

# POSTOPERATIVE COMPLICATIONS AND RISK FACTORS IN ABDOMINAL AORTIC ANEURYSM REPAIR: A RETROSPECTIVE STUDY

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## Abstract

**Aim:** The study aimed to determine the prevalence of postoperative complications and identify preoperative, intraoperative, and postoperative risk factors affecting patients undergoing Abdominal Aortic Aneurysm (AAA) repair, with a focus on Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR).

**Methodology:** This retrospective cohort study included 104 patients aged 50–89 years undergoing AAA repair. Preoperative demographic, clinical, aneurysm, and surgical data were collected. Complications within 30 days were considered short-term and those after 30 days long-term. Risk factors across perioperative phases were analyzed using logistic regression in SPSS (version 26). Ethical approval was obtained, and  $p < 0.05$  was considered significant.

**Results:** OSR was conducted for larger ( $6.8 \pm 1.2$  cm) and ruptured aneurysms, while EVAR was favored for smaller ( $5.7 \pm 1.1$  cm) and unruptured patients ( $p < 0.001$ ). OSR led to extended ICU hospitalizations (4.86 days) and prolonged hospital admissions (5.04 days), elevated hydration needs ( $p = 0.032$ ), and augmented dopamine use ( $p = 0.003$ ). OSR patients had a higher incidence of complications, including wound infections, hemorrhage, stroke, and renal failure ( $p < 0.05$ ), with higher long-term risks of graft thrombosis, endoleaks, and aneurysm recurrence ( $p < 0.05$ ). These data underscore that OSR has higher perioperative risk, while EVAR offers a less disruptive option with fewer consequences.

**Conclusion:** Postoperative complications in AAA repair are significantly influenced by age, comorbidities, and operative duration. Further studies are needed to validate findings and improve perioperative management.

**Keywords:** Abdominal Aortic Aneurysm, Endoleaks, Endovascular Aneurysm Repair, Open Surgical Repair, Postoperative Complications.

## INTRODUCTION

Abdominal aortic aneurysm (AAA) is a disease condition which implies a focal enlargement of the abdominal aortic wall, usually defined as a swelling greater than 50% of its normal size or measuring greater than 3 cm in the anteroposterior diameter. AAA is a polygenic condition facilitated by chronic inflammation, genetics and hemodynamic factors, all contributing to the aortic wall degeneration [1]. During AAA rupture, there is an increased risk of death, and the surviving rate is expected to be lower than 20%, subject to no surgical intervention [2]. It has become more critical to develop effective intervention because of the elevated death rate.

In 2019, Kim et al., observed AAA to mostly occur within older adults who smoke and are prone to hypertension and hyperlipidemia [3]. Over the years, AAA has been found to exist in 2% to 5% of men above the age of 65, while it is considerably less prevalent in women due to hormonal and biological differences [4]. Furthermore, the creation of such technologies as ultrasound and CT scan has transitioned the focus towards single vessel vasospasm allowing for earlier diagnosis and more effective treatment intervention [5].

There are two main methods for AAA repair. These include Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR). Surgeons have been employing OSR as the standard technique for a long time and it

requires them to cut out the aneurysmal segment and replace it with a synthetic graft. Although OSR is reasonably effective at averting rupture, it does come with a downside since it has high rates of perioperative morbidity and extended recovery times [6]. Nevertheless, in the end of the 1990s, a different approach was formed that is known as EVAR – this method is less invasive as it employs the use of a catheter through the femoral artery to insert stent grafts. Surgeons prefer using EVAR as it has a significant reduction in operative time, lesser complication rates post-surgery, and a smaller number of days spent in a hospital [7]. Even though these benefits do exist, EVAR cannot be used by everyone, especially those who have intricate anatomical structures of their vessels; hence, OSR is used.

Postoperative care after AAA repair is always an area of concern. This literature highlights numerous short-term complications that are expected during such surgery, for instance, wound differential, bleeding as well as myocardial infarction [8], another class of the complications that clinicians deal with now are long term complications such as graft failure, new aneurysm formation, endoleaks [9]. In 2022, Chen et al., highlighted the importance of the risk factors that were noted before the surgery in relation to the age of the patient, other diseases they suffer from, the surgical method used, and the predictions made after the surgery procedure, among others [10].

While addressing these associations has been explored in prior research works, there remains a gap with respect to how patient-specific factors are related to the patient's surgery as well as the post-surgery performance outcomes, specifically during long-term comparative effectiveness analysis of EVAR versus OSR. A 2012 study by Vandy and associates pointed to the critical need to assess, compared with the traditional placement of graft examination of early results such as EVAR adoption, the later persistent outcomes of EVAR technologies [11,12].

This study aims to evaluate the spectrum of postoperative complications and identify preoperative, intraoperative, and postoperative risk factors influencing outcomes in patients undergoing abdominal aortic aneurysm surgery. This study used a retrospective cohort methodology to rectify shortcomings in existing studies and provide insights that might improve perioperative care practices for AAA repair.

## **MATERIALS AND METHODS**

### **Study Design**

This retrospective cohort research was performed at Columbia Asia Hospitals to examine the postoperative complications and risk variables associated with patients who had abdominal aortic aneurysm (AAA) repair. The investigations focused on individuals who had undergone surgery from ... to ..., including clinical, surgical, and follow-up characteristics. The focus shifted primarily to two major surgical procedures: Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR).

### **Study Participants**

Patients aged 50–89 years diagnosed with AAA and treated with OSR or EVAR have been protected within the study. The participants were chosen based on inclusion criteria. They were required to have an imaging confirmed diagnosis of AAA along with readily available medical records and surgical files. Patients with prior AAA repairs, those with thoracic aortic aneurysms, as well as patients with active systemic infection or malignancy at the time of surgery were excluded from the study. In total, 104 participants who met the eligibility criteria were enrolled, which provided sufficient data for the analysis.

### **Clinical Evaluations**

In the baseline assessment, patient demographic details including age, sex, and BMI along with lifestyle variables such as smoking and drinking were taken into consideration. An assessment of all concomitant diseases such as diabetes, hypertension, and hyperlipidemia was undertaken to determine how these might affect the surgery results. Preoperative imaging studies, especially CT angiography, were the most important part of the assessment as they determined aneurysm size, shape, wall characteristics, and if it was ruptured, which subsequently determined whether OSR or EVAR was undertaken. Data collected during operations included the type of operation, time taken for the procedure, anesthesia administered, estimated blood loss, and intraoperative complications, for example, vessel injuries or changes in hemodynamic status. After surgery, ICU monitoring was performed during the first 24 hours which included the duration of ICU stay, time on a ventilator, total days spent in the hospital, and all secondary operative interventions, such as blood transfusing and treating the complication with drugs.

### **Postoperative Complications**

Postoperative complications were systematically categorized and analyzed into short-term and long-term classifications.

- **Short-term complications:** Short-term complications emerged within 30 days after the surgery, which included wound infections, hemorrhage, Angio cardiosclerosis, stroke, and acute renal failure. Primarily, these complications were assessed via patient clinical records, laboratory analysis and other forms of post-operative imaging and diagnostics.
- **Long-term complications:** Long-term complications were identified during follow-up evaluations and included graft thrombosis, endoleaks, and recurrence of aneurysms. These were evaluated with sophisticated clinical examinations, as well as with imaging studies like CT angiography, Doppler ultrasound, and others.

### **Risk Factor Assessment**

The study evaluated risk factors around three domains, which include preoperative components like patient's demographics, comorbidities and aneurysm features as assessed by CT angiography (CT-Angio); intraoperative components like surgical method orbital surgery or endovascular aortic repair (OSR or EVAR), operating period, and bleeding all of which were measured using validated equipment; and postoperative components which include, but are not limited to, ICU admission, duration on ventilation, and the length of the stay in the facility.

### **Data Collection**

Patient information, which includes age, gender, BMI, and smoking status was captured through medical records. Comorbidities like diabetes, hypertension and hyperlipidemia were confirmed using clinical documents and active treatment documents. Anesthesia, type of surgery performed (OSR or EVAR), duration and blood loss were obtained from surgical and clinical notes. CT imaging was mostly utilized before the operation which provided distal aorta at aneurysm level and rupture information, while the postoperative ones were mostly intended for effective treatment. The post-operative issues were further stratified in the short and long term -the former included wound infection, namely, hemorrhage and acute renal failure while the latter included graft thrombosis, recurrent aneurysm and endoleaks. While tackling risk factors, the preoperative set which included demographics and comorbidities, intraoperative set which included, type of surgery and blood loss, and lastly the postoperative which included admission into kidney pend showcases the depth of variance that exists in the set scopes.

### **Ethical Considerations**

This study involved human patients and utilized retrospective, anonymized hospital records. Ethical approval was obtained from the Institutional Ethics Committee. As per institutional and national guidelines, the requirement for informed consent was waived because no direct patient contact occurred and no identifiable information was used. The study adhered to the principles of the Declaration of Helsinki, ensuring confidentiality and ethical handling of patient data.

### **Statistical Analysis**

Statistical analyses were conducted with SPSS software (version 26). Descriptive statistics were used to encapsulate demographic and clinical variables. Continuous variables were represented as mean  $\pm$  standard deviation (SD) and analyzed using independent t-tests or Mann-Whitney U tests, whilst categorical variables were assessed using chi-square or Fisher's exact tests. Multivariate logistic regression was used to ascertain independent predictors of postoperative complications. A p-value  $< 0.05$  was deemed statistically significant.

## **RESULT**

### **Demographic characteristics**

The Table 1 highlighted the demographic analysis of the study participants (N=104) indicates that the majority are within the 60–79-year age group (n = 67, 65%), with a male preponderance (n = 88, 85%). The BMI distribution indicates that around 48 participants (46%) of individuals have a normal weight, while 51 participants (49%) are classified as overweight or obese, potentially increasing their risk for metabolic illnesses. Lifestyle characteristics reveal a significant history of smoking, with 40 participants (38%) identified as past smokers and 31 participants (29%) as current smokers, while 60 participants (58%) indicate various levels of alcohol intake. Comorbidities are prevalent, with hypertension being the most frequent (n = 72, 69%), followed by coronary artery disease (n = 29, 28%) and diabetes mellitus (n = 17, 16%). These data highlight a significant prevalence of cardiovascular and metabolic comorbidities, which may facilitate the onset of illness and consequences in this group. The identified occurrence of chance variables indicates a need for targeted treatments addressing modifiable lifestyle choices and thorough management of existing comorbid illnesses.

**Table 1:** Demographic analysis of study participants

Characteristics	Frequency (N)	Percentage (%)
<b>Age Range (years)</b>		
50–59	20	19%
60–69	35	34%
70–79	32	31%
80–89	17	16%
<b>Gender</b>		
Male	88	85%
Female	16	15%
<b>BMI Classification (kg)</b>		
Underweight (<18.5)	5	5%
Normal weight (18.5–24.9)	48	46%
Overweight (25–29.9)	33	32%
Obese (≥30)	18	17%
<b>Lifestyle Factors</b>		
Current Smoker	30	29%
Former Smoker	40	38%
Non-Smoker	34	33%
<b>Alcohol Consumption</b>		
Regular Drinker	25	24%
Occasional Drinker	35	34%
Non-Drinker	44	42%
<b>Concomitant Diseases</b>		
Hypertension	72	69%
Coronary artery disease	29	28%
Diabetes mellitus	17	16%
Chronic obstructive pulmonary disease	10	10%
Cerebrovascular disease	8	8%
Chronic renal failure	6	6%
Hyperlipidemia	22	21%

Body Mass Index (BMI)

### Surgical and Preoperative Outcomes

Table 2 demonstrated that Patients with AAA exhibited significant disparities between OSR and EVAR interventions. The aneurysm length was significantly larger in open surgical repair (6.8 cm) compared to endovascular aneurysm repair (5.7 cm,  $p < 0.001$ ). Ruptured aneurysms were more prevalent in open surgical repair (OSR) (32 cm) compared to endovascular aneurysm repair (EVAR) (18 cm,  $p < 0.01$ ), although unruptured aneurysms were more common in EVAR (82 cm) than in OSR (68 cm,  $p = 0.50$ ). No significant differences were observed in aneurysm development ( $p = 0.5$ ) or wall calcification ( $p = 0.106$ ). These data indicate that open surgical repair (OSR) is preferred for big, ruptured aneurysms, whereas endovascular aneurysm repair (EVAR) is more prevalent for smaller, unruptured cases.

**Table 2:** Preoperative baseline characteristics of AAA patients

Parameter	OSR Group (n = 47)	EVAR Group (n = 57)	p-value (t-test)
Aneurysm Size	6.8 ± 1.2 cm	5.7 ± 1.1 cm	< 0.001
<b>Aneurysm Shape</b>			
Saccular	48 ± 7.29 cm	37 ± 6.39 cm	p = 0.085
<b>Wall Characteristics</b>			
Calcified	42 ± 7.20 cm	33 ± 6.23 cm	p = 0.106
Ruptured Aneurysms	32 ± 6.80 cm	18 ± 5.09 cm	p < 0.01
Unruptured Aneurysms	68 ± 6.80 cm	82 ± 5.09 cm	p = 0.035

Abdominal Aortic Aneurysm (AAA), Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR)

### Comparison of the effects of ICU stay and Hospital stay

Table 3 illustrates a statistically significant decrease in both ICU and total hospital stay lengths, with  $p < 0.001$  for both comparisons (ICU stay:  $t = 12.189$  days,  $df = 103$ ; hospital stay:  $t = 11.350$  days,  $df = 103$ ). The suggested difference in ICU stay duration was  $-4.86$  days, with a 95% confidence interval ranging from  $4.27$  days to  $5.45$  days, while the mean difference for hospital stay duration was  $-5.04$  days, with a 95% confidence interval of  $4.13$  days to  $5.95$  days. The data indicate that the intervention or research context results in a significant reduction in hospitalization duration, which could additionally contribute to improved patient outcomes, reduced healthcare burden, and optimum resource use. The identified reductions in ICU and healthcare facility stay lengths suggest potential medical and economic benefits, highlighting the requirement for further investigation into the underlying processes driving these improvements.

**Table 3:** Illustration of Paired differences for ICU and hospital stay durations.

	Paired Differences					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
ICU stays	12.189	103	0.000	-4.86	5.45	4.27
Hospital stays	11.350	103	0.000	-5.04	5.95	4.13

ICU (Intensive Care Unit)

### Intraoperative Fluid and Blood Management

Table 4 delineates the intraoperative baseline characteristics of AAA patients, emphasizing significant disparities in fluid supply and hemodynamic management. Significantly, crystalloid administration resulted in much higher averages ( $4,198$  mL,  $P = 0.032$ ) and throughout the clamping duration ( $1,387$  mL,  $p = 0.040$ ), indicating an increased need for volume replacement throughout the surgical process. The delivery of colloids, while greater overall ( $892$  mL,  $P = 0.05$ ) and at some phases of the clamp period ( $531$  mL,  $P = 0.071$ ), did not achieve statistical significance. RBC transfusion did not exhibit significant variation either overall ( $640$  mL,  $P = 0.210$ ) or during the clamp period ( $P = 0.150$ ), showing very stable transfusion demand. Hemodynamic control revealed a significant increase in dopamine administration ( $5.1$   $\mu\text{g}/\text{kg}/\text{min}$ ,  $P = 0.003$ ), indicating a greater need for inotropic support, whereas vasopressor and vasodilator use was documented at  $17\%$  ( $n = 18$ ) and  $41\%$ , ( $n = 43$ ) respectively, but no statistical comparisons were offered. These data indicate that AAA procedures require substantial fluid resuscitation and circulatory support, with crystalloid administration and dopamine use being significantly linked to intraoperative management.

**Table 4:** Intraoperative baseline characteristics of AAA patients

Parameter	(Mean $\pm$ SD)	P-value
Blood Loss	1,300 mL	-
<b>Vessel injury</b>		
Crystalloid	$4,198 \pm 2,385$ mL	0.032
Colloid	$892 \pm 496$ mL	0.055
RBC Transfusion	$640 \pm 2,667$ mL	0.210
<b>During Clamp Period</b>		
Crystalloid	$1,387 \pm 994$ mL	0.040
Colloid	$531 \pm 319$ mL	0.071

RBC Transfusion	640 ± 2,667 mL	0.150
<b>Hemodynamic Changes</b>		
Dopamine Administration	5.1 ± 3.2 µg/kg/min	0.003
Vasopressors	18 (17%)	-
Vasodilators	43 (41%)	-

Abdominal Aortic Aneurysm (AAA)

### Postoperative Complications

Table 5 highlighted the comparative assessment of postoperative headaches between Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR) revealing statistically significant variations in several short-term and long-term outcomes. During the short-term follow-up period (≤30 days), OSR was associated with a higher incidence of wound infections (p=0.05), haemorrhage (p=0.032), stroke (p=0.041), and acute renal failure (p=0.038) compared to EVAR, whereas angio cardiosclerosis did not demonstrate a significant difference (p=0.078). In the extended follow-up, OSR revealed a significantly higher incidence of graft thrombosis (p=0.029), end leaks (p=0.036), and aneurysm recurrence (p=0.044) compared to EVAR. These findings indicate that while OSR could raise the likelihood of immediate postoperative complications, it also predisposes patients to more severe long-term vascular issues, highlighting the necessity for personalized treatment strategies based on individual risk profiles.

**Table 5:** Comparison of Postoperative Complications Between OSR and EVAR Groups

Complication Type	Complication	OSR (n=62) (Mean ± SD)	EVAR (n=42) (Mean ± SD)	p-value
Short-term Follow-up (≤30 days)	Wound infections	3.2 ± 1.1	2.5 ± 0.9	0.045
	Hemorrhage	4.1 ± 1.3	3.2 ± 1.0	0.032
	Angio cardiosclerosis	2.8 ± 1.0	2.4 ± 0.8	0.078
	Stroke	3.5 ± 1.2	2.7 ± 0.9	0.041
	Acute renal failure	3.9 ± 1.4	3.1 ± 1.1	0.038
Long-term Follow-up	Graft thrombosis	5.2 ± 1.6	4.3 ± 1.2	0.029
	Endoleaks	4.7 ± 1.5	3.9 ± 1.3	0.036
	Recurrence of aneurysms	5.5 ± 1.8	4.8 ± 1.4	0.044

Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR)

## DISCUSSION

Acute kidney injury (AKI) is a significant postoperative complication after abdominal aortic aneurysm (AAA) surgery, resulting in heightened morbidity and mortality [13]. Identifying risk variables associated with postoperative AKI is crucial for improving early detection, prevention, and therapy strategies [14]. Nevertheless, previous studies have shown conflicting outcomes owing to variations in observed demographics, definitions of AKI, and perioperative methodologies [15]. Standardized classification methods, such as the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria and the Acute Kidney Injury Network (AKIN) criteria, provide a framework for defining acute kidney injury (AKI); however, discrepancies in reported incidence and outcomes persist [16]. This retrospective study intends to evaluate the prevalence, risk factors, and clinical implications of AKI in AAA patients, therefore facilitating more effectively perioperative management and patient outcomes.

The research indicates a male majority (85%), a considerable incidence of overweight and obesity, and notable smoking prevalence (current: 29%, former: 38%). The majority of individuals (65%) are between the ages of 60 and 79, consistent with AAA's correlation with ageing. Comorbidities include hypertension (69%), coronary artery disease (28%), and diabetes (16%), exacerbate AAA development and surgical results. However, Hohneck et al., (2019) indicated that the prevalence of AAA escalates with age, especially in persons over 60, aligning with the demographic patterns that were observed in the present research [17]. Similarly, Chen et al. (2016) identified a significant link between increasing age and aneurysm development, underscoring the susceptibility of older persons to vascular degenerative alterations [18].

The current study analyzed aneurysm size distribution between the OSR and EVAR groups using mean values and statistical significance. The findings indicate a significant difference in patient selection between the two procedures. Open surgical repair (OSR) was primarily performed on patients with larger aneurysms, with a mean size of 6.8 cm, whereas endovascular aneurysm repair (EVAR) was preferred for smaller aneurysms, with a mean size of 5.7 cm. This difference was statistically significant ( $p < 0.001$ ), suggesting a clear distinction in the selection criteria for each intervention. This corresponds with other research, which includes that of Patel et al., (2023), which indicated that open surgical repair (OSR) is often advised for aneurysms larger than 5.5 cm, in particular in more youthful sufferers with few comorbidities [19]. Similarly, Bulder et al., (2019) evaluated that EVAR effects decrease perioperative mortality than OSR, even though famous accelerated lengthy period reintervention prices [20].

The considerably lower in ICU and health facility live lengths after the operation ( $p < 0.001$ ) corroborates the growing records advocating for minimally invasive surgical strategies. Similarly, Salata et al., (2019) discovered that EVAR substantially decreases health center length of stay in evaluation to OSR, a declaration supported with the aid of the present-day research [21]. In contrast, Karthikesalingam et al., (2016) located a discounted ICU duration for EVAR patients, correlating with decreased healthcare prices and stronger affected person recovery [22]. The hemodynamic control implications highlight the complexity of fluid resuscitation in abdominal aortic aneurysm repair. The expedited administration of crystalloids ( $p = 0.032$ ) and substantial use of dopamine ( $p = 0.003$ ) highlight the need for rigorous amount and inotropic regulation. Sultan et al., (2024) additionally observed increased fluid adjustments in OSR due to extended surgical exposure and elevated blood loss [23]. However, the lack of a significant difference in RBC transfusion ( $p > 0.05$ ) contradicts the findings of Choi et al., (2018), who reported heightened transfusion requirements in OSR patients [24]. This discrepancy should reflect variations in surgical techniques and transfusion protocols across institutions.

The assessment of postoperative complications between the OSR and EVAR corporations substantiates the modern literature about the benefits as well as disadvantages of every method. OSR correlated with expanded occurrences of wound infections, bleeding, stroke, and acute renal failure. Similarly, Aytekin et al., (2024) discovered that long-term troubles, together with graft thrombosis and endoleaks, had been appreciably improved in OSR patients ( $p < 0.05$ ) [25].

Moreover, the findings of the current study are consistent with previous studies, underscoring the significance of demographic risk stratification, selection of surgical technique, and postoperative management in patients with AAA. While EVAR reduces hospital stay and perioperative risks, OSR is crucial for managing big and more complex burst aneurysms. Future observations must focus on enhancing patient selection criteria and improving long-term results for both procedures. Retrospective design inherently restricts the ability to control confounding variables and introduces the possibility of information and selection bias. The sample size ( $n = 104$ ) is modest and derived from a single tertiary care center, which may limit the external validity and generalizability of the findings. Additionally, certain perioperative variables such as exact medication dosages, intraoperative hemodynamic parameters, and the timing or modality of postoperative imaging were not consistently documented across all records, potentially influencing the completeness and accuracy of the dataset. Long-term follow-up relied primarily on hospital-based records, which may not have captured complications or reinterventions managed at outside institutions, possibly leading to an underestimation of late adverse events. Future research should incorporate larger, multicenter prospective cohorts with standardized data-collection methodologies to validate these findings and minimize inherent retrospective biases.

## CONCLUSION

In conclusion, this retrospective analysis highlights the prevalent postoperative complications and related risk factors in abdominal aortic aneurysm surgery, underscoring the urgent need for enhanced perioperative care protocols. The data indicates that advanced age, prior comorbidities such as cardiovascular disorders and diabetes, and prolonged running duration substantially impact adverse postoperative outcomes. This study provides valuable insights; however, its limitations include a retrospective design, possible selection bias, and dependence on scientific data, which could potentially lead to data bias. Future research should emphasize prospective, multicenter studies with substantial sample sizes to validate these findings and examine the impact of innovative perioperative strategies, including enhanced healing protocols and precision treatment approaches, on reducing postoperative risks and enhancing patient outcomes.

## Author Contributions

Dr. Kanchan Goyal conceptualized and designed the study, supervised the research work, and contributed to data interpretation and critical revision of the manuscript.

Dr. Rewant Pal Singh was responsible for data collection, statistical analysis, and interpretation of results, and contributed to drafting the manuscript.

Dr. Anjali assisted in data collection, literature review, and manuscript preparation, and contributed to editing and final approval of the manuscript.

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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### Conflict of interest

The authors declare no conflict of interest.

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