. Many researchers have shown a cause-and-effect relationship between AP and DM. A systemic review that included a total of 31 relevant studies with 13,894 subjects clarified that 23% patients with AP developed DM after discharge from hospital. Moreover, with the disease severity increasing, the occurrence of DM after AP similarly increased [3]. Other research in children with AP also showed that 6% of patients diagnosed with AP were subsequently diagnosed with DM when the exposure risk for DM was much higher, about 30-fold higher than expected in the general pediatric population [4]. In the case of chronic pancreatitis, DM was detected in more than 10% of pediatric patients and 31% of adult patients [5]. Alternatively, DM was one potential risk factor in patients that developed AP, especially when they were also diagnosed with severe hypertriglyceridemia [6]. A meta-analysis with eight cohort studies that included 14,124 cases and 5.7 million participants showed that DM was linked with a 74% increase in the risk of AP, a 39% increase in the risk of pancreatitis overall and a 40% increase in risk of chronic pancreatitis [7].

Recently, AP patients with DM have increasingly been admitted to hospitals. However, few studies have investigated the clinical characteristics of AP in the presence of DM. In the study reported here, the aim was to analyze the differences in clinical features between AP with DM and AP without DM to explore the implications for treatment of AP in the presence of DM.

2. Methods

2.1 Study design and patients

From January 2016 until December 2018, all patients with AP admitted to the Changsha Central Hospital were included in this retrospective study. Inclusion criteria were defined as follows: age $\geq$ 18 and confirmed diagnosis of AP. Study exclusion criteria included: death, age $<$ 18, chronic pancreatitis, malignant tumors, chronic organ dysfunction (kidney, heart or

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TABLE 1. General characteristics in DM group and non-DM group.

Characteristics	DM group (n = 139)	Non-DM group (n = 730)	Total (n = 869)	*P* value
Age (years)	47.62 ± 15.78	46.17 ± 14.13		0.277
18-44 (n, %)	70 (50.36%)	363 (49.73%)		0.220
45-65 (n, %)	46 (33.09%)	281 (38.49%)		0.234
> 65 (n, %)	23 (16.55%)	86 (11.78%)		0.522
BMI (kg/m^2)	25.44 (23.97, 27.10)	25.92 (22.95, 28.68)		0.193
Sex (n,%)				
Male	96 (69.06%)	516 (70.68%)	612	0.701
Female	43 (30.94%)	214 (29.32%)	257	
Smoking (n, %)	40 (28.78%)	220 (30.82%)		0.105
Comorbidities (n, %)				
Hypertension				
Yes	38 (27.34%)	118 (16.16%)	156	0.002
No	101 (72.66%)	612 (83.84%)	713	
COPD				
Yes	3 (2.16%)	9 (1.23%)	12	0.392
No	136 (97.84%)	721 (98.77%)	857	
Coronary heart disease				
Yes	11 (7.91%)	20 (2.74%)	31	0.003
No	128 (92.09%)	710 (97.26%)	838	
Etiologies (n, %)				
Alcohol				
Yes	27 (19.42%)	178 (24.38%)	205	0.207
No	112 (80.58%)	552 (75.62%)	664	
Hypertriglyceridemia				
Yes	69 (49.64%%)	297 (40.68%)	366	0.045
No	70 (50.36%)	433 (59.32%)	503	
Cholelithiasis				
Yes	22 (15.83%)	161 (22.05%)	183	0.099
No	117 (84.17%)	569 (77.95%)	686	
CT grade (n, %)				
D, E grade	12 (8.63%)	49 (6.71%)	61	0.417
A, B, C grade	127 (91.37%)	681 (93.29%)	808	
Pleural effusion (n, %)				
Yes	29 (20.86%)	128 (17.53%)	157	0.350
No	110 (79.14%)	602 (82.47%)	713	
Abdominal effusion (n, %)				
Yes	26 (18.71%)	111 (15.21%)	137	0.299
No	113 (81.29%)	619 (84.79%)	732	
Lung infection (n, %)				
Yes	25 (17.77%)	116 (15.89%)	141	0.539
No	114 (82.01%)	614 (84.11%)	728	
ICU admission (n, %)				
Yes	24 (17.27%)	100 (13.70%)	124	0.270
No	115 (82.73%)	630 (86.30%)	745	

TABLE 1. Continued.

Characteristics	DM group (n = 139)	Non-DM group (n = 730)	Total (n = 869)	*P* value
Mechanical ventilation (n, %)				
Yes	2 (1.47%)	17 (2.33%)	19	0.525
No	126 (98.53%)	666 (97.67%)	792	
Organ dysfunction (n, %)				
ARDS	12 (8.63%)	50 (6.84%)		0.472
Liver dysfunction	17 (12.2%)	120 (16.44%)		0.253
Scoring system				
BISAP	1 (0,1)	0 (0,1)		< 0.001
SOFA	0 (0,0.75)	0 (0.1)		0.870
RANSON	1 (1,2.75)	1 (0,1)		< 0.001
LOS in hospital (days)	7 (5,10)	6 (5,9)		0.045
Recurrence (n, %)				
Yes	45 (32.37%)	174 (23.84%)	219	0.034
No	94 (67.63%)	556 (76.16)	650	

Abbreviations: *AP = acute pancreatitis, DM = diabetes mellitus, BMI = body mass index, ARDS = acute respiratory distress syndrome, LOS = length of stay, SOFA = sequential organ failure assessment, BISAP = bedside index of severity in acute pancreatitis.*

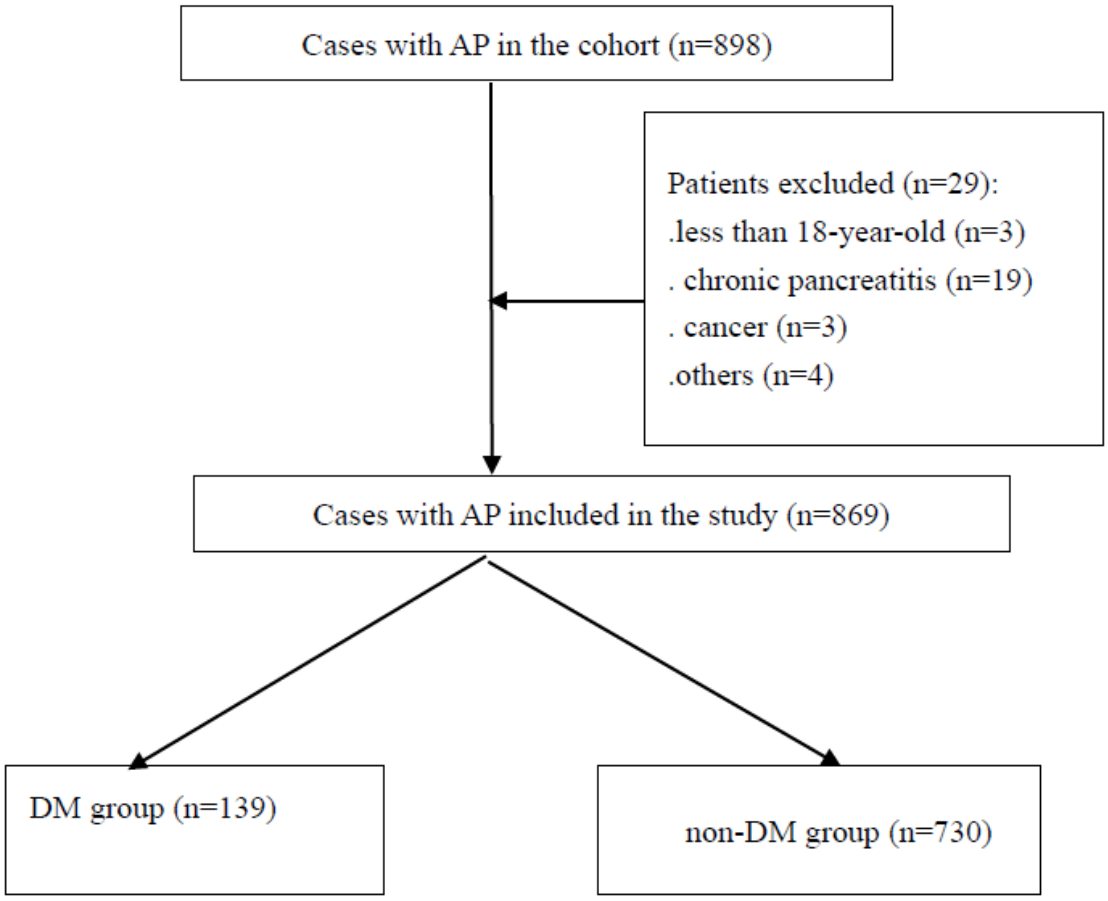

FIGURE 1. Flow chart for patients enrollment and study design. Abbreviations: AP = acute pancreatitis.

liver dysfunction), pregnancy and patients with missing data.

AP was diagnosed based on its typical gastrointestinal symptoms (abdominal pain, distention or vomiting), laboratory tests (amylase or lipase) and medical imaging (abdominal ultra-

TABLE 2. Comparison of laboratory characteristics between DM group and non-DM group.

Variables	DM group (n = 139)	non-DM group (n = 730)	*P* value
WBC (ˆ10^9/L)	12.75 ± 5.98	12.58 ± 4.45	0.756
Neutrophi l(ˆ10^9/L)	9.94 ± 4.39	10.04 ± 4.51	0.808
HCT	0.44 (0.41, 0.48)	0.45 (0.41, 0.48)	0.152
PLT (ˆ10^9/L)	223.50 (174.25, 253.50)	203.00 (165.50, 246.00)	0.881
PDW (%)	13.83 ± 2.73	13.32 ± 4.95	0.242
Blood sugar (mmol/L)	14.50 (11.80, 16.48)	7.25 (6.20, 8.98)	< 0.001
Glycated hemoglobin (mmol/L)	10.15 (7.93, 11.17)	5.60 (5.30, 6.10)	< 0.001
PT (s)	11.83 ± 1.53	12.00 ± 5.76	0.745
APTT (s)	24.45 (21.73, 27.95)	27.65 (25.05, 29.80)	0.221
Fbg (mg/dL)	3.30 (2.65, 4.93)	3.26 (2.59, 4.37)	0.084
ALB (g/l)	44.11 ± 7.27	43.16 ± 5.62	0.088
ALT (u/L)	32.40 (22.23, 49.33)	25.75 (17.48, 44.08)	0.003
AST (u/L)	26.50 (19.55, 33.90)	24.00 (17.30, 31.05)	0.032
Total bilirubin (mmol/L)	14.00 (10.97, 20.74)	15.53 (10.54, 20.42)	0.264
BUN (mmol/L)	4.35 (3.30, 5.25)	4.29 (3.52, 5.05)	0.017
Creatinine (ummol/L)	77.18 ± 60.12	70.77 ± 36.06	0.003
Urea acid (ummol/L)	350.10 ± 122.48	350.75 ± 113.06	0.953
Amylase (u/L)	269.50 (71.25, 644.00)	218.00 (95.03, 491.00)	0.189
Lipase (u/L)	344.00 (85.50, 865.25)	311.50 (81.25, 693.00)	0.169
LDH (u/L)	242.00 (172.50, 315.50)	196.00 (165.50, 256.25)	0.191
Total Cacium (mmol/L)	2.35 (2.25, 2.55)	2.33 (2.23, 2.49)	0.057
Cholesterol (mmol/L)	7.49 (4.92, 12.22)	6.13 (4.79, 8.10)	< 0.001
LDL (mmol/L)	1.95 (1.16, 3.16)	1.80 (1.30, 2.62)	< 0.001
HDL (mmol/L)	0.69 (0.51, 1.31)	0.80 (0.66, 1.20)	0.984
TG (mmol/L)	14.76 (2.08, 22.76)	9.48 (1.71, 15.01)	< 0.001

Abbreviations: *AP = acute pancreatitis, DM = diabetes mellitus, WBC = white blood cell, HCT = hematocrit, PLT = platelet, PDW = platelet distribution width, PT = prothrombin time, APTT = activated partial thromboplastin time, Fbg = fibrinogen, ALB = albumin, LDH = lactate dehydrogenase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglyceride.*

sonography or CT). Recurrent AP (RAP) was defined as: [1] confirmed AP, and [2] the interval between two or more separate attacks of AP with complete recovery was more than 3 months.

In this study, patients with a medical history of diabetes before an AP attack (based on medical records) and patients without a medical history of diabetes diagnosed with DM when admitted in hospital due to AP attack were included in the DM group. Following several AP attacks, only the clinical and laboratory data of the first attack were analyzed.

2.2 Data collection

The medical information of AP patients admitted within 24 hours of an attack was recorded. Data collected included: age, gender, body mass index (BMI), etiology (alcohol, hyperlipidemia, cholelithiasis), comorbidities (hypertension, COPD, coronary heart disease (CHD)) and laboratory variables. Laboratory variables including white blood cell (WBC), neutrophil, hematocrit (HCT), platelet (PLT), platelet distribution width (PDW), blood sugar, glycated hemoglobin, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fbg), albumin (ALB), total bilirubin, creatinine, urea acid, amylase, lipase, lactate dehydrogenase (LDH), total calcium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride (TG).

CT images were also recorded including CT grades, pleural effusion, abdominal effusion and lung infection. The scores of sequential organ failure assessment, bedside index of severity in acute pancreatitis (BISAP) and Ranson were calculated based on clinical and laboratory variables.

Clinical managements and outcomes included in-hospital incidence of acute respiratory distress syndrome (ARDS) and liver dysfunction, ICU admission, mechanical ventilation, length of stay (LOS) in hospital and AP recurrence.

2.3 Statistical analysis

Statistical results were given as mean ± standard deviation for normal data, while for non-normal data, interquartile range (IQR) and median were utilized. Categorical data were given as percentage and value. Comparison between two groups was made by a chi-squared test or Mann-Whitney U-test.

3. Results

Initially, a total of 898 patients with AP were enrolled. Based on the exclusion criteria, 29 patients were excluded and 869 patients with AP included. 139 patients in the DM group and 730 patients in non-DM group were analyzed retrospectively (Fig. 1). In the DM group, 118 patients had a medical history of diabetes while 21 patients were diagnosed with DM when admitted to hospital due to an AP attack. The general characteristics of the two groups are given in Table 1. There were no significant differences in age, BMI and sex within these two groups. In the DM group, the proportion of hypertension and CHD were 27.34% and 7.91% respectively, which were higher than that of the non-DM group. Hypertriglyceridemia, 49.64% in the DM and 40.68% in the non-DM group, was the most common etiology, followed by alcohol (19.42% vs. 24.38%) and cholelithiasis (15.83% vs. 22.05%). CT images showed no difference in grades, pleural effusion, abdominal effusion and lung infection between two groups. Only a few patients (1.47% vs. 2.33%) needed mechanical ventilation and CRRT was applied in some patients (13.67% vs. 14.11%). The scores of BISAP and Ranson were significantly higher in the DM group. The incidence of ICU admission (17.27% vs. 13.7%), ARDS (8.63% vs. 6.84%) and liver dysfunction (12.2% vs. 16.44%) in the two groups showed no significant differences. The median length of stay in hospital in the DM and non-DM groups was seven days (IQR5-10 days) and 6 days (IQR5-9 days), respectively. The recurrence incidence of AP in DM the group was significant higher than that seen for the non-DM group (32.37% vs. 23.84%).

Laboratory variables are given in Table 2. There were no significant differences in WBC (P = 0.756), neutrophil (P = 0.808), HCT (P = 0.152), PLT (P = 0.881), PDW (P = 0.242), PT (P = 0.745), APTT (P = 0.221), Fbg (P = 0.084), ALB (P = 0.088), total bilirubin (P = 0.264), urea acid (P = 0.953), amylase (P = 0.189), lipase (P = 0.169), LDH (P = 0.191), total calcium (P = 0.057) and HDL (P = 0.984) between two groups. The levels of blood sugar ($P < 0.001$), glycated hemoglobin ($P < 0.001$), ALT (P = 0.003), AST (P = 0.032), BUN (P = 0.017), creatinine (P = 0.003), cholesterol ($P < 0.001$), LDL ($P < 0.001$) and TG ($P < 0.001$) were significantly higher in the DM group.

4. Discussion

This study showed that in the DM group hypertension and CHD were more likely to be comorbidities and hypertriglyceridemia was more common than in the AP group. Much clinical research shows that DM, CHD, hypertension and hypertriglyceridemia affect each other. One study with a total of 643,439 subjects showed that hypertension and DM were the main manifestations of metabolic syndrome and that the incidence of hypertension in patients with DM was 43.7%, a factor of 1.49 times greater than that in patients without DM [8]. In a hypertensive population, systolic blood pressure (SBP) was associated with DM occurrence The higher the level of SBP, the higher the morbidity of DM [9]. Moreover, DM increased both the incidence and mortality of CHD by at least a factor of two due to dyslipidemia [10]. Hypertriglyceridemia as an abnormality of lipid metabolism is associated with insulin resistance. In a study with 15,932 participants, hypertriglyceridemia that persisted for more than two years was significantly associated with the incidence risk of DM [11].

BISAP and Ranson scores were higher and hospital LOS days were longer in the DM group, which indicated that disease severity was greater for those patients. A retrospective research study showed AP patients with DM to be more likely to developing severe pancreatitis and that DM was correlated with the MRI characteristics of pancreatic necrosis, infection, hemorrhage, and abdominal wall edema [12]. Previous studies have shown that the blood glucose level of patients with DM had a significant impact on AP progression, which may aggravate the development of local fluid collections or necrosis formation and lead to a prolonged disease period [13]. DM, as a one of the systematic metabolic disorders, was shown to impair immune system function and infection occurrence [14]. In the study reported here, no significant differences were found in lung infection and fluid collection, which was partly explained by the difference of clinical characteristics in patients between different hospitals.

Compared with the occurrence incidence of AP, patients with DM were prone to repeated AP attacks. Factors including alcohol, hypertriglyceridemia, higher CT scores and systemic inflammatory reaction have been associated with AP recurrence [15–17]. Hypertriglyceridemia is also an important risk factor for the development and recurrence of AP [18]. The excess hydrolyzed particles of TG in circulation are capable of ruining the vascular bed of the pancreas and vascular endothelium in microcirculation, which results in systemic inflammation and damage to pancreatic acinar cells [19].

In a comparison of laboratory variables between the two group, not only the level of blood sugar and glycated hemoglobin but also organ function indicators including ALT, AST, BUN and creatinine were significantly higher in the DM group. DM was associated with long-term damage to blood vessels including macrovascular and microvascular systems, which results in kidney and liver disfunction [20, 21]. A study of 9,621 DM patients verified that ALT and AST levels exceeding the upper limit of the normal range were present in 16.0% and 8.8%, respectively [22]. Higher levels of BUN and creatinine were associated with an increased risk of DM, while DM exacerbated kidney dysfunction [23].

Dyslipidemia, including elevated cholesterol, TG and LDL occurred in more AP patients with DM in this study. More patients in the DM group were diagnosed with AP due to hypertriglyceridemia, while DM was also associated with dyslipidemia.

A retrospective study of 1,999 DM patients concluded that the proportion with elevated LDL, TG and HDL were 34.8%, 27.8% and 15.4% of patients, respectively [24]. In children

and youth with DM from India the prevalence of dyslipidemia was shown to be approximately 47.2% [25].

A recent study of the association of clinical features and outcomes of AP between diabetic and non-diabetic hospitalized patients showed that, with the exception of serum albumin, major clinical features and laboratory markers were significantly higher in a DM group and DM increased the disease severity of AP [26]. However, in the study reported here, larger samples were enrolled and the incidence of hypertriglyceridemia in AP was likely higher due to sample differences in the different studies and countries.

The strength of this study was that various significant clinical characteristics in AP with DM were identified. AP patients with DM were prone to having comorbidities with higher levels of kidney and liver function indicators and a higher incidence of dyslipidemia. During the COVID-19 pandemic period, clinical evidence suggested that the overall survival time of patients may be shortened, their quality of life reduced and that the risk of complications and need for critical care in the most severe cases would increase [27]. Hence, monitoring vital signs and laboratory variables more frequently is necessary for AP patients with DM.

One limitation of this study was that it was conducted at a single center in China and differences compared to other countries and populations should be considered. Another was that in this retrospective study, with some data missing, although patients in the DM group had a medical history of diabetes or had been diagnosed with DM after admission, T3cDM could not be clearly made as a diagnosis for them. Further research should be conducted to analyze the association of different types of diabetes with the effect of AP on clinical characteristics and outcomes. Finally, due to its retrospective design, longer patient follow-ups were not performed and data were collected from electronic clinical records and only clinical characteristics were analyzed. Future studies should focus on constructing models for predicting the risk of disease progression, evaluating the management of patients with severe complications and the discovery of indicators linked to different disease stages.

5. Conclusions

In this study, AP patients with DM were prone to having comorbidities with higher levels of organ function indicators and higher incidence of dyslipidemia and recurrence of AP.

ABBREVIATIONS

ALB, albumin; ALT, alanine aminotransferase; AP, acute pancreatitis; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHD, coronary heart disease; DM, diabetes mellitus; Fbg, fibrinogen; HCT, hematocrit; HDL, high density lipoprotein; IQR, interquartile range; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LOS, length of stay; PDW, platelet distribution width; PLT, platelet; PT, prothrombin time; RAP, recurrent acute pancreatitis; SBP, systolic blood pressure; TG: triglyceride; WBC, white blood cell.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was provided by the Medical Ethics Committee of Changsha central Hospital (NO.CSH2020088). Due to the nature of retrospective study, informed consent was waived.

AVAILABILITY OF DATA AND MATERIALS

Datasets used and/or analyzed in the present study were availed by the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

The manuscript writing and patient's data recording were done by Kun Song and Cuirong Guo. Ning Ding assisted in information collection. Changluo Li and Ning Ding analyzed and interpreted the patients' general indices. The final manuscript was read and ratified by all authors.

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CONFLICT OF INTEREST

The authors have no conflict of interest in this article.

DISCLOSURE STATEMENT

There are no real or apparent conflicts of interest to disclose.

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