

Effect of weight loss on the estimated glomerular filtration rates of obese patients at risk of chronic kidney disease: the RIGOR-TMU study

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Abstract

Background Weight-reduction therapies, including bariatric surgery (BS), are standard treatments for severely obese patients with type 2 diabetes; however, the outcomes of these therapies are inconclusive for obese patients with chronic kidney disease (CKD). This study aimed to investigate the effects of BS or non-surgical interventions on the estimated glomerular filtration rate (eGFR) and to determine whether BS can be recommended for renal function preservation based on body mass index (BMI) and eGFR changes in obese patients with CKD.

Methods This study used data from the weight Reduction Intervention on GFR in Obese Patients with Renal Impairment-Taipei Medical University (TMU) study, which was a large, long-term, propensity score-matched cohort study based on clinical data from patients who registered at weight-reduction centres at TMU and its affiliated hospitals from 2008 to 2016. The patients were stratified according to whether they had undergone BS and into the mild, moderate, and high CKD risk groups using the Kidney Disease: Improving Global Outcomes guidelines. The primary outcome was the eGFR calculated using the Taiwan Chronic Kidney Disease-Epidemiology Collaboration equation. Cox regression models were used to determine hazard ratios (HRs) for eGFR decreases $\geq 25\%$.

Results A total of 4332 obese patients were enrolled in this study. After propensity score matching, 1620 patients, including 60.2% women, with a mean age of 36.5 (9.9) years were divided into BS or non-surgery groups ($n = 810$ per group). The overall mean eGFRs increased by 4.4 (14) mL/min \cdot 1.73 m² and decreased by 6.4 (16.0) mL/min \cdot 1.73 m² in the BS and non-surgery groups, respectively. The decrease in BMI in the BS and non-surgery groups were 2.5 and 1.3 kg/m², respectively. In the moderate/high CKD risk BS group, a significant correlation was evident between an increased eGFR and a reduced BMI (Spearman's correlation -0.229 , $P < 0.001$). The Cox regression analysis showed that the BS group had a significantly lower risk of an eGFR decline $\geq 25\%$ at 12 months [adjusted HR (aHR) 0.47, $P = 0.03$]. After BS, obese patients with hypertension or albuminuria had significantly lower risks of eGFR declines $\geq 25\%$ (aHR 0.37, $P = 0.02$ and aHR 0.13, $P = 0.0018$, respectively).

Conclusions Bariatric surgery was associated with eGFR preservation in all obese patients and, particularly, in those with moderate-to-high CKD risks. A longer term outcome study is warranted to determine the benefits of BS for CKD patients.

Keywords Albuminuria; Bariatric surgery; Chronic kidney disease; Estimated glomerular filtration rate; Obesity

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Introduction

The worldwide prevalence of obesity has more than doubled since 1980, and approximately 1.9 billion people were obese in 2006.¹ The obesity prevalence rates were 11.8%, 17.9%, and 22.1% in 1993–96, 2005–08, and 2013–14, respectively, according to the Nutrition and Health Survey in Taiwan.² Obesity is associated with comorbidities, including hypertension, diabetes, cardiovascular disease, cancer, and chronic kidney disease (CKD).³ Compared with patients with body mass indexes (BMIs) <25 kg/m², patients with severe obesity, that is, a BMI >35 kg/m², have a 341% increased risk of developing end stage renal disease (ESRD).⁴ Potential factors underlying the increased risks for CKD and ESRD include obesity-mediated hypertension, insulin resistance, obesity-related glomerulonephropathy, renin–angiotensin–aldosterone system activation, inflammation, and dysregulated adipocytokine production.^{5,6}

Weight-reduction therapy improves blood pressure,⁷ insulin resistance, dyslipidaemia, and obstructive sleep apnoea.⁸ A previous study's findings showed that compared with usual care, obese patients with type 2 diabetes benefitted more from bariatric surgery (BS), which included a lower incidence of nephropathy⁹; however, the study was limited to patients with type 2 diabetes. Regarding CKD, a recent, large, long-term cohort study's findings showed that the CKD risk categories improved in patients who underwent BS, but this study was limited by the absence of a control group.¹⁰ In addition, the obesity paradox suggests that obesity-associated advantages in CKD patients could prevent inflammation and atherosclerosis.¹¹ BS may induce kidney oxalate nephropathy and acute kidney injury.¹² Furthermore, there are no guidelines regarding the use of BS to treat obese patients who are at risk of CKD and especially those at a high risk of CKD.

This study aimed to investigate the effects of BS or non-surgical interventions on estimated glomerular filtration rates (eGFRs) and to determine whether BS can be recommended for renal function preservation based on BMI and eGFR changes in obese patients with CKD.

Materials and methods

The weight Reduction Intervention on GFR in Obese Patients with Renal Impairment-Taipei Medical University (TMU) study was based on data from an institutional clinical database collected by Taipei Medical University Taipei Medical University Hospital (TMUH) and its affiliated hospitals, namely, Wan Fang Hospital and Shuang Ho Hospital, which have 3000 beds collectively. The database comprises three million patients' data that describe their demographic and clinical characteristics, outpatient and emergency room visits, hospital admissions, laboratory test results, and drug prescriptions;

the data have been collected since 1997. All of the patients and physicians were anonymized, and the need for informed consent was waived. TMU's institutional review board exempted this study from a full review (TMU-JIRB No. N201705035).

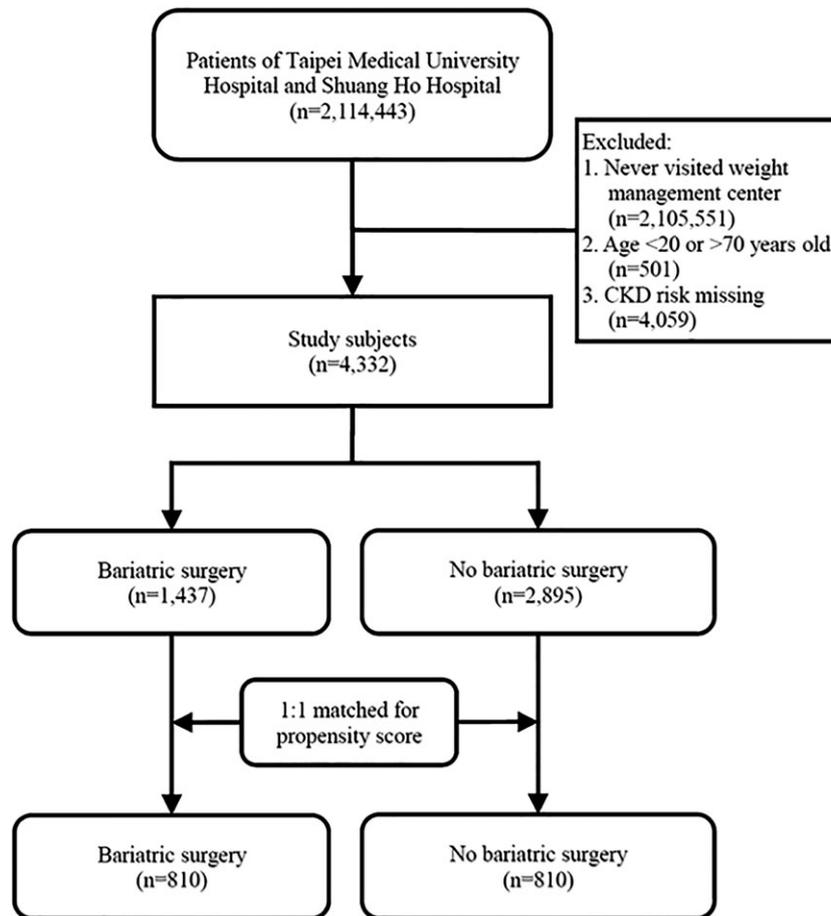
The Comprehensive Weight Management Center at TMUH provided guidance for efficient and healthy weight reduction. The BS teams at TMUH and its affiliated hospitals performed minimally invasive laparoscopic weight loss surgery and provided advice about lifestyle modifications, nutritional support, and professional physical training. Data from the subjects who registered to participate in the weight management programmes at TMUH and its affiliated hospitals were extracted from the clinical database at TMUH. The subjects' BMIs were recorded from electronic charts, and their eGFRs were calculated using the Taiwan Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.¹³

Study subjects

We identified 4332 patients aged 20–70 years who visited the weight management centres at TMUH and Shuang Ho Hospital between 1 January 2008 and 31 August 2016. The exclusion criteria were patients who had never visited the weight management centres, were aged <20 or >70 years, and whose CKD risk was unknown (*Figure 1*). The index dates were defined as the date of BS in the BS group and the cohort entry date, which was the first date on which the weight management centres were visited, in the non-surgery group. The eGFR was calculated using the serum creatinine (sCr)-based Taiwanese modification of the CKD-EPI equation,¹³ that is, $1.262 \times \text{CKD-EPI}^{0.914}$; the CKD-EPI equation follows: $141 \times \text{minimum} (\text{sCr}/\kappa, 1)^{\alpha} \times \text{maximum} (\text{sCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}}$ (if female). The CKD risk groups were defined using the Kidney Disease: Improving Global Outcomes guidelines¹⁴ that consider the eGFR and the extent of proteinuria. The patients were assigned to three categories based on their CKD risks in the year before their index dates, as follows: low CKD risk: eGFR ≥ 90 mL/min·1.73 m² and albuminuria <30 mg/g; moderate CKD risk: eGFR 60–89 mL/min·1.73 m² or albuminuria ≥ 30 mg/g; and high CKD risk: eGFR <60 mL/min·1.73 m². The interval between the collection of two samples for the sCr and urine protein measurements was >3 months; hence, a moderate CKD risk with proteinuria or a high CKD risk was considered to indicate pre-existing CKD.

Interventions

Bariatric surgery was defined using the procedure codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and was based on (i) a laparoscopic adjustable gastric banding (ICD-9-CM: 44.99

Figure 1 Flow chart of patient selection. CKD, chronic kidney disease.

and 54.21), (ii) a sleeve gastrectomy (ICD-9-CM: 43.89 and 54.21), (iii) a Roux-en-Y gastric bypass (ICD-9-CM: 43.7 and 54.21), or (iv) a bioenteric intragastric balloon placement (ICD-9-CM: 44.93).

Study endpoint

Based on a previous cohort study,¹⁵ a slower GFR decline, that is, 30% over 2 years, may be strongly associated with ESRD and all-cause mortality. Our primary endpoint, which represented CKD progression, was defined as an eGFR decline $\geq 25\%$ during the 1-year follow-up period. The follow-up period began on the index date and continued until death, an eGFR decline $\geq 25\%$, 1 year after the index date, or until 31 August 2016, whichever came first.

Covariates

The medication prescriptions were extracted from the pharmaceutical data using the World Health Organization's

Anatomical Therapeutic Chemical (ATC) classification system (<https://www.whocc.no>). Medications were defined as drugs prescribed within the 2-year period before the index date. Comorbidities were defined as two or more diagnostic records within the 2-year period before the index date. The potential risk factors associated with the outcome included age, sex, the CKD risk, hypertension (ICD-9-CM: 401–405), diabetes mellitus (ICD-9-CM: 250), coronary artery disease (ICD-9-CM: 410–414), nephrolithiasis (ICD-9-CM: 592, 594, 274.11), statins (ATC: C10AA, C10B), diuretics (ATC: C03, C09DA04), metformin (ATC: A10BA02), insulin (ATC: A10A), and the laboratory results, including the albumin, cholesterol, glutamic pyruvic transaminase, and triglyceride levels within 180 days before the index operation, and smoking, the BMI, and the surgery type.

Statistical analyses

The risk estimates were computed based on the risk factors using univariate analyses and multivariate analyses with additional adjustments for potential confounders. Propensity

scoring methods have been widely used to reduce confounding in observational studies.^{16,17} Each patient's probability of undergoing BS was derived from a logistic regression model that included baseline covariates, namely, age, sex, the CKD risk, hypertension, diabetes mellitus, coronary artery disease, nephrolithiasis, statins, diuretics, metformin, insulin, and the albumin, cholesterol, glutamic pyruvic transaminase, and triglyceride levels, the baseline BMI, smoking, and the cohort entry year. The propensity scores were matched using the nearest neighbour, 1:1 pair matching within 0.2 standard deviations (SDs) of the logit of the propensity score.^{17,18} By calculating the standardized differences of the means or proportions of each covariate after matching, baseline covariates with standardized differences <0.1 indicated a good balance between the BS group and the non-surgery group.^{19,20}

Within the matched sample, the 95% confidence intervals (CIs) for incidence rates from the Poisson regression models, and the hazard ratios (HRs), and 95% CIs from the Cox proportional hazard regression models were used to estimate the risks of eGFR declines $\geq 25\%$. The times to eGFR declines $\geq 25\%$ were determined using the Kaplan–Meier method and compared using the log-rank test. We modelled the eGFR trajectories during the follow-up period by using restricted cubic splines with five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. Stratified analyses of the relative risks of the subjects' outcomes according to albuminuria, hypertension, and diabetes mellitus were performed. Spearman's correlation coefficient was used to determine associations between BMI declines and eGFR changes from baseline until 1 year, and scatter plots were drawn. All of the data management and analyses were performed using SAS Enterprise Guide software, version 7.11 (SAS Institute, Cary, NC, USA), and a value of $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of the propensity score-matched obese study population

The mean (SD) ages of the BS and non-surgery groups (both $n = 810$) were 36.6 (10) years and 36.3 (9.8) years, respectively, and 36.0% and 35.3% of the patients in the BS and non-surgery groups, respectively, had moderate risks of CKD with albuminuria ≥ 30 mg/day. The average BMIs in the BS and non-surgery groups were 37.8 and 37.7 kg/m², respectively. There were no differences between the groups (Table 1). Supporting Information, Table S1 presents the raw data from the whole population ($n = 4332$).

Times to an estimated glomerular filtration rate decline of $\geq 25\%$

Overall, the eGFR was significantly less likely to decline $\geq 25\%$ in the BS group than in the non-surgery group (log rank $P =$

0.02) (Figure 2A). The likelihood of the eGFR declining $\geq 25\%$ was lower in the BS group compared with that in the non-surgery group among the patients with a low CKD risk, but the difference was not significant (Figure 2B). Among the patients with a moderate CKD risk, the eGFR in the BS group was significantly less likely to decline $\geq 25\%$ compared with that in the non-surgery group (log rank $P < 0.001$) (Figure 2C). For the patients with a high CKD risk, the eGFR in the BS group was significantly less likely to decline $\geq 25\%$ compared with that in the non-surgery group (log rank $P = 0.039$) (Figure 2D). Significantly more patients in the high CKD risk group than those in the low and moderate CKD risk groups showed eGFR decreases $\geq 25\%$ ($P < 0.001$) (Figure 2E). After stratifying the patients into six groups according to the CKD risk and BS, the high CKD risk group that did not undergo BS had a significantly higher likelihood of an eGFR decrease $\geq 25\%$ compared with the other groups ($P < 0.001$) (Figure 2F).

Estimated glomerular filtration rate trajectories in the patients who underwent bariatric surgery and matched control patients

The BS group's continuous eGFR curve showed an upward trend and that of the non-surgery group showed a downward trend (Figure 3A). The upward trajectory was more pronounced in the groups of patients with eGFRs < 90 mL/min \cdot 1.73 m² who underwent BS (Figure 3B). In the BS group, the eGFR improvement began immediately and plateaued at an elevation of approximately 10% within about 3 months. A 10% decrease in the eGFR that became more stable after 3 months was observed in the non-surgery group. Supporting Information, Figure S1 shows the stratification of the groups according to an eGFR of 60 mL/min \cdot 1.73 m².

Changes in the estimated glomerular filtration rate and body mass index trajectories from baseline

Figure 4 shows the relationships between time and the BMI and eGFR. The eGFRs did not improve in the patients with moderate or high risks of CKD who did not undergo BS (Figure 4A). In the patients with moderate or high risks of CKD who underwent BS, the eGFRs had improved at 3 months, the BMI reductions peaked at 6 months, and the eGFR improvements continued for up to 12 months (Figure 4B). In the patients at a low risk of CKD, the eGFR did not improve in those who did not undergo BS (Figure 4C), and it remained the same during the 12-month study period in those who underwent BS (Figure 4D). Hence, patients with moderate and high CKD risks experienced the greatest eGFR improvements after BS.

Table 1 Demographic data from patients in the weight management centres after propensity score matching

	Overall (n = 1620)		Bariatric surgery (n = 810)		No bariatric surgery (n = 810)		ASD ^b
	n	(%)	n	(%)	n	(%)	
Age, years, mean (SD)	36.5	(9.9)	36.6	(10.0)	36.3	(9.8)	0.04
20–29	407	(25.1)	203	(25.1)	204	(25.2)	
30–39	692	(42.7)	339	(41.9)	353	(43.6)	
40–49	336	(20.7)	171	(21.1)	165	(20.4)	
50–59	148	(9.1)	75	(9.3)	73	(9.0)	
60–70	37	(2.3)	22	(2.7)	15	(1.9)	
Female, n (%)	975	(60.2)	495	(61.1)	480	(59.3)	0.04
CKD risk ^a							0.01
Low	985	(60.8)	488	(60.2)	497	(61.4)	
Moderate	578	(35.7)	292	(36.0)	286	(35.3)	
High	57	(3.5)	30	(3.7)	27	(3.3)	
Comorbidities							
Hypertension	501	(30.9)	259	(32.0)	242	(29.9)	0.05
Diabetes mellitus	307	(19.0)	157	(19.4)	150	(18.5)	0.02
Coronary artery disease	58	(3.6)	35	(4.3)	23	(2.8)	0.08
Nephrolithiasis	23	(1.4)	12	(1.5)	11	(1.4)	0.01
Medications							
Statins	91	(5.6)	44	(5.4)	47	(5.8)	0.02
Diuretics	70	(4.3)	37	(4.6)	33	(4.1)	0.02
Metformin	133	(8.2)	69	(8.5)	64	(7.9)	0.02
Insulin	84	(5.2)	42	(5.2)	42	(5.2)	0.00
Laboratory							
Albumin, g/dL, mean (SD)	4.5	(0.3)	4.5	(0.3)	4.5	(0.3)	0.02
Cholesterol, mg/dL, mean (SD)	199.0	(39.4)	201.0	(36.5)	196.9	(42.1)	0.00
GPT, IU/L, mean (SD)	51.4	(53.4)	52.2	(55.5)	50.6	(51.2)	0.05
TG, mg/dL, mean (SD)	174.3	(198.1)	173.6	(132.1)	175.0	(246.7)	0.02
Smoking	18	(1.1)	10	(1.2)	8	(1.0)	0.02
Baseline BMI, kg/m ² , mean (SD)	37.7	(6.9)	37.8	(5.7)	37.7	(7.9)	0.02
Surgery type							
Laparoscopic adjustable gastric banding	75	(4.6)	75	(9.3)	—		
Sleeve gastrectomy	722	(44.6)	722	(89.1)	—		
Roux-en-Y gastric bypass	6	(0.4)	6	(0.7)	—		
Bioenteric intragastric balloon	7	(0.4)	7	(0.9)	—		
Follow-up frequency							
Mean (SD)	5.9	(5.0)	8.6	(5.0)	3.2	(3.1)	
Median (Q1–Q3)	5	(2–8)	8	(5–11)	2	(1–4)	

ASD, absolute standardized difference; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GPT, glutamic pyruvic transaminase; SD, standard deviation; TG, triglyceride.

^aLow: eGFR \geq 90 and albuminuria $<$ 30 mg/g; moderate: eGFR 60–89 or albuminuria \geq 30 mg/g; high: eGFR $<$ 60.

^bAn imbalance was defined as a value $>$ 0.1.

Relationships between body mass index declines and estimated glomerular filtration rate changes according to the chronic kidney disease risk category and surgery

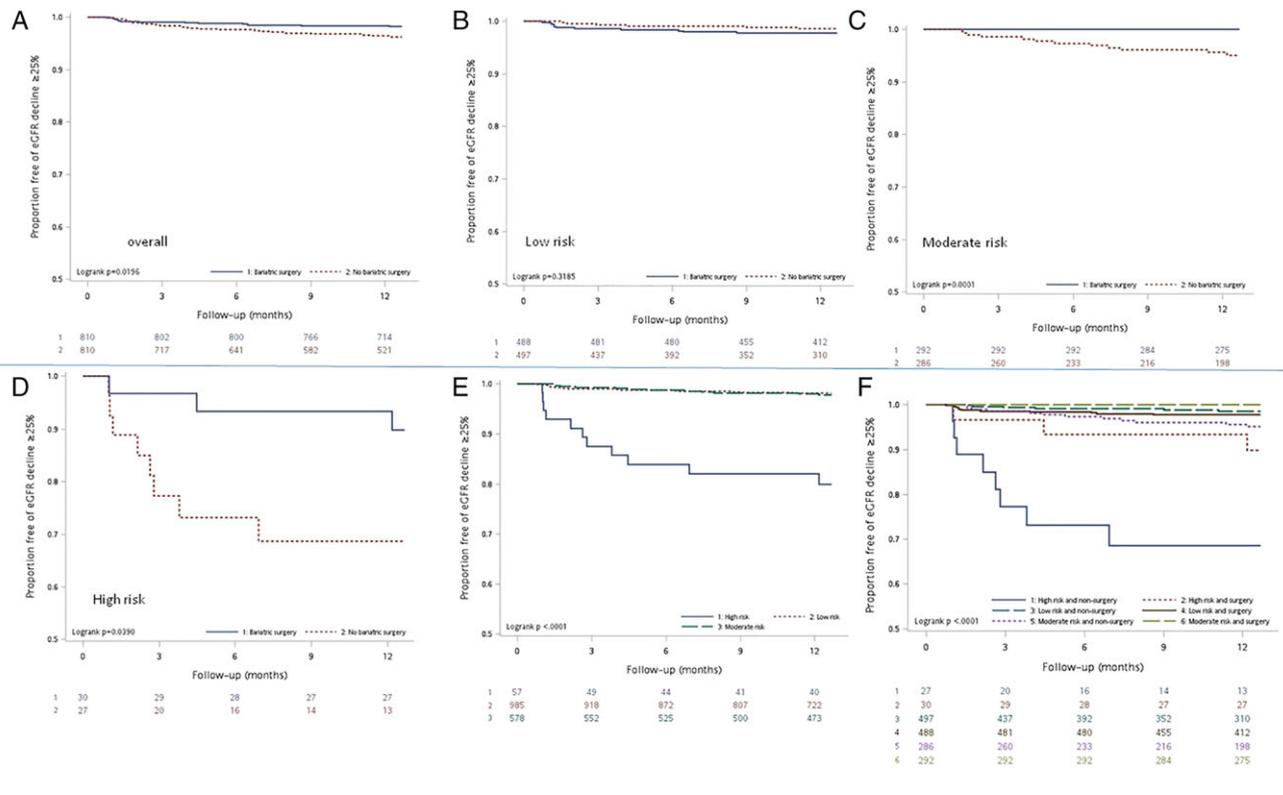
The BS group showed a greater BMI decline (2.5 kg/m²) at 12 months than the non-surgery group (1.3 kg/m²), and similar BMI declines across the CKD risk categories (Table 2). Overall, the eGFR increased by a mean (SD) of 4.4 (14) mL/min·1.73 m² in the BS group and it decreased by a mean (SD) of 6.4 (16.0) mL/min·1.73 m² in the non-surgery group at 12 months. The greatest mean (SD) eGFR increase of approximately 10.2 (18.6) mL/min·1.73 m² occurred among the patients with moderate or high CKD risks in the BS group (Table 3). A BMI decline was significantly correlated with an eGFR change in the patients with moderate or high risks of CKD (Spearman's correlation -0.229 , $P < 0.001$) (Figure 5A),

but a correlation was not evident among the patients with a low risk of CKD (Spearman's correlation 0.02, $P = 0.67$) (Figure 5B).

Subgroup analysis

In the BS group, there was a 53% lower risk of an eGFR decrease \geq 25% (HR 0.47, 95% CI 0.24–0.91, $P = 0.03$) compared with that in the non-surgery group (Table 4) after adjusting for the confounding factors, including the baseline eGFR and propensity scores. The adjusted multivariate model determined that a subgroup comprising obese patients with albuminuria \geq 30 mg/g who had undergone BS had an 87% lower risk of an eGFR decrease \geq 25% (HR 0.13, 95% CI 0.04–0.47, $P = 0.002$) compared with that in the non-surgery group. The subgroup comprising obese

Figure 2 Kaplan–Meier curves estimating the time to the kidney outcome in the surgery and non-surgery groups in the patients (A) overall, (B) with a low risk of low chronic kidney disease (CKD), (C) with a moderate risk of CKD, (D) with a high risk of CKD, (E) stratified according to CKD risk, and (F) according to CKD risk and surgery. eGFR, estimated glomerular filtration rate.



patients with hypertension who had undergone BS had a 63% lower risk of an eGFR decrease $\geq 25\%$ (HR 0.37, 95% CI 0.16–0.86, $P = 0.02$) compared with that in the non-surgery group. The effect of BS was of borderline significance in the group of patients with type 2 diabetes mellitus.

Discussion

This study's findings demonstrated the beneficial effect of BS on the eGFRs in obese patients at risk of CKD; hence, BS improved the patients' renal function, and the effect lasted for

Figure 3 Estimated glomerular filtration rate (eGFR) trajectories in the bariatric surgery patients and matched control patients. (A) Overall and (B) stratified according to a baseline eGFR < 90 and ≥ 90 mL/min \cdot 1.73 m 2 . The follow-up period was modelled using restricted cubic splines with five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.

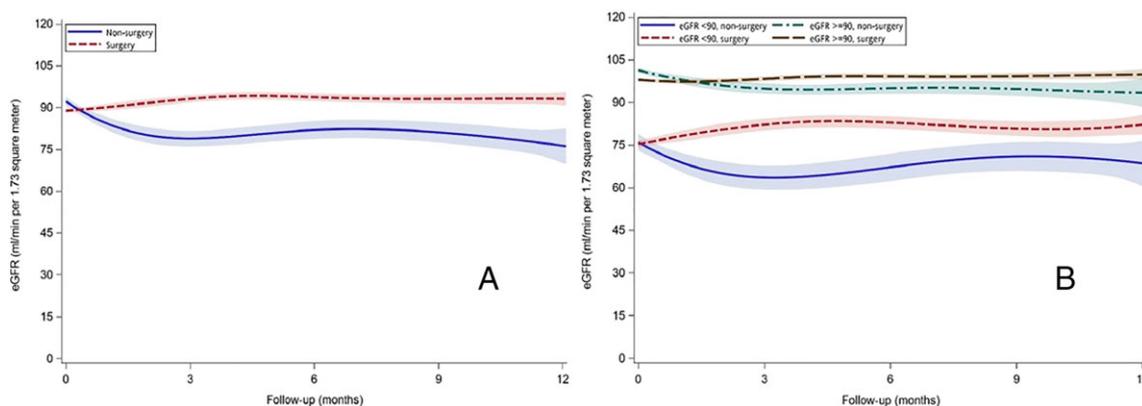
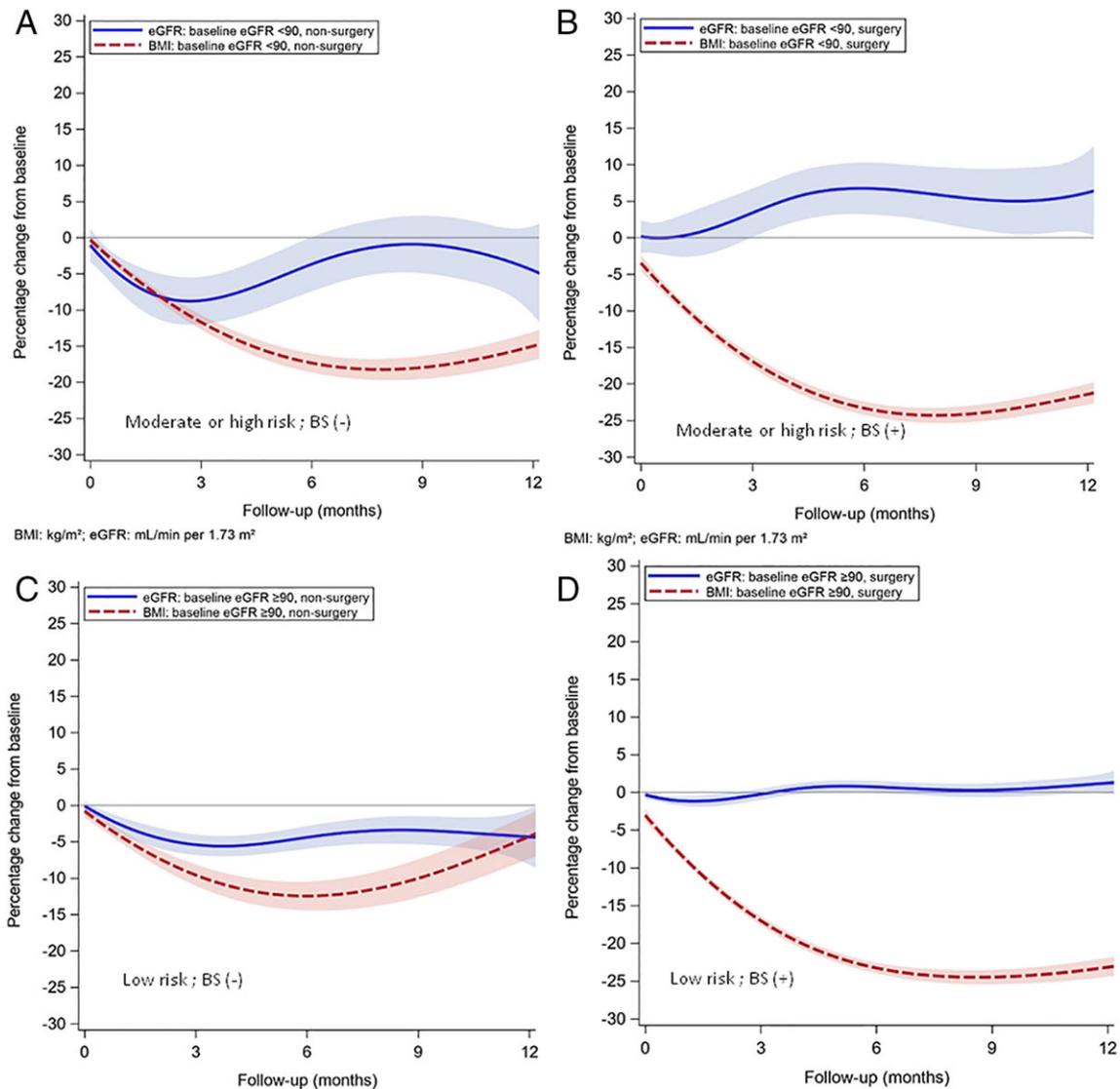


Figure 4 Trajectories of the percentage change in the estimated glomerular filtration rates (eGFR) and body mass indexes (BMIs) from baseline in the bariatric surgery (BS) patients and matched control patients. (A) Baseline eGFR <90 mL/min \cdot 1.73 m 2 , non-surgery, (B) baseline eGFR <90 mL/min \cdot 1.73 m 2 , surgery, (C) baseline eGFR ≥ 90 mL/min \cdot 1.73 m 2 , non-surgery, and (D) baseline eGFR ≥ 90 mL/min \cdot 1.73 m 2 , surgery.



>1 year. BS, which mainly comprises laparoscopic sleeve gastrectomy, is a novel and effective obesity treatment for patients with CKD.²¹ BS has become standard therapy for patients with type 2 diabetes who are severely obese with BMIs >40 kg/m 2 or >35 kg/m 2 if their glucose levels are poorly controlled, because it reduces insulin resistance, proteinuria, and cardiovascular risks.²² Our study has generated evidence that will help determine whether all severely obese patients with renal disease should undergo BS and whether BS is appropriate for all CKD stages. This study's strength relates to our use of a large propensity score-matched long-term cohort from an electronic clinical database at TMUH. However, BS did not improve the eGFR in the group of patients with a

low CKD risk. After BS, kidney hypertrophy/hyperfiltration may reverse, thereby normalizing the GFR in obese patients with a low risk of CKD; thus, the eGFR may also decrease.²³ Our results that showed eGFR declines in the group with a low risk of CKD concur with these findings. Similar results have been reported from other studies.^{24,25} At 3 months after BS, the eGFR increased in the moderate and high CKD risk groups by up to 10 mL/min \cdot 1.73 m 2 . The findings from a study of 25 patients with CKD who underwent BS showed similar eGFR elevations of up to 20 mL/min \cdot 1.73 m 2 ,²⁶ and a larger cohort study's findings showed that BS had long-term benefits for the eGFR that persisted for 5 years in obese patients with CKD.²⁷ Although a large cohort study's findings

Table 2 Mean body mass index decline over the 1-year follow-up period stratified according to the baseline chronic kidney disease risk category

Visit (n)	Overall	Low risk ^a	Moderate and high risk ^a
	Mean (SD)	Mean (SD)	Mean (SD)
3 months (494)	1.1 (2.5)	1.1 (2.4)	1.2 (2.6)
12 months (186)	2.1 (3.7)	2.1 (3.7)	2.1 (3.7)
Bariatric surgery			
3 months (379)	1.1 (2.5)	1.0 (2.5)	1.2 (2.6)
12 months (170)	2.5 (4.0)	2.4 (3.9)	2.7 (4.1)
No bariatric surgery			
3 months (115)	1.2 (2.2)	1.3 (2.0)	1.1 (2.7)
12 months (16)	1.3 (2.9)	1.5 (3.1)	1.0 (2.6)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.

^aLow CKD risk: eGFR ≥ 90 mL/min $\cdot 1.73$ m² and albuminuria < 30 mg/g; moderate CKD risk: eGFR 60–89 mL/min $\cdot 1.73$ m² or albuminuria ≥ 30 mg/g; high CKD risk: eGFR < 60 mL/min $\cdot 1.73$ m².

showed that at 30 days after BS, each incremental CKD stage correlated with a 1.3-times increase in complications, there were no long-term follow-up assessments.²⁸ Therefore, despite increases in short-term post-operative complications, the long-term benefit of BS-induced weight reductions on CKD cannot be underestimated.

Overall, the mean (SD) decline in the BMI over 1 year in the study subjects who underwent BS was only 2.1 (3.7) kg/m² or 6%. Two reasons may explain this small BMI decline. First, the follow-up duration was only 1 year, and meta-analyses have shown long-term weight reductions²⁹ of 5.2 kg/m² or 32%²⁵ after BS during follow-up periods of up to 5 years. Second, the patients were Asian people whose mean (SD) BMI was 37.7 (6.9) kg/m², and they were not very fat; thus, the effect of BS on weight reduction may not be pronounced. Interestingly, the BMI decline was proportional to the eGFR changes in the moderate and high CKD risk groups, but this was not observed in the low CKD risk group. After BS, the eGFR may have improved in the moderate and

Table 3 Percentage change in the estimated glomerular filtration rate over 1-year the follow-up period stratified according to the baseline chronic kidney disease risk category

Visit (n)	Overall	Low risk ^a	Moderate or high risk ^a
	Mean (SD)	Mean (SD)	Mean (SD)
3 months (494)	0.6 (12.2)	−1.5 (6.5)	3.9 (17.3)
12 months (186)	2.2 (15.2)	−0.4 (7.2)	5.0 (20.5)
Bariatric surgery			
3 months (379)	1.9 (10.2)	−0.8 (5.5)	6.4 (14.0)
12 months (170)	4.4 (14.0)	0.2 (7.2)	10.3 (18.6)
No bariatric surgery			
3 months (115)	−3.9 (16.5)	−4.1 (8.8)	−3.5 (23.6)
12 months (16)	−6.4 (16.6)	−4.7 (5.3)	−7.2 (19.8)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.

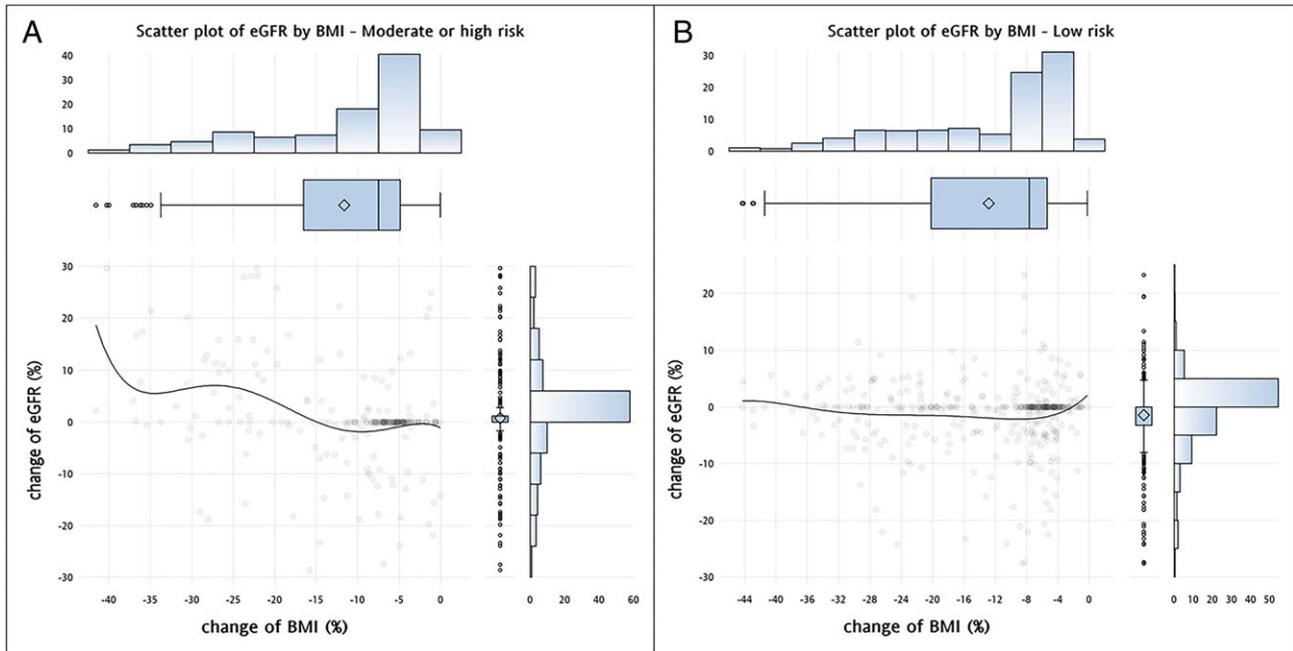
^aLow CKD risk: eGFR ≥ 90 mL/min $\cdot 1.73$ m² and albuminuria < 30 mg/g; moderate CKD risk: eGFR 60–89 mL/min $\cdot 1.73$ m² or albuminuria ≥ 30 mg/g; high CKD risk: eGFR < 60 mL/min $\cdot 1.73$ m².

high CKD risk groups following a rapid decline in muscle mass during the weight-reduction intervention that did not occur in the patients who did not have CKD. Patients with CKD are prone to muscle wasting caused by uraemia-induced alterations, including increased energy expenditure and persistent inflammation, which lead to the excessive catabolism of muscle and fat.³⁰ BS increases gastric emptying and intestinal transit as consequences of the activation of glucagon-like peptide-1, and ghrelin inhibition without weight changes may occur after BS.³¹ The findings from an animal study suggest that glucagon-like peptide-1 might increase the GFR by 30–50% by inhibiting tubular reabsorption, increasing renal blood flow/natriuresis, and inhibiting inflammation and reactive oxygen species production,³² which are induced by increased levels of markers of inflammation, including interleukin-6 or tumour necrosis factor- α , in adipose tissue.³³ In addition, the findings from a study of obese patients with CKD who underwent BS showed that leptin and β -2 microglobulin, rather than the BMI and the fat mass, correlated with kidney function.³⁴ Similarly, the findings from a recent meta-analysis showed that the GFR increased in a subgroup of patients with CKD and decreased in a hyperfiltration subgroup.³⁵ Furthermore, compared with other forms of calorie restriction that induce transient visceral fat decreases, a larger loss of fat-free mass accompanies BS.³⁶ Although a high-protein diet comprising 1–1.2 g/kg ideal body weight is recommended to patients who undergo BS, but not to CKD patients,³⁷ many patients continue to consume low-protein diets. While a low-protein diet did not correlate with GFR changes in normal obese patients after BS,³⁸ a low-protein diet preserved renal function, particularly in patients with CKD.³⁹ Hence, our study's findings showed that the eGFR improvements correlated with the BMI declines in the patients with CKD, but this was not observed in the patients who did not have CKD; this may have been caused by different rates of muscle wastage between the patients with and without CKD, improvements in the microenvironment, and the inhibition of inflammation.

Whether BS has more favourable effects on renal function is a matter of debate, because an accurate equation is not available that can determine the eGFR and the sCr and serum cystatin C levels are affected by extrarenal factors that are modulated by BS. Compared with measured GFRs, eGFRs determined using the original Modification of Diet in Renal Disease (MDRD) or CKD-EPI equations are not accurately predicted for obese patients undergoing BS.²³ A meta-analysis of 23 cohort studies included measured GFRs in only one study, and this meta-analysis showed that GFRs determined using the MDRD, CKD-EPI, and Cockcroft–Gault equations were homogenous.³⁵ Hence, it might be acceptable to use eGFRs to predict renal function in obese patients who are undergoing weight-reduction therapy.

The subgroup analysis showed that BS might act independently to slow eGFR declines and, similarly, that patients with

Figure 5 Scatter plots of the estimated glomerular filtration rates according to the BMI in patients with a (A) moderate or high CDK risk and (B) low CKD risk. BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.



proteinuria or hypertension might benefit significantly more from weight-reduction programmes than patients who do not have proteinuria or hypertension. Although the effect of BS on patients with type 2 diabetes was of borderline significance in relation to preserving the eGFR, the trend suggested a benefit. Recently, a Cochrane meta-analysis indicated that even dietary interventions in patients with CKD increased the eGFR and lowered blood pressure.⁴⁰ Therefore, clinicians may suggest that obese patients with CKD risks comprising

either proteinuria or hypertension should enter weight-reduction programmes to preserve the eGFR.

Limitations

Our study's limitations are described next. First, the follow-up period was only 1 year, and the study involved Asian subjects whose levels of obesity are lower relative to those of

Table 4 Incidence rates of and hazard ratios for an estimated glomerular filtration rate decline $\geq 25\%$

	n	Person month	Events, No.	Rate per 1000 person-months (95% CI)	Model 1 ^a		Model 2 ^b	
					HR (95% CI)	P	HR (95% CI)	P
Total	1620	18 031	40	2.22 (1.58–3.02)				
No bariatric surgery	810	8160	26	3.19 (2.08–4.67)	(Reference)		(Reference)	
Bariatric surgery	810	9871	14	1.42 (0.78–2.38)	0.47 (0.25–0.90)	0.02	0.47 (0.24–0.91)	0.03
Albuminuria								
<30 mg/g	985	10 843	17	1.57 (0.91–2.51)	1.49 (0.54–4.10)	0.44	1.50 (0.54–4.15)	0.43
≥ 30 mg/g	635	7188	23	3.20 (2.03–4.80)	0.14 (0.04–0.48)	0.002	0.13 (0.04–0.47)	0.002
HTN								
No	1119	12 644	13	1.03 (0.55–1.76)	0.77 (0.25–2.36)	0.65	0.77 (0.25–2.35)	0.65
Yes	501	5387	27	5.01 (3.30–7.29)	0.36 (0.16–0.85)	0.02	0.37 (0.16–0.86)	0.02
DM								
No	1313	14 715	22	1.50 (0.94–2.26)	0.50 (0.21–1.21)	0.16	0.50 (0.21–1.22)	0.13
Yes	307	3316	18	5.43 (3.22–8.58)	0.41 (0.15–1.08)	0.07	0.41 (0.15–1.07)	0.07

CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTN, hypertension.

^aAdjusted for the baseline eGFR.

^bAdjusted for the baseline eGFR and the propensity score.

Caucasian individuals. According to a study conducted by Navarro-Diaz *et al.*,²⁴ eGFRs do not change significantly or remain stable in severely obese patients for 12–24 months after BS; therefore, a cohort study with a longer follow-up period that includes other ethnic groups is warranted to corroborate the effects of BS on eGFRs and to generate generalizable data. Second, the eGFR may not accurately reflect measured renal function, especially with regard to predicting exogenous creatinine clearance. Indeed, an equation does not exist that can accurately estimate the GFR following significant body weight changes, and, in this situation, the MDRD equation is comparable with the CKD-EPI equation for GFR predictions.⁴¹ Third, we did not record the lean body mass of the obese patients to prove that the effect of BS on the eGFR resulted from muscle wasting, which is commonly seen in advanced CKD patients, especially those who have been on long-term dialysis.

In conclusion, the findings from this 1-year large, propensity score-matched cohort study showed that BS is beneficial for preserving the eGFR in obese patients and that it is associated with BMI declines, particularly among those with moderate and high risks of CKD. Clinicians may arrange weight-reduction programmes for obese patients with CKD risks, including proteinuria or hypertension, to preserve their eGFRs. Further studies with longer follow-up durations that evaluate changes in endocrine biomarkers or inflammatory markers and muscle wasting after BS are warranted to elucidate the relationship between muscle mass decreases and microenvironmental changes in the GFR. In addition, more data are needed that describe long-term outcomes, for example, ESRD, hospitalization, or death, to gain a better understanding of the beneficial effects of weight-reduction surgery and subsequent renoprotection in patients with CKD.

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Authors' contributions

Y.-C.L. acted as the chief executor taking the whole responsibility of the study design, progress monitoring, data interpretation, and part of manuscript writing. Y.-Z.L. performed the experiments and part of manuscript writing. M.-S.W. discussed, analysed, interpreted the data, and was responsible for the discussion and trouble shooting. Y.-C.L., M.-S.W., K.-C.C., and C.-C.P. contributed reagents/materials. M.-T.C. and T.-H.C. contributed assistance in drafting the article and reformatting all plots in this manuscript.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Estimated glomerular filtration rate trajectories in the bariatric surgery patients and the matched controls stratified according to the chronic kidney disease (CKD) risk. The follow-up period was modeled using restricted cubic splines with 5 knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Table S1. Demographic data from the patients in the weight management center before propensity score matching

Conflicts of interest

The authors declare no conflicts of interest.

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