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ORIGINAL CONTRIBUTIONS

Impact of Bariatric Surgery on Outcomes of Patients with Sickle Cell Disease: a Nationwide Inpatient Sample Analysis, 2004–2014

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Abstract

Background With advances in disease-specific treatments and improved overall survival, obesity rates are rising among patients with sickle cell disease (SCD). The primary aim of this study was to evaluate the role of bariatric surgery on clinical outcomes among hospitalized obese patients with SCD.

Methods The United States Nationwide Inpatient Sample database was queried between 2004 and 2014 for discharges with co-diagnoses of morbid obesity and SCD. The primary outcome was in-hospital mortality. Secondary outcomes included vaso-occlusive crisis, acute chest syndrome, biliary-pancreatic complications, renal failure, urinary tract infection, malnutrition, sepsis, pneumonia, respiratory failure, thromboembolic events, strictures, wound infection, length of stay, and hospitalization costs. Using Poisson regression, adjusted incidence risk ratios (IRR) were derived for clinical outcomes in patients with prior-bariatric surgery compared to those without bariatric surgery.

Results Among 2549 patients with a discharge diagnosis of SCD and morbid obesity, only 42 patients (1.7%) had bariatric surgery. On multivariable analysis, bariatric surgery did not influence mortality ($P = 0.98$). Bariatric surgery was not associated with increased risk for acute chest syndrome, sepsis, multi-organ failure, biliary-pancreatic, or surgery-related complications (all $P > 0.05$). Interestingly, bariatric surgery decreased risk of vaso-occlusive crises (IRR 0.21; 95% CI, 0.07–0.69; $P = 0.01$) in these patients and was associated with a shorter length of stay ($P < 0.001$) but higher hospitalization costs ($P < 0.001$).

Conclusions Bariatric surgery may lower rates of vaso-occlusive crises in morbidly obese sickle cell patients without significantly affecting mortality and other adverse outcomes. In spite of this, these weight loss surgeries are underutilized in this select population.

Keywords Sickle cell disease (SCD) · Obesity · Bariatric surgery · Weight loss · Weight gain · Vaso-occlusive crisis

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Introduction

Sickle cell disease (SCD) is a group of genetic or inherited multi-system disorders that primarily affects individuals of sub-Saharan African, Hispanic, Mediterranean, or Asian Indian descent, characterized by a mutation in hemoglobin molecule leading to formation of hemoglobin S (HbS). The most common variant of SCD is an autosomal recessive form, HbSS or homozygous HbS disease. Other variants include sickle cell beta^0 thalassemia, HbSC, and sickle beta$^+$ thalassemia. HbSS and sickle cell beta^0 thalassemia have been associated with the most severe presentation among the SCD variants. Sickle cell trait is a heterozygous variant and is usually a benign carrier state [1–3]. A national population-based study in 2010 estimated approximately 100,000 patients with SCD in the United States [4]. Since its first description by Herrick in 1910, SCD has been associated with significant morbidity and

mortality, both globally and in the United States [5–7]. Underlying cardinal pathophysiology involves intracellular gelation and polymerization of hemoglobin molecule leading to shorter RBC life span, vaso-occlusion, and RBC destruction by hemolysis [8]. SCD usually presents in early childhood with variable presentation primarily comprising of vaso-occlusive crises (e.g., stroke, acute chest syndrome, priapism, venous thromboembolism, and bone infarction), hemolytic anemia, infections, and other chronic medical conditions. These episodes of crises are often triggered by dehydration, infection, hypoxia, and cold weather [9].

For many years, SCD was stereotypically represented by an undernourished child with delayed growth and poor immunologic function [10–12]. This slowing of growth and maturity has been explained by various possible mechanisms which include hyper-metabolism of protein from hemolysis and rapid red cell turnover, increased myocardial energy demand, increased resting energy expenditure, and decreased oral intake from IL-6 related appetite suppression [13–16]. However, there has been a significant improvement in the management of SCD patients over the past few decades. Early diagnosis coupled with introduction of disease-modifying therapy has significantly improved life expectancy of SCD patients [14]. A significant decrease in mortality rate for African-American children younger than 4 years of age noted after 1999 to 2002 coincided with the introduction of seven-valent pneumococcal conjugate vaccine [17]. Life expectancy of these patients has increased over the past four decades with current SCD childhood mortality similar to that of the general population [18, 19]. Median survival for SCD patients is currently estimated at 60 years [20]. Newborn screening, better medical care, parent education, and immunization have all contributed to improved outcomes [17, 21]. With increased longevity, SCD patients are susceptible to developing chronic medical problems such as obesity [22–25]. However, data is limited on prevalence of obesity in this population and recommended weight reduction strategies. Information regarding the role of bariatric surgery in obesity management in SCD patients is not currently available in any resources.

Given this, the aim of this study was to examine the impact of bariatric surgery on clinical outcomes in morbidly obese hospitalized patients with SCD. We hypothesized that bariatric surgery would be associated with better outcomes for this unique population of patients.

Methods

Data Source and Study Population

The study sample originated from the Nationwide Inpatient Sample database, which includes hospitalized patients in the United States during the 2004 to 2014 period. This registry is part of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality [26]. The Nationwide Inpatient Sample is a database of hospital inpatient stays derived from billing data submitted by hospitals to statewide data organizations across the United States. Inpatient data includes clinical and resource use information typically available from discharge abstracts. Each discharge is coded with a principal diagnosis for that specific hospitalization in addition to the potential for 14 secondary diagnoses and 15 associated procedures. The Nationwide Inpatient Sample is the largest United States inpatient care database, encompassing hospitals from a total of 46 states, which serve 97% of the United States population.

Inclusion and Exclusion Criteria

Patients were included if they had a primary or secondary diagnosis of SCD and morbid obesity. These conditions were identified using the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes. SCD was defined based upon ICD-9-CM codes 282.6, 282.60, 282.61, 282.62, 282.63, 282.64, 282.65, 282.66, 282.67, 282.68, 282.69, 282.41, and 282.42 based upon previously validated literature [27]. Morbid obesity was defined by ICD-9-CM codes 278.01, V85.35, V85.36, V85.37, V85.37, V85.38, V85.39, V85.40, V85.41, V85.42, V85.43, V85.44, and V85.45 [28, 29].

Assessment of Bariatric Surgery

Among the included patients with morbid obesity and SCD, hospitalizations with a history of prior-bariatric surgery were identified using the following ICD-9-CM code: V45.86 (bariatric surgery status); laparoscopic or open Roux-en-Y gastric bypass (ICD-9-CM 44.31, 44.38, and 43.39), laparoscopic adjustable band (ICD-9-CM 44.95), and laparoscopic sleeve gastrectomy (ICD-9-CM 43.82) [28, 29].

Covariates

We compared demographic and clinical characteristics between SCD patients with and without a history of bariatric surgery. The covariates included demographic data (age, gender, and race/ethnicity), as well as characteristics related to metabolic syndrome and SCD-related outcomes. These outcomes were classified as: overall complications, biliary-pancreatic complications, surgical-related complications, and nutritional-associated complications. Hospitalization data such as day of admission

(weekday or weekend), route of admission, mean length of hospital stay, hospitalization cost, and primary payer source was also included.

Statistical Analysis

Categorical variables were presented as counts and proportions, and differences tested using Pearson's chi-square test. Continuous variables were presented as mean (standard deviation), and differences between groups were tested using the *t* test. The age-adjusted mortality rate was calculated for each year of study by summing the product of age-specific mortality rates by the age-specific weights. For population trends, the total number of cases were standardized per 100,000 based upon total population derived from the United States census data for specific year (2004 to 2014) [30]. The weights used in the age adjustment of the data were the proportion of the year 2000 standard United States population within each age group [31].

Secular trends in mortality rates were assessed using linear Poisson regression models. The models were used to investigate the effect of the period of diagnosis (independent variable) on the in-hospital mortality rate (dependent variable), while controlling for other variables (i.e., adjusting for age, sex, race, income, insurance status, type of admission, and modified Elixhauser comorbidity index including diabetes, hypertension, hyperlipidemia, coronary artery disease, and polycystic ovarian syndrome). Risk estimates and 95% confidence intervals (CIs) were calculated for all independent variables in the final model. The Poisson regression with robust (Huber–White) standard errors was also used to determine incident risk ratios (IRR) for predictors of in-hospital mortality. Prior to our analysis, we tested the Poisson models for over-dispersion using a Pearson goodness-of-fit test. Models were not over dispersed; thus, the Poisson regression was then used to determine incident risk ratios (IRR) for clinical outcomes in patients with prior-bariatric surgery compared to those without bariatric surgery.

All the analyses accounted for clustering and sampling weights. The Healthcare Cost and Utilization Project Nationwide Inpatient Sample has a two-stage cluster design incorporating clustering at the hospital level and discharge level. The weighting of discharges is based on the hospital type and volume of discharges relative to the sampling region. Analyses were performed using Stata version 13.0 (Stata Corp LP, College Station, TX). All *P* values were based on two-sided tests and were considered statistically significant at *P* value < 0.05. According to the data user agreement, any individual table cell counts of 10 or fewer cannot be presented to preserve patient confidentiality. In such instances, data are suppressed and labeled as IS, information suppressed.

Results

Demographic and Patients Characteristics

A total of 2549 patients with discharge diagnoses of morbid obesity and SCD were included in our study, of which 42 (1.7%) had prior bariatric surgery. The baseline demographic and hospitalization characteristics of patients by bariatric surgery status are presented in Table 1. The mean age of patients who underwent bariatric surgery was 37.4 ± 9.6 years. There was a significantly higher proportion of women in the bariatric surgery group compared to the non-surgical group (95.2% versus 76.5%, $P = 0.004$). Patients with obesity and SCD with or without a history of bariatric surgery were not significantly different in terms of their baseline comorbidities including hypertension ($P = 0.08$), coronary artery disease ($P = 0.53$), hyperlipidemia ($P = 0.08$), polycystic ovarian syndrome ($P = 0.42$), and stroke ($P = 0.71$).

Trends in Obesity and Bariatric Surgery Use

Trends of bariatric surgery rates among SCD patients as adjusted for the proportion of discharges demonstrated an annual percent change of + 0.1% from 2004 to 2014 ($P_{trend} < 0.05$; Fig. 1). Annual trends in bariatric surgery among patients with morbid obesity and sickle cell disease are highlighted in Supplemental Table 1.

Clinical Outcomes

On multivariate analysis, patients without history of a surgical weight loss procedure were found to have no significant in-hospital mortality difference when compared to those that underwent a bariatric procedure ($P = 0.98$). Prior bariatric surgery did not significantly affect rates of a majority of the complications—Table 2. A history of weight loss procedure was however associated with significantly lower rates of vaso-occlusive crisis (IRR 0.21; 95% CI, 0.07–0.69; $P = 0.01$). In comparison to patients without weight loss surgery, obese patients with SCD and prior bariatric surgery had higher hospitalization costs ($60,207 ± 65,762 versus $36,446 ± 45,570; $P < 0.001$), but shorter length of hospital stay (3.1 ± 3.5 versus 6.4 ± 6.6 days; $P < 0.001$)—Table 2.

Discussion

There is paucity of literature evaluating trends of bariatric surgery in weight loss in morbidly obese patients with SCD. The rising trends in obesity in SCD patients and overall low rates of bariatric surgery are concerning. However, the finding of steadily increasing trends of bariatric surgery over the past decade is encouraging. Moreover, patients with SCD in this

Table 1 Characteristics of hospitalized patients with morbid obesity and sickle cell disease

Variable	Bariatric surgery ($N = 42$; 1.7%)	No. of bariatric surgery ($N = 2507$; 98.3%)	*P* value
Demographic characteristics			
Age (years)[a]	37.4 (9.6)	37.0 (13.0)	0.02
Gender			0.004
Male gender	4.8	23.5	
Female gender	95.2	76.5	
Race/ethnicity			0.74
White	2.4	3.5	
Black	87.8	91.1	
Hispanic	7.3	3.2	
Other	2.5	2.2	
Hypertension	47.6	34.8	0.08
Coronary artery disease	IS	0.92	0.53
Hyperlipidemia	14.3	7.2	0.08
PCOS	IS	0.6	0.42
CVA	IS	0.3	0.71
Hospital-related characteristics			
Elective admission	87.8	10.3	< 0.001
Weekend admission	IS	23.5	< 0.001
Primary payer source			< 0.001
Private insurance	21.4	38.5	
Medicaid	21.4	34.8	
Medicare	57.2	17.9	
Other payment source	IS	6.3	
Self-pay	IS	0.3	
No charge	IS	2.2	

Data are counts (percentage), [a] mean (SD); *PCOS*, polycystic ovarian syndrome; *CVA*, cerebrovascular accident; *IS*, information suppressed. According to the data user agreement, any individual table cell counts of 10 or fewer cannot be presented to preserve patient confidentiality. In such instances, data are suppressed

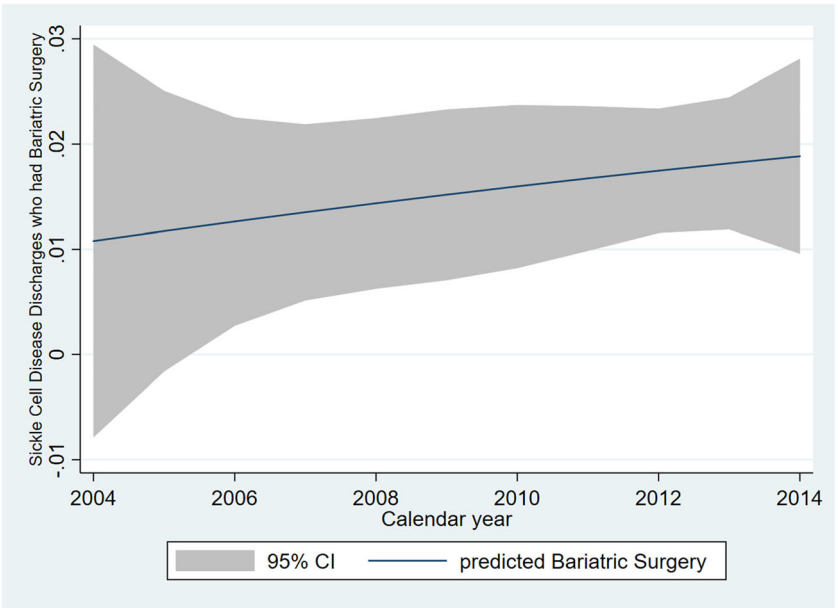

Fig. 1 Proportion of discharges in patients with sickle cell disease and bariatric surgery, 2004–2014

Table 2 Multivariable regression analysis for outcomes with prior bariatric surgery versus no bariatric surgery in patients with morbid obesity and sickle cell disease

Outcome	Bariatric surgery (%)	No bariatric surgery (%)	*P* value	IRR[a] (95% CI)	*P* value
Overall					
VOC	7.1	65.5	< 0.001	0.21 (0.07–0.69)	0.01
Acute chest syndrome	IS	4.0	0.20	–	–
Priapism	IS	0.4	0.70	–	–
Renal failure	2.4	6.6	0.27	–	–
Malnutrition	IS	0.8	0.56	–	–
Thromboembolism	IS	0.32	0.72	–	–
Pneumonia	2.4	7.8	0.19	–	–
Sepsis	2.4	5.0	0.44	–	–
Respiratory failure	IS	3.6	0.21	–	–
UTI	IS	8.7	0.04	–	–
Biliary-pancreatic complications					
Choledocholithiasis	IS	0.04	0.89	–	–
Jaundice	IS	0.92	0.53	–	–
Pancreatitis	IS	0.5	0.64	–	–
Surgical					
Wound infection	IS	0.96	0.52	–	–
Hemorrhage	2.4	0.36	0.04	5.3 (0.4–72.6)	0.21
Strictures	7.1	0.14	< 0.001	3.5 (0.8–15.1)	0.09
Repeat surgery	2.4	IS	< 0.001	#	0.99
Nutritional				–	–
Anemia	IS	4.5	0.16	–	–
Thiamine deficiency	4.8	0.3	< 0.001	625.7 (0.96–408,106)	0.051
Zinc deficiency	IS	0.5	0.64	–	–
Vitamin D deficiency	IS	2.1	0.35	–	–
LOS, costs, mortality					
LOS	3.1 (3.5)	6.4 (6.6)	< 0.001	0.50 (0.42–0.60)	< 0.001
Total costs	60,207 (65762)	36,446 (45570)	< 0.001	1.55 (1.54–1.55)	< 0.001
Mortality	IS	0.84	0.55	#	0.98

CI, confidence interval; *VOC*, vaso-occlusive crisis; *PEP*, post-ERCP pancreatitis; *UTI*, urinary tract infection; *LOS*, length of stay; *IS*, information suppressed. [a] *IRR*, incident risk ratios adjusted for age, sex, race, income, insurance status, type of admission, modified Elixhauser comorbidity index including diabetes, hypertension, hyperlipidemia, coronary artery disease, and obstructive sleep apnea. According to the data user agreement, any individual table cell counts of 10 or fewer cannot be presented to preserve patient confidentiality. In such instances, #data are suppressed.

sample who underwent bariatric surgery had overall lower rates of vaso-occlusive crises with no difference in mortality suggesting an important role of weight reduction surgery in the management of this specific population.

Changing Pattern of Presentation and Consequences of Obesity

SCD has been classically characterized by undernutrition, lean body mass, and stunted growth [10–12]. However, recent studies and case reports have established a rising trend of obesity among the SCD patients [22–25]. In a study by Pells et al., nearly half of the patients with SCD were overweight, and 20% were obese [32]. In another study, 22.4% of the study sample was overweight or obese, whereas only 6.7% was underweight. It was also suggested that for each 1-g/dL increase in baseline Hb levels, there were 36% increased odds of overweight and obesity [24]. Higher BMI and obesity have usually been associated with HbSC variant compared to the HbS disease and have attributed to lower basal metabolic rate and normal energy utilization in this particular variant [15, 24]. The rising obesity trend has been explained by the overall improvement in nutritional status in SCD patients as a result of improved dietary options and advancement in SCD therapies such as splenectomy, hydroxyurea, chronic transfusions, and bone marrow transplant [15, 32]. Hydroxyurea in particular has been associated with overall weight gain and improvement in the physical capacity of SCD patients [33].

We noted a similar trend of increasing prevalence of obesity among the SCD patients from 2004 to 2014 in our present study. Obesity and weight gain in this select population may however give rise to a wide range of complications which need to be considered while caring for these patients. Although Pells et al. did not note a statistically significant association between body mass index (BMI) and pain severity, more than 40% of patients in their sample reported that their pain perception was influenced by their weight [32]. In another study by Santanelli et al., overweight and obese individuals with SCD were reported to have a higher pain burden and higher rates of utilization of medical care [34]. With a surge in obesity, there has been a simultaneous rise in obesity-related comorbidities such as obesity hypoventilation syndrome and obstructive sleep apnea [35]. Sleep apnea is usually associated with nocturnal oxyhemoglobin desaturations, and this intermittent nocturnal hypoxia is further associated with metabolic risk in the obese population [36]. Similarly, hypoxia and particularly low nocturnal oxygen saturation have been associated with a significantly higher rate of painful crisis in SCD patients [8]. With rising obesity rates among SCD patients, it is plausible that they may have higher rates of obstructive sleep apnea and higher nocturnal desaturation leading to increased rates of vaso-occlusive crises.

Trends and Safety of Bariatric Surgery

As data on safety and efficacy of bariatric procedures have become more accessible, the total number of bariatric procedures have increased in the United States and abroad in the past 10 years [37, 38]. These weight loss surgeries have also shown a significant improvement in outcomes for several other inflammatory and autoimmune conditions (e.g., inflammatory bowel disease and non-alcoholic fatty liver disease) [28, 29]. Surgical procedures, however, expose SCD patients to the usual triggers for sickle cell crises, and 25–30% of them develop a post-operative complication [39]. Thus, surgical approach in patients with SCD requires a different and diligent clinical approach than general population. In SCD patients undergoing abdominal surgery, transfusion prior to surgery has been associated with lower rates of SCD-related complications [40]. However, there is no prior literature on outcomes of bariatric procedures or guidelines on perioperative management of bariatric procedures in these patients. Though a very small (1.7%) portion of our morbidly obese SCD patient population underwent bariatric surgery, our study demonstrates that the proportion of morbidly obese patients with SCD and bariatric surgery steadily increased from 2004 to 2014. This points towards a rising awareness among morbidly obese SCD patients and their physicians to consider bariatric surgery as the best therapeutic option for their obesity.

The role of bariatric surgery's safety and efficacy in patients with SCD has not yet been clearly defined. An important finding in our current study is the significant role bariatric surgery played in reducing rates of vaso-occlusive crisis. A possible explanation of the lowering of vaso-occlusive events after bariatric surgery is decreased rates of obstructive sleep apnea and hypoxic episodes, which are familiar triggers for these crises. Also, it is encouraging that prior bariatric surgery did not increase rates of usual SCD-related complications such as acute chest syndrome, priapism, jaundice, and biliary stones in our study sample. Similarly, prior bariatric surgery was not associated with other life-threatening complications such as multi-organ failure, sepsis, and post-surgical complications (e.g., strictures, fistula, and wound infection). The exact mechanisms by which bariatric surgeries may have reduced vaso-occlusive crises in our study population require investigation in further studies.

SCD carries a significant healthcare burden. Historically, SCD patients tend to have frequent and prolonged hospitalizations, frequent emergency department visits, early exposure to opioids, psychosocial dysfunctions, and higher healthcare utilization [32]. An average of 75,000 SCD hospitalizations occurred in the United States from 1989 to 1993, resulting in healthcare utilization costs amounting to $475 million [21]. Our data suggests that morbidly obese patients with SCD who had prior bariatric surgery have a shorter hospital stay but higher costs of hospitalizations. However, previous studies have shown that bariatric procedures incur significant initial cost and morbidity but tend to be cost-effective when assessed over a post-operative period of 5 years [41, 42]. This affirms the need for educating physicians and SCD patients about possible benefits of bariatric procedures in order to reduce complications and overall healthcare utilization.

Strengths and Limitations

Our study has limitation characteristic to its retrospective and observational design. Using an inpatient sample database, we are only able to asses in-hospital outcomes but unable to assess long-term outcomes upon discharge. Furthermore, administrative databases such as NIS carry a risk of coding errors. Additionally, the NIS database does not provide SCD treatments, immunization, and laboratory (hemoglobin electrophoresis and DNA analysis) results. We were also unable to find information on dietary habits and dietary modifications, pharmacological therapy, and other weight loss reduction methods applied by these patients. Additionally, post-bariatric surgery patients with significant weight loss that no longer have morbid obesity are not captured in these cohorts. Given

the low numbers of patients that underwent bariatric surgery, our sample may not be representative of the average sickle cell patient. We cannot truly exclude the possibility of duplicate entries (e.g., multiple admission for the same patient). Due to the small sample size, we are also unable to compare trends and outcomes between malabsorptive and restrictive type of bariatric surgery. There is also a possibility of residual confounding as some important covariates (e.g., percent excess weight loss and BMI) were not available in the database.

Despite the limitations, our study has several strengths. To the best of our knowledge, this is the first ever study to be published on this topic. It includes the largest number of patients from a nationwide sample evaluating trends and outcomes over a period of 10 years among morbidly obese patients with SCD and includes several racial/ethnic groups. This minimizes the possible biases that may be seen in single-center studies and also provides data to generalize our observations to clinical practice in the United States. Furthermore, we have included a vast array of relevant outcomes (i.e., vaso-occlusive crises, acute chest syndrome, renal failure, pneumonia, sepsis, biliary-pancreatic disorders, strictures, fistula, thromboembolic events, malnutrition, and micronutrient deficiency), which would reliably indicate a response to bariatric surgery above and beyond percent weight loss and change in BMI.

Conclusion

Our study suggests that bariatric surgery may reduce the rates of vaso-occlusive crises in obese patients with SCD. In addition, there was no significant difference in in-hospital mortality or other major complications between SCD patients who underwent bariatric surgery and those who did not. We are hopeful that our results will motivate physicians to consider bariatric surgery as a safe and effective treatment option for SCD patients with morbid obesity. Although the results of this study are narrowed based upon database and study design limitations, we hope our study encourages future exploration on the subject of sickle cell disease and bariatric surgery. Prospective studies, although difficult to design given the incidence of bariatric surgery and sickle cell disease, are needed to validate our findings.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval Statement For this type of study, formal consent is not required.

Informed Consent Statement Informed consent statement does not apply.

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