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Cortisol secretion autonomy associated with weight loss outcome after laparoscopic sleeve gastrectomy: a prospective cohort study in Asian patients

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Abstract. – OBJECTIVE: Laparoscopic sleeve gastrectomy (LSG) is a widely recognized effective bariatric surgery. However, variable weight loss outcomes post-surgery remained a clinical challenge. Currently, there is no established consensus on the factors influencing weight loss failure following LSG. This study aimed to explore the association between preoperative cortisol secretion autonomy and postoperative weight loss in obese patients undergoing LSG.

PATIENTS AND METHODS: A cohort of 181 patients with simple obesity (BMI ≥ 28 kg/m^2) who underwent LSG and were followed up for one year was analyzed. Weight loss was measured by the percentage of excess weight loss (%EWL), and cortisol secretion autonomy was evaluated using a 1-mg dexamethasone suppression test (DST). Regression models were used to analyze the correlation between preoperative 1-mg DST results and %EWL one year after laparoscopic sleeve gastrectomy (LSG).

RESULTS: Cortisol secretion autonomy was significantly lower in the %EWL ≥ 75% group and higher in the %EWL < 75% group, showing a negative correlation with %EWL (R = -0.336, p = 0.001). Logistic regression analysis indicated that high cortisol secretion autonomy was significantly correlated with %EWL < 75% after LSG. The likelihood of %EWL being < 75% was 10.47 times greater in patients with high cortisol secretion autonomy compared to those with low cortisol secretion autonomy (odds ratio 10.472, confidence interval: 1.660-66.048, p = 0.012).

CONCLUSIONS: Cortisol secretion autonomy emerges as an independent predictor of weight loss outcomes in Asian patients undergoing LSG. This finding suggests the potential for cortisol secretion autonomy to inform preoperative assessments and personalized treatment strategies in bariatric surgery.

Key Words:
Obesity, Cortisol secretion autonomy, Laparoscopic sleeve gastrectomy, Weight loss.

Introduction

Obesity has become a global epidemic disease[1], posing a huge threat to human health and social economy[2-4]. Bariatric surgery is the most effective treatment in achieving and maintaining weight change and reducing obesity-related comorbidities, and laparoscopic sleeve gastrectomy (LSG) is one of the most commonly performed procedures worldwide[5,6]; it is both effective and safe[7]. However, there are still underweight loss and weight regain in some patients after LSG[8,9]. To date, there is no consensus on the causes of poor weight loss. Reported factors include psychiatric issues, dietary nonadherence, physical inactivity, race/ethnicity, gender, endocrine and metabolic diseases, and surgical specificity[10]. However, even when these conditions are excluded, poor weight loss persists. So, further investigation of the causes of underweight loss after LSG is warranted.

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Glucocorticoids play a vital role in fat metabolism regulation. As an archetypal glucocorticoid, cortisol has been shown to promote fat accumulation in adipocytes and weight gain in animal models[11,12]. Population-based cohort studies have repeatedly demonstrated a positive correlation between chronically elevated cortisol levels and both obesity and metabolic syndrome[13-18]. The impact of cortisol on weight loss is an ongoing area of interest, with studies such as those by Ruffing et al[19] and Martín-Pérez et al[20] showing negative associations between cortisol levels and weight loss outcomes through diet control. Cortisol secretion autonomy, defined as the adrenals' autonomous secretion of cortisol, has been identified as an independent risk factor for metabolic syndrome and obesity[21-24]. This relationship becomes more pronounced as additional criteria for metabolic syndrome are met[25]. However, the specific impact of cortisol secretion autonomy on weight loss post-LSG remains under-researched.

In response to this gap in knowledge, our study conducted a prospective cohort analysis. We utilized the percentage excess weight loss (%EWL) to evaluate the effectiveness of weight loss 1 year after LSG[26], with the 1-mg dexamethasone suppression test (DST) employed to assess cortisol secretion autonomy[27,28]. The primary objective of our study was to investigate whether preoperative cortisol secretion autonomy correlates with postoperative weight loss at one year following LSG.

Patients and Methods

Study Population

From September 2013 to August 2019, we enrolled 456 patients with obesity between the ages of 16 and 65 years with body mass index (BMI) ≥ 28 kg/m^2. Based on inclusion and exclusion criteria[29], finally, we included 181 patients with obesity who were treated with conventional LSG and followed up with the bariatric patients for 1 year (**Supplementary Figure 1**). The inclusion criteria were as follows: (1) BMI of 37.5 kg/m² or higher; (2) BMI between 32.5 and 37.5 kg/m² with more than 2 components of metabolic syndrome; (3) BMI between 28 and 32.5 kg/m² with type 2 diabetes mellitus (T2DM) or more than 2 components of metabolic syndrome that are not controlled by lifestyle intervention and conservative treatment; and (4) suitability and willingness to undergo LSG surgical treatment. Exclusion criteria were as follows: (1) Cushing's syndrome and 1-mg DST ≥ 138 nmol/L; (2) hypothyroidism and other secondary obesity patients; (3) history of chronic kidney disease, intestinal disease, liver disease, thyrotoxicosis, rheumatism and blood disease; (4) non-obese type 1 diabetes had a definite diagnosis, gestational diabetes and certain specific types of diabetes; (5) use drugs that affect dexamethasone metabolism or drugs that affect cortisol secretion and metabolism; (6) the presence of bilateral adrenal masses; (7) dependence on drugs or alcohol or uncontrolled mental illness; (8) mental retardation or immaturity and uncontrollable behavior; (9) unrealistic expectations about surgery; (10) unwillingness to risk potential complications from surgery; (11) inability to cooperate with postoperative dietary and lifestyle changes, poor compliance; (12) patients with a poor general condition who are unable to tolerate general anesthesia or surgery.

Data Collection and Outcome Assessment

Prior to surgery, a specialist physician interviewed 181 patients about their medical history and medication use. Anthropometric measurements, including height, weight, waist circumference, and blood pressure, were taken. Biochemical markers such as blood glucose, lipids, kidney and liver function were measured. These anthropometric and biochemical indices were followed up 1 year after LSG. Baseline biochemical indicators, including serum cortisol, adrenocorticotrophic hormone (ACTH), and dehydroepiandrosterone (DHEA), were obtained after at least 8 hours fast. The 1-mg DST followed the 2008 Endocrine Society guidelines for diagnosing Cushing's syndrome[30]: 1-mg of dexamethasone was administered between 23:00 and 24:00, followed by serum cortisol measurement at 8 am the next day. A 2 mg low-dose dexamethasone suppression test (LDDST) was performed if the serum cortisol levels were ≥ 50 nmol/L after 1-mg DST. The operations of 2 mg LDDST were as follows: dexamethasone 0.5 mg orally every 6 hours for 2 days was given, and serum cortisol was measured after dosing. Serum lipid concentrations were measured using an automated analyzer (Hitachi Inc., Chiyoda Ward, Tokyo, Japan), and serum cortisol and ACTH levels were quantified *via* an automated chemiluminescence immunoassay (Beckman Coulter Inc., Hormone Analyzer, Brea, CA, USA). DHEA levels were determined by a liquid chromatograph-mass spectrometer

(Thermo Inc., Waltham, MA, USA). Plasma glucose and liver and kidney function indicators were measured using an automated biochemical analyzer (Olympus Inc., Shinjuku, Tokyo, Japan).

The percentage excess weight loss (%EWL) was calculated as [(initial weight - actual weight) / (initial weight - ideal weight)] × 100 to evaluate the effect of weight loss one year after LSG[26]. Cortisol secretion autonomy was assessed as a continuous variable using the 1-mg DST.

Statistical Analysis

In this study, we employed various statistical methods to analyze the collected data. For variables following a normal distribution, we expressed them as mean ± standard deviation. In contrast, non-normally distributed variables were represented by median and interquartile range (IQR). Skewness and kurtosis tests were performed to evaluate the distribution of continuous variables. Log-transformed values were used for the analysis of non-normally distributed variables. Categorical variables were reported as frequencies and proportions and analyzed using Chi-square tests.

Pearson correlation analyses were conducted to explore the relationships among individual variables. The association between %EWL one year after bariatric surgery (dependent variable) and preoperative 1-mg DST (independent variable) was assessed using multiple linear regression analysis. This analysis was incrementally adjusted for confounders, including variables suspected of impacting weight loss but not significantly different between groups and those significantly different among groups.

Additionally, logistic regression analysis was utilized to determine parameters associated with %EWL ≥ 75%. These parameters were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We divided patients into two groups using 1-mg DST = 50 nmol/L as the cut-off point. Similar to the multiple linear regression analysis, multiple models were created to adjust for confounders. The ORs for 1-mg DST were calculated relative to the lower of the two categories. Multivariable logistic regression was performed to quantify the association between 1-mg DST and weight loss outcomes, with the reference outcomes being high %EWL. All statistical analyses were conducted using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA), with a significance level set at $p < 0.05$.

Results

The study's baseline characteristics are summarized in Table I, focusing on a subset of patients with %EWL = 75% as the entry point. In the %EWL < 75% group, BMI, weight, hip circumference (HC), and waist circumference (WC) were significantly higher compared to the %EWL ≥ 75% group. However, there were no significant differences between the two groups in terms of hypersensitive C-reactive protein, serum lipid levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum uric acid, systolic blood pressure (SBP), diastolic blood pressure (DBP), glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), blood urea, and serum creatinine levels. Notably, cortisol secretion autonomy was significantly higher in the %EWL < 75% group compared to the %EWL ≥ 75% group ($p = 0.04$). Additionally, no significant differences were observed in cortisol, ACTH, and DHEA levels between the groups at 8 a.m.

Simple correlation analysis (Figure 1) revealed that baseline cortisol secretion autonomy was significantly and negatively correlated with %EWL one year after LSG (R = -0.336, $p = 0.001$). Multivariate linear regression analysis was conducted in three models: Model 1 (crude), Model 2 (adjusted for sex, age, and BMI), and Model 3 (adjusted for sex, age, BMI, FBG, T2DM, hypertension, and dyslipidemia). In all models, baseline cortisol secretion autonomy showed a significant negative association with %EWL at one year after LSG (β = -0.336, $p = 0.001$ for Model 1; β = -0.234, $p = 0.015$ for Model 2; β = -0.216, $p = 0.029$ for Model 3) as detailed in Table II.

Univariate logistic regression models were used to evaluate the influence on %EWL < 75% post-LSG. The age-and sex-adjusted single-factor logistic regression analysis identified cortisol secretion autonomy and BMI as predictors of %EWL < 75% [odds ratio 1.032 (95% CI 1.007-1.056), $p = 0.010$ for 1-mg DST; odds ratio 1.087 (95% CI 1.021-1.158), $p = 0.009$ for BMI] as shown in Table III. The baseline 1-mg DST was categorized into two components: low (0-49.9 nmol/L) and high (50-138 nmol/L). In multivariate logistic analysis, Model 1 adjusted for sex, age, and BMI, and Model 2 further adjusted for sex, age, BMI, FBG, T2DM, hypertension, and dyslipidemia. The risk of %EWL < 75% compared to low cortisol secretion autonomy increased with higher cortisol secretion autonomy levels [Model 1: OR 7.894 (95% CI 1.777-35.062),

Table I. Differences in characteristics between patients grouped at %EWL = 75% (%EWL < 75%, %EWL ≥ 75%).

Variable	Total	Grouped by %EWL = 75%		p
		%EWL < 75%	%EWL ≥ 75%	
At baseline				
Age (years)	29.8 ± 10.7	29.9 ± 9.1	28.1 ± 10.1	0.344
Males/females	74/107	25/36	37/71	0.243
Weight (kg)	110.2 ± 22.7	119.6 ± 22.5	108.0 ± 20.3	0.004
Height (cm)	166.3 ± 8.6	167.1 ± 8.8	165.8 ± 8.9	0.425
BMI at baseline (kg/m²)	38.8 (35.3, 42.7)	41.2 (38.7, 46.8)	37.5 (35.2, 41.3)	< 0.001
HC (cm)	119.0 (113.0, 127.0)	124.0 (117.4, 134.8)	117.5 (113.0, 125.0)	0.005
WC (cm)	117.5 (110.0, 130.4)	125.5 (117.0, 138.0)	114.0 (106.0, 125.0)	0.001
SBP (mmHg)	132.0 (125.0, 143.8)	135.0 (127.0, 147.5)	131.0 (122.0, 142.8)	0.099
DBP (mmHg)	82.0 (75.0, 90.0)	83.0 (74.5, 88.8)	82.0 (74.3, 91.8)	0.92
HbA1c (%)	6.0 (5.6, 6.8)	6.1 (5.8, 6.5)	6.0 (5.6, 6.9)	0.557
FBG (mmol/L)	5.8 (5.3, 7.0)	5.8 (5.3, 7.0)	5.6 (5.2, 6.9)	0.619
TG (mmol/L)	1.7 (1.2, 2.5)	1.7 (1.2, 2.9)	1.7 (1.2, 2.4)	0.806
TC (mmol/L)	4.8 ± 1.0	4.8 ± 0.8	4.8 ± 1.1	0.921
LDL-c (mmol/L)	3.1 ± 0.9	3.1 ± 0.7	3.1 ± 1.0	0.958
HDL-c (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.895
hs-CRP (mg/L)	4.3 (2.4, 7.2)	5.1 (3.1, 9.3)	3.9 (2.2, 7.2)	0.069
AST (U/L)	28.0 (21.0, 46.0)	28 (20.0, 45.0)	27.0 (21.0, 51)	0.709
ALT (U/L)	46.0 (29.0, 83.0)	44.0 (29.0, 77.5)	46.5 (29.0, 88.5)	0.902
Serum creatinine (μmol/L)	59.0 (52.0, 71.5)	59 (52.0, 75.0)	58.0 (52.0, 68.8)	0.722
Blood urea (mmol/L)	4.5 (3.7, 5.2)	4.55 (4.0, 5.3)	4.55 (3.8, 5.3)	0.443
Uric acid (μmol/L)	433.4 ± 115.2	454.4 ± 110.1	417.6 ± 111.5	0.082
Cortisol (nmol/L)	276.4 (233.0, 373.0)	267.0 (229.5, 344.0)	274.5 (232.1, 372.9)	0.348
ACTH (pg/mL)	33.5 ± 20.7	31.9 ± 18.1	33.7 ± 23.4	0.696
1-mg DST (nmol/L)	23.4 ± 19.2	34.6 ± 30.5	20.9 ± 13.9	0.040
DHEA (ug/dL)	230.1 ± 123.6	202.8 ± 104.6	246.1 ± 133.69	0.094
Hypertension (%)	45.1	44.2	47.7	0.703
Dyslipidemia (%)	72.8	70.7	79.8	0.261
T2D (%)	58.7	50.0	64.7	0.117
Hyperuricemia (%)	58.2	64.3	62.9	0.880
Fatty liver (%)	76.1	88.4	82.9	0.169
At 1 year after LSG				
BMI (kg/m²)	26.6 ± 4.1	31.0 ± 3.0	24.7 ± 2.8	< 0.001
%EWL (%, 1 year)	84.0 (70.0, 103.3)	66.0 (57.3, 69.6)	95.3 (83.9, 110.8)	< 0.001

BMI, body mass index; HC, hip circumference; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; FBG, fast blood glucose; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; hs-CRP, hypersensitive C-reactive protein; T2D, type 2 diabetes; ALT, alanine transaminase; AST, aspartate transaminase; %EWL, percentage of excess weight loss; DST, overnight dexamethasone suppression test; DHEA, dehydroepiandrosterone. Data are mean ± SD, %, or median (intertertile range).

p = 0.007 for high cortisol secretion autonomy; Model 2: OR 10.472 (95% CI 1.660-66.048), p = 0.012 for high cortisol secretion autonomy], as illustrated in Table IV.

Discussion

Patients who lost less weight after LSG surgery exhibited significantly higher cortisol secretion autonomy compared to those who lost more weight. Following LSG, there was a negative association between cortisol secretion autonomy and postoperative weight loss. This association persisted even after adjusting for confounders such as gender, age, BMI, FBG, T2DM, hypertension, and dyslipidemia, indicating that cortisol secretion autonomy could be an independent factor affecting weight loss outcomes after LSG. Multivariable logistic analysis was performed by categorizing patients into low and high cortisol secretion autonomy groups based on their baseline 1-mg DST levels. After accounting for confounding factors, the risk of %EWL < 75% compared to low cortisol secretion autonomy increased with higher cortisol secretion autonomy

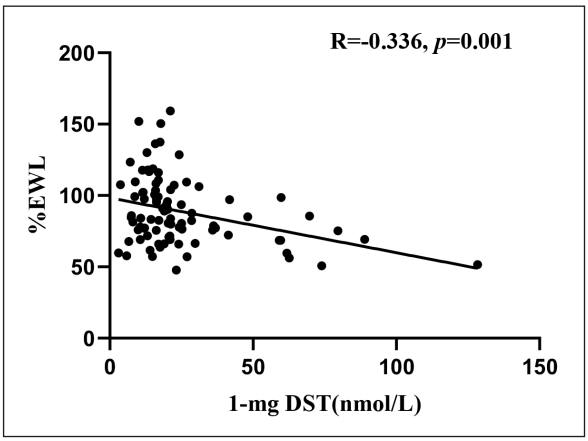

Figure 1. Simple correlation analysis of the %EWL with 1-mg DST. %EWL, percentage of excess weight loss; DST, overnight dexamethasone suppression test.

Table II. The correlation of postoperative %EWL with baseline 1-mg DST was analyzed by multiple regression models.

	%EWL	
Model	**Standard β**	***p***
Model 1	-0.336	0.001
Model 2	-0.234	0.015
Model 3	-0.216	0.029

Model 1: crude; Model 2: adjusted for sex, age, and BMI; Model 3: adjusted for adjusted for sex, age, BMI, FBG, T2D, hypertension, and dyslipidemia. DST, overnight dexamethasone suppression test; %EWL, percentage of excess weight loss; BMI, body mass index; FBG, fasting blood glucose; T2D, type 2 diabetes.

levels. This suggests that preoperative cortisol secretion autonomy may be an independent risk factor associated with weight loss following LSG. Patients with high cortisol secretion autonomy

Table III. Age- and sex-adjusted univariate logistic regression analysis for %EWL < 75% at 12 months postoperatively.

	Grouped by %EWL	
Variable	**OR (95% CI)**	***p***
1-mg-DST (nmol/L)	1.032 (1.007, 1.056)	0.010
BMI (kg/m²)	1.087 (1.021, 1.158)	0.009
SBP (mmHg)	1.002 (0.981, 1.024)	0.847
DBP (mmHg)	0.994 (0.996, 1.022)	0.659
FBG (mmol/L)	0.914 (0.764, 1.094)	0.328
T2D (%)	0.449 (0.200, 1.005)	0.051
Dyslipidemia (%)	0.609 (0.256, 1.444)	0.260

%EWL, percentage of excess weight loss; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fast blood glucose; T2D, type 2 diabetes.

are at an increased risk for poor weight loss outcomes compared to those with low cortisol secretion autonomy.

In our study, cortisol secretion autonomy differed between groups when using %EWL = 75% as a threshold and was found to be negatively correlated with weight loss at 1 year after LSG. Even when adjusting for BMI, higher cortisol secretion autonomy was still associated with lower %EWL, implying a potential negative correlation between cortisol secretion autonomy and weight loss. Previous studies, such as those by Still et al[31] and Coupaye et al[32] have indicated that conditions like T2D, dyslipidemia, and hypertension may influence weight loss outcomes and could potentially affect cortisol secretion autonomy. Our findings also reveal that even after controlling for these conditions, cortisol secretion autonomy remained an independent factor associated with %EWL. For instance, a study in Japan[33] found cortisol levels at 8 am negatively correlated with weight loss

Table IV. Multivariate analysis of logistic regression of patients with %EWL < 75% at 12-month follow-up after LSG according to baseline serum cortisol concentration after DST.

	%EWL < 75%		
	1-mg DST < 50 nmol/L	**50 nmol/L ≤ 1-mg DST < 138 nmol/L**	
Model	**OR (95% CI)**	**OR (95% CI)**	***p***
Model 1	Reference	7.894 (1.777, 35.062)	0.007
Model 2	Reference	10.472 (1.660, 66.048)	0.012

The baseline serum cortisol concentration after DST Two groups: the range of low, high cortisol autonomy of serum cortisol concentration after 1-mg DST was 0-49.9 and 50.0-138.0 nmol/L. Model 1: adjusted for sex, age, BMI; Model 2: adjusted for sex, age, BMI, FBG, T2D, hypertension, dyslipidemia. %EWL, percentage of excess weight loss; DST, overnight dexamethasone suppression test.

after LSG, although our study did not find a similar correlation. This discrepancy could be due to the variability and potential inaccuracy of a single cortisol measurement. In contrast, 1-mg DST proved to be a more reliable method for assessing cortisol secretion, and cortisol concentrations after 1-mg DST could be a valuable indicator for assessing glucocorticoid autonomy[27,28]. Consistent with this, Öztürk et al[34] reported cortisol concentration after 1-mg DST was higher in the group with poor weight loss than in the group with good weight loss 6 months after LSG, which was consistent with our study's conclusion. However, their follow-up period was only 6 months, which was insufficient, and weight loss results for LSG appeared to plateau after the 1-year mark. Meanwhile, we further demonstrated the correlation between preoperative 1-mg DST and weight loss effect by using linear regression and logistic regression statistical methods and also excluded the influence of some confounding factors, making the conclusion more reliable. Our results indicate that cortisol secretion autonomy is an independent predictor of weight loss outcomes one year after LSG surgery, with higher cortisol secretion autonomy leading to poorer weight loss effects. Patients with high cortisol secretion autonomy showed worse weight loss outcomes compared to those with low cortisol secretion autonomy.

In this study, we propose several potential mechanisms for the association between cortisol secretion autonomy and postoperative weight loss following LSG. First, long-term chronic increases in cortisol may induce fat production, lead to ectopic fat deposition, and promote inflammation of visceral adipose tissue and insulin resistance. By comparing chronic glucocorticoid overdose with diet-induced obesity in a murine model, García-Eguren et al[35] found that in comparison to HFD-induced obesity, long-term hypercortisolemia can induce adipogenesis, promote the accumulation of palmitic acid, and promote the inflammatory response in visceral adipose tissue, leading to elevated systemic unesterified fatty acids (NEFA), hyperinsulinemia and insulin resistance. Chimin et al[36] have also found that chronic glucocorticoid treatment can lead to obesity, particularly the generation of visceral adipose tissue. Secondly, compared to high-fat diet-induced obesity, chronic increases in cortisol lead to more persistent and potentially permanent enlargement of visceral fat, and the mechanism for this is thought to be linked to increased macrophage infiltration[37]. Lastly, cortisol may directly or indirectly affect the appetite regulation center, inducing obesity by increasing energy intake.

Our study has some strengths; we used 1-mg DST as a continuous variable and a useful index for a more accurate assessment of glucocorticoid levels, thereby providing an evaluation of cortisol secretion autonomy. However, there are limitations to consider. The study was conducted at a single center, and its findings predominantly pertain to the Asian population, potentially limiting the generalizability of the results to other ethnic groups. Furthermore, the relatively small and predominantly young sample size may introduce bias. Consequently, further validation with a larger and more diverse sample is necessary to confirm our findings and ensure their applicability to a broader population.

Conclusions

Our study indicates that cortisol secretion autonomy is significantly and negatively associated with weight loss outcomes in the postoperative period of LSG in Asian patients with BMI ≥28 kg/m^2. This study establishes cortisol secretion autonomy as an independent factor influencing weight loss after LSG over one year. Patients exhibiting high cortisol secretion autonomy are at a substantially increased risk of poor weight loss compared to those with low cortisol secretion autonomy following LSG. These findings underscore the importance of considering cortisol secretion autonomy in predicting weight loss outcomes after LSG and suggest potential avenues for personalized treatment approaches in bariatric surgery.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval

This study received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Ethics Committee Approval No.: 2013-37, Approval Date: Sep 23, 2013), and was conducted in accordance with the Helsinki guidelines.

Informed Consent

Informed consent was signed by patients included in the study.

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Authors' Contributions
Conception and design: G.L., Z.L.; acquisition of data: G.F., L.X., C.X., L.F., G.L., T.T., Z.Y.; analysis and interpretation of data: Z.L., C.X., H.J.; drafting the article: Z.L., Z.M.; validation and final approval: all authors.

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Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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