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Change in urea to creatinine ratio is associated with postoperative complications and skeletal muscle wasting in pancreatic cancer patients following pancreatoduodenectomy

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ABSTRACT

Background and Objectives: Surgical Patients with depleted skeletal muscle mass tend to have a worse outcome. Whether perioperative change of urea to creatinine ratio (CUCR) can reflect muscle wasting and predict postoperative complications have not been investigated. This study aimed to evaluate the relationship of perioperative CUCR with postoperative complications and skeletal muscle wasting in pancreatic cancer patients undergoing pancreatoduodenectomy (PD). **Methods and Study Design:** Pancreatic cancer patients undergoing PD were included retrospectively. The association between postoperative complications and perioperative CUCR as well as other nutritional biomarkers was analyzed. In a subset of patients with serial CT scans, the correlation of the CUCR and the changes of CT-derived skeletal muscle area (SMA) were tested. Furthermore, the capacity of complication prediction of CUCR and CT-derived parameter were compared in these patients. **Results:** A total of 321 surgical patients were included. Univariable and Multivariable logistic regression demonstrated CUCR was a strong predictor for complications in these patients, independent of age, BMI and comorbidity. Patients with CUCR above the median have higher complication rate ($p=0.007$) and longer postoperative days to discharge ($p=0.017$). In a subset patients with both pre- and postoperative digital abdominal CT scans, spearman correlation analysis shown both L3 muscle area and L4-psoas area were significantly correlated with CUCR ($R^2=0.64$, $p<0.05$; $R^2=0.62$, $p<0.05$, respectively). **Conclusions:** Perioperative CUCR is an independent predictor for postoperative complications in pancreatic cancer patients undergoing PD. Elevated CUCR is a reflection of skeletal muscle wasting in postoperative surgical patients.

Key Words: muscle wasting, urea to creatinine ratio, complications, cancer, pancreatoduodenectomy

INTRODUCTION

Pancreatic cancer is one of the leading causes of death worldwide, with 1 year and 5 years survival rates of 24% and 9%, respectively.¹ Even though much progress has been made in chemoradiotherapy and targeted therapy, surgery remains the only curative option for pancreatic cancer.² For tumors located in the head of the pancreas, pancreatoduodenectomy (PD) is the main surgical treatment. This invasive and complex surgery has a high rate of complications, such as postoperative pancreatic fistula (POPF), abdominal infection, bleeding, etc., thus increasing the financial burden and reducing the quality of life of patients.^{3,4}

Therefore, identifying the patients with high risk of postoperative complications seems pragmatic to address this issue. Recently, body composition analysis has been demonstrated to effectively stratify critical and surgical patients.⁵⁻⁸ Especially, among pancreatic cancer patients, reduced skeletal muscle mass or density was associated with higher surgical site infection and decreased overall survival.⁹ Meanwhile, sarcopenia has been shown to be a risk factor for POPF after pancreatic surgery.⁸ However, in these studies, most of the skeletal muscle information was obtained from preoperative CT scans. This data may be lost if the patients had no CT scans or did the test in another hospital. Thus, it is important to identify a more general and stable laboratory indicator to represent skeletal muscle condition in clinical practice.

The protein-catabolic state of critical illness can be reflected by some routinely collected clinical data, such as albumin, creatinine and urea levels.^{10,11} Albumin is mainly synthesized in the liver from its precursor amino acid, which may come from exogenous intake and muscle protein degradation. However, the relatively long half-life of albumin may limit its usage in timely evaluation of the metabolic status and muscle condition.¹² Creatinine is the final product of creatine, which is mainly present in muscle tissue and converted into creatinine at a stable rate. Creatinine is released into circulation and exclusively excreted by the kidney. During normal renal function, serum creatinine concentration is closely related to its production.¹³ Therefore, serum and urinary creatinine has been widely utilized to estimate muscle mass in stable outpatients.^{14,15} Recently, the predictive value of creatinine on survival and muscle catabolism has been established in critically ill population.^{10,16} However, the role of creatinine in major abdominal surgery has not been evaluated. Hence, this study tested whether the changes of urea to creatinine ratio (CUCR), as a reflection of muscle catabolism, was related to postoperative complications in pancreatic cancer patients who underwent PD. The relationship between CUCR and CT-derived muscle wasting was also examined.

MATERIALS AND METHODS

Patients and data

In this retrospective study, we analyzed the laboratory data and clinical outcomes of 321 pancreatic cancer patients who underwent PD at a tertiary hospital (The First Affiliated Hospital of Soochow University) between January 2014 and July 2020. Inclusion criteria were age ≥ 18 years, patients underwent PD and were diagnosed with pancreatic ductal adenocarcinoma (PDAC) by postoperative pathology. Exclusion criteria were renal or other organ failure, and incomplete medical data. The primary outcome was major postoperative

complications with Clavien-Dindo classification (CDC) ≥ 3 .¹⁷ Among the recorded major complications (CDC ≥ 3), POPF and infection were further analyzed. POPF was defined according to the International Study Group for Pancreatic Fistula classification.¹⁸ Postoperative infection included confirmed incision infection, abdominal infection and lung infection, which needed specific treatment, such as upgrading antibiotics, secondary closure and additional drainage. Secondary outcomes included 28-day mortality, and length of postoperative hospitalization. This study was approved by the medical ethical committee of the First Affiliated Hospital of Soochow University, and since it involved analysis of anonymized laboratory and clinical data collected during standard clinical care, informed consent was not required.

Patient data including age, sex, weight, body mass index (BMI), pre- and postoperative routine blood parameters, including C-reactive protein (CRP), hemoglobin, pre-albumin, albumin, urea, creatinine and urea to creatinine ratio (UCR) (concentrations in mmol/L) were recorded. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, with serum creatinine, gender, and age as input variables.¹⁹ Skeletal muscle area (SMA) was assessed in a subset of patients with both preoperative and postoperative digital abdominal CT scans. Total abdominal SMA was measured at the level of the third lumbar (L3) vertebrae, and psoas SMA was calculated at the L4 level.²⁰ We then examined the relationship between the CUCR and the perioperative changes of SMA.

Surgical procedure and perioperative management

All patients underwent Whipple or pylorus-preserving PD conducted by experienced pancreatic surgeons. A two-layer duct to mucosa pancreato-jejunostomy with either Child or Roux-en-Y technique was used for reconstruction with at least two surgical drains in the abdomen, one next to the bilio-jejunal anastomosis and one close to the pancreato-jejunal anastomosis. Somatostatin or its analogue was routinely administered for three to seven days. Enteral nutrition was initiated as early as possible and supplementary parenteral nutrition was used according to the patients' condition. Other management included proton pump inhibitor, antibiotics, anti-coagulation and early mobilization. In our hospital, all PD patients underwent routine postoperative CT scan or MRI test according to preoperative test in 7-10 days after surgery to find potential complications, such as encapsulated abdominal abscess and pulmonary infection.

Statistics

Data were expressed as mean \pm standard deviation (SD) when normally distributed or median and 25–75% interquartile range (IQR) when skewed. For normally distributed categorical or continuous variables, chi-square test or analysis of variance (ANOVA) were utilized to determine variances between groups, and Kruskal-Wallis test was used for continuous variables that were not normally distributed. Patients with CUCR lower than the median were allocated into CUCR-L group, and those with CUCR higher than the median into CUCR-H group. Univariable analyses were conducted in a set of selective factors as continuous or dichotomous variables. Then, multivariable regression analyses cumulatively included adjustment for age (model 1), BMI (model 2), and comorbidity (model 3).

A dynamic alteration of UCR was compared between patients with and without postoperative major complications. The onset time of postoperative complication was compared between CUCR-L and CUCR-H group by chi-square test. Spearman's correlation coefficient was employed to characterize the association between CUCR and abdominal SMA alteration derived from CT scans. The diagnostic capability of CUCR and abdominal SMA for major complications was compared in ROC curves.

SPSS Statistics 22.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. All statistical tests were two-sided. A $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

During the study period, a total of 495 patients underwent PD, of which 362 patients were diagnosed with pancreatic cancer from postoperative pathology. Thirty-two patients had renal or other organ dysfunctions, and seven were excluded because of incomplete data. Therefore, 321 patients were eligible for the final analysis. Furthermore, a subgroup of 71 patients with both pre- and postoperative digital abdominal CT scans was analyzed to examine the relationship between skeletal muscle information and clinical markers.

Patient characteristics are presented in Table 1, grouped by CDC values. The mean age and BMI of all patients were 59.5 ± 13.9 years and 22.6 ± 3.7 kg/m², respectively. The postoperative creatinine and urea levels in Table 1 indicate those tested about one week after surgery. Serum creatinine level was reduced after surgery, from 69.4 ± 25.8 μ mol/L to 49.3 ± 26.1 μ mol/L ($p < 0.05$), whereas serum urea increased from 5.7 ± 2.7 mmol/L to 7.9 ± 2.9 mmol/L ($p < 0.05$).

Association between CUCR and postoperative complications

To identify the possible risk factors for postoperative complications, univariable and multivariable logistic regression analyses were conducted. In the univariable analysis, major complications were associated with baseline albumin (OR 0.77, 95% CI: 0.65-0.92, $p=0.021$), creatinine (OR 0.92, 95% CI: 0.82-1.04, $p=0.043$), the change of creatinine (OR 0.87, 95% CI: 0.75-1.07, $p=0.029$) and CUCR (OR 2.31, 95% CI: 1.87-2.92, $p=0.000$). However, in the multivariable logistic regression analyses, after adjustment for sex, age and BMI, only CUCR remained significantly associated with postoperative complications (OR 1.89, 95% CI: 1.52-2.14, $p=0.015$) (Table 2).

The detailed primary and secondary outcomes were listed in table 3 grouped by CUCR level. The rate of major complications was 26.2% (84/321), including 19.0% for POPF and 2.1% for infections. The postoperative time to discharge and 28-day mortality were 12.1 ± 5.3 days and 2.2%, respectively. Patients in CUCR-H group had significantly higher complication rate (35.0% vs 17.4%, $p=0.007$). Specifically, the rate of POPF, delayed gastric emptying, nosocomial infection and pulmonary events were higher in CUCR-H group. The length of hospitalization and postoperative time to discharge were shorter in CUCR-L group. The 28-day mortality showed no difference in two groups.

Trajectory of UCR and the temporal distribution of complication onset

The dynamic changes of UCR were depicted in Figure 1. Data was allocated to four time points: baseline (preoperative value), and postoperative 1-3 days, 4-7 days and 8-12 days. The complication group (CDC ≥ 3) had a significantly higher UCR at the third and fourth time points (102, 87.2-139 vs. 94.3, 68.1-118, $p<0.05$; 163, 118-190 vs. 105, 87.2-129, $p<0.01$), while the first two time points showed no difference. The temporal distribution of major complication onset time was demonstrated in figure 2. Compared to CUCR-L group, the CUCR-H group has significantly higher incidence of complication during two (19.3% vs. 6.8%, $p<0.05$) and three weeks (8.1% vs. 4.4%, $p<0.05$) after surgery, however, in the first and fourth postoperative week it showed no difference between the two groups.

Relationship between CUCR and the alteration of CT-derived abdominal SMA

In a subset of 71 patients, both pre and postoperative digital abdominal CT scans were obtained. Preoperative CT was examined within one week of surgery, and postoperative CT was examined in 7-10 days after surgery. The corresponding CUCR was calculated at the time of second CT scan. The median L3 muscle area had decreased by 14%, from 163 cm²

(145-181) to 140 cm² (126-167), and L4-psoas by 16%, from 31 cm² (24-45) to 26 cm² (15-36). The median CUCR in these patients was increased by 76.8% (31.6-132). Through Spearman's correlation analysis, both L3 muscle area and L4-psoas area were significantly correlated with CUCR ($R^2=0.635$, $p<0.05$; $R^2=0.624$, $p<0.05$, respectively) (Figure 3).

Furthermore, ROC curve was utilized to compare the predictive capacity of major complications among CUCR, baseline skeletal muscle area (BSMA) and the change of skeletal muscle area (CSMA). As shown in Figure 4, the areas under the curves (AUCs) were 0.781 and 0.735 for CUCR and CSMA, respectively. However, the AUC for BSMA was only 0.622.

DISCUSSION

This was the first study to demonstrate that the perioperative CUCR was associated with postoperative major complications in pancreatic cancer patients who underwent PD, independent of important covariates and confounders. The CUCR correlated well with the change of SMA derived from CT scans, and could be used as a clinical parameter for complication prediction.

Risk stratification of surgical and critical patients is important to target those who might benefit the most from treatment. Traditionally, performance status and nutritional status have been widely adopted.²¹⁻²⁴ However, the former is relatively subjective and the latter lacks unified standard. BMI was considered to be a prominent factor affecting short and long-term status of patients.²⁵ In critical patients, a J-shaped association between BMI and mortality was observed.²⁶ Several observational studies also found worse outcome in ICU patients with lower or extremely higher BMI.^{27,28} Sarcopenic or obese patients may have normal BMI. Therefore, body composition analysis has increasingly gained attention in nutritional assessment and risk stratification.²⁹ Martin et al. demonstrated that skeletal muscle depletion was a powerful prognostic factor, independent of BMI, in cancer patients.³⁰ Similarly, in critical patients, both muscle quantity and quality affect the survival.^{5,31} In surgical patients, preoperative sarcopenia could predict postoperative complications.⁷⁻⁹ However, data acquisition of skeletal muscle or body composition requires CT or special instrument, which limits its clinical application.

Patients with skeletal muscle wasting may display various phenotypes, such as reduced BMI, cachexia, frailty and deranged biochemical indicators. Two large observational studies have revealed that low baseline serum creatinine was an independent predictor for mortality in critical patients.^{32,33} In addition, the alteration of serum creatinine was associated with the

short-term mortality in acute kidney injury (AKI) patients.³⁴ Since urinary creatinine is closely related to serum creatinine and its production, early low urinary creatinine excretion was a strong risk factor for both short and long-term mortality in ICU patients without renal dysfunction.¹⁶

The present study showed that serum creatinine concentration reduced by 29.0%, from 69.4 ± 25.8 $\mu\text{mol/L}$ to 49.3 ± 26.1 $\mu\text{mol/L}$, and urea concentration increased by 38.6%, from 5.7 ± 2.7 mmol/L to 7.9 ± 2.9 mmol/L , one week after PD in all patients. The potential pathophysiology underlying these changes needs further study. Before the reduction of total muscle mass, decreased mitochondrial biogenesis and dysregulated lipid oxidation were observed in critical illness, which was a reflection of compromised skeletal muscle bioenergetic status.³⁵ Meanwhile, reduced phosphor-creatine content has been demonstrated early in these critical patients.³⁵ Given the close relationship between serum and intramuscular creatine contents,¹³ the early reduction of serum creatinine in the present study may result from the altered metabolism and bioenergetic failure in skeletal muscle. The elevation of urea lasted for more than ten days after surgery. This may be a reflection of skeletal muscle catabolism and amino acid release. Thus, combining the two divergent markers might distinguish patients with different catabolism levels.

The CUCR-H group showed higher rate of complications, including POPF and nosocomial infections, and longer postoperative time to discharge. Subsequent multivariable analysis revealed that CUCR was the only risk factor for complications, after adjustment for age, BMI and comorbidity. This result was consistent with previous studies. In patients with AKI, a raised UCR has been demonstrated to be a risk factor for survival.^{36,37} A large retrospective study reported that elevated UCR was significantly associated with prolonged persistent critical illness after trauma.¹⁰ These changes are an indication of skeletal muscle wasting.³² In the present study, CUCR correlated well with the changes of SMA in L3 level and psoas derived from CT scans. This was in line with the results of Haines' research, which focused on critical trauma patients. They found that the decrease of SMA in L3 and psoas correlated with time elapsed. Of note, in those with persistent critical illness, the rate of muscle decrease was significantly greater and the UCR at the time of second CT negatively correlated with these muscle areas.¹⁰

Several potential mechanisms may have contributed to the muscle wasting observed in our patients. Systemic inflammation as reflected by elevated CRP levels may play a crucial role in the process. Mechanistic studies have shown that several cytokines, including $\text{TNF-}\alpha$, $\text{IL-1}\beta$, and $\text{NF-}\kappa\text{B}$ activation can cause severe muscle wasting.³⁸⁻⁴¹ Besides, a close and direct

relationship was observed between intramuscular inflammation and anabolic signaling.³⁵ Particularly, in PD patients, the relatively insufficient insulin could impair the PI3K-AKT-mTOR pathway, which was pivotal for protein synthesis.³⁹ In addition, major surgery and trauma may increase glucocorticoid level, which is a stronger inducer of muscle wasting.^{39,41-43}

The present study demonstrated dynamic changes of UCR in PD patients. Notably, the splitting point occurred around 4-7 days after surgery. The temporal distribution of complication onset revealed the majority occur after one week postoperatively and displayed with significant difference between CUCR-L and CUCR-H group. This time trend coincided with the dynamic changes of UCR. This metabolic trajectory is akin to that observed in ICU patients. Acute illness always rapidly develops an acute phase, which is characterized by metabolic instability and uncontrolled catabolism.⁴⁴ During this period, muscle wasting occurs and cannot be reversed by nutritional support.^{35,45,46} About one week later, the late phase ensues when anabolism increases leading to restoration of lost body components.⁴⁴ This trend implied the shift from catabolism to anabolism, which may provide some information for nutritional support to mitigate muscle wasting. In the ROC curves, CUCR and CSMA had a comparable potency in predicting postoperative complications, which was superior to that of BSMA. This result indicates that the wasting process is more detrimental than the baseline nutritional conditions.

The present study had some intrinsic limitations. First, the retrospective nature of the study precluded the absolute unification of testing time in perioperative period, hence time interval was employed. Second, even though the initial time and contents of parenteral nutrition showed no significant difference, the serum urea and creatinine levels could be affected by hypovolemia, bleeding and renal function. Third, the analyzed CUCR was from about one week after surgery, but a small portion of the recorded complications occurred within a week after surgery. Therefore, the predictive capability of CUCR in ROC curves should be taken with cautions. Whether postoperative CUCR in a much earlier period can be used in clinical practice need further research. Finally, we only compared the routine tests and short-term outcome in these PD patients. Analyses of histological and molecular markers as well as long-term outcome are required in the future.

In conclusion, perioperative CUCR is an independent predictor for postoperative complications in pancreatic cancer patients following PD. The CUCR is significantly related to muscle wasting obtained from CT scan. Thus, CUCR constitutes a simple and readily available indicator for patient evaluation and nutritional support.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Characteristics of included patients grouped by CDC

Contents	CDC <3 (n=237)	CDC ≥3 (n=84)	All patients (n=321)	<i>p</i>
Male (%)	122 (51.4)	41 (48.8)	163 (50.8)	0.075
Age	56.7±11.7	67.3±14.2	59.5±13.9	0.019
BMI	23.2±2.6	24.7±3.7	22.6±3.7	0.042
NRS2002	2.5±1.7	3.2±2.1	2.8±1.9	0.267
Systemic comorbidity (n, %)	69 (29.1)	38 (45.2)	107 (39.2)	0.032
Hypertension	64 (27.0)	28 (33.3)	92 (28.7)	0.342
Diabetes mellitus	32 (13.5)	27 (32.1)	59 (18.4)	0.012
Others	19 (8.0)	7 (8.3)	26 (8.1)	0.572
Preoperative creatinine (umol/L)	69.2±25.4	64.1±27.3	67.4±25.3	0.627
Preoperative urea (mmol/L)	6.1 ±2.4	5.4±3.1	5.7±2.7	0.221
Urea to creatinine ratio (UCR)	83.2 (31.3-92.1)	77.3 (34.1-95.5)	79.5 (30.7-96.6)	0.251
eGFR (mL/min/1.73m ²)	98.1±12.1	103.1±11.5	101.2±13.4	0.475
Albumin (g/L)	38.7±4.2	37.3±2.7	38.2±4.1	0.253
Hemoglobin (g/L)	115 (93-130)	111 (92-125)	113 (94-128)	0.316
Postoperative CRP (mg/L)	8.9 (3.3-22.1)	19.3 (7.1-36.4)	10.7 (4.3-29.6)	0.029
Postoperative creatinine (umol/L)	51.3±23.9	41.8±25.7	46.3±26.6	0.036
Postoperative urea (mmol/L)	7.7±2.5	8.2±3.7	7.9±2.7	0.424
Postoperative UCR	125 (53.4-142)	141 (75.2-171)	130 (57.2-156)	0.012
Change of urea to creatinine ratio (CUCR) (%)	68.1 (23.1-89.7)	98.7 (69.2-161)	73.3 (24.2-135)	0.003
Cancer Stage: (n, %)				
I	31 (13.1%)	12 (14.3%)	43 (14.6%)	0.241
II	92 (38.8%)	31(36.9%)	123 (38.3%)	0.461
III and IV	102 (43.0%)	49 (58.3%)	151 (47.0%)	0.043
ACD (kcal/d)	813±214	747±235	806±286	0.321
APD (g/kg/d)	1.15±0.32	1.21±0.29	1.19±0.25	0.453

BMI: body mass index; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ACD: average calorie delivery; APD: average protein delivery.

Table 2. Logistic regression analysis of postoperative complications^{†‡}

	Univariable		Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Albumin	0.77 (0.65-0.92)	0.021	0.83 (0.71-0.97)	0.039	0.93 (0.82-1.13)	0.124	0.97 (0.89-1.08)	0.312
CRP	1.19 (0.95-1.31)	0.123	1.12 (0.94-1.41)	0.189	1.05 (0.91-1.14)	0.372	1.07 (0.83-1.31)	0.413
Creatinine	0.92 (0.82-1.04)	0.043	0.89 (0.71-1.12)	0.040	0.94 (0.83-1.16)	0.081	0.98 (0.81-1.27)	0.112
UCR	1.21 (0.21-1.63)	0.071	1.41 (1.12-1.74)	0.031	1.26 (1.11-1.45)	0.047	1.12 (0.79-1.30)	0.173
Change of Creatinine	0.87 (0.75-1.07)	0.029	0.76 (0.54-0.89)	0.021	0.89 (0.77-1.13)	0.039	0.95 (0.81-1.38)	0.058
CUCR	2.31 (1.87-2.92)	0.000	2.65 (1.91-3.21)	0.000	2.41 (1.78-3.12)	0.005	1.89 (1.52-2.14)	0.015

UCR: XX; CRP: XXX; CUCR: XXX.

[†]UCR and CUCR were analyzed as dichotomous variables with the cohort median as cut-off value. Other factors were analyzed as continuous data.

[‡]Model 1 adjusted for age. Model 2 adjusted for age and BMI. Model 3 adjusted for sex, age and age, BMI and comorbidity.

Table 3. Primary and secondary outcome measures[†]

	All (n=321)	CUCR-L (n=161)	CUCR-H (n=160)	<i>p</i>
Overall major complication (n, %)	84 (26.2)	28 (17.4)	56 (35.0)	0.007
POPF	61(19.0)	23 (14.3)	38 (23.8)	0.013
Biliary leak	23 (7.2)	11 (6.8)	12 (7.5)	0.638
Hemorrhage	17 (5.3)	7 (4.3)	10 (6.2)	0.652
Delayed gastric emptying	23 (7.2)	8 (5.0)	15 (9.4)	0.026
Nosocomial infection	39 (12.1)	12 (7.4)	27 (16.9)	0.014
Cardiac events	11 (3.4)	6 (3.7)	5 (3.1)	0.778
Pulmonary events	33 (10.3)	13 (8.1)	20 (12.5)	0.043
Heptic dysfunction	16 (5.0)	7 (4.3)	9 (5.6)	0.653
Length of hospitalization (d)	18.5±7.9	16.4±5.2	20.6±6.3	0.021
Postoperative time to discharge (d)	12.1±5.3	9.6±4.3	14.6±5.5	0.017
28-day mortality (n, %)	7 (2.2)	3 (1.9)	4 (2.5)	0.078

CUCR: change of urea to creatinine ratio. POPF: postoperative pancreatic fistula; CUCR-L; XXXXXXXX,??

[†] Patients were divided into L-CUCR and H-CUCR group by the median CUCR level of the whole cohort (not consistent, CUCR-L or L-CUCR??)

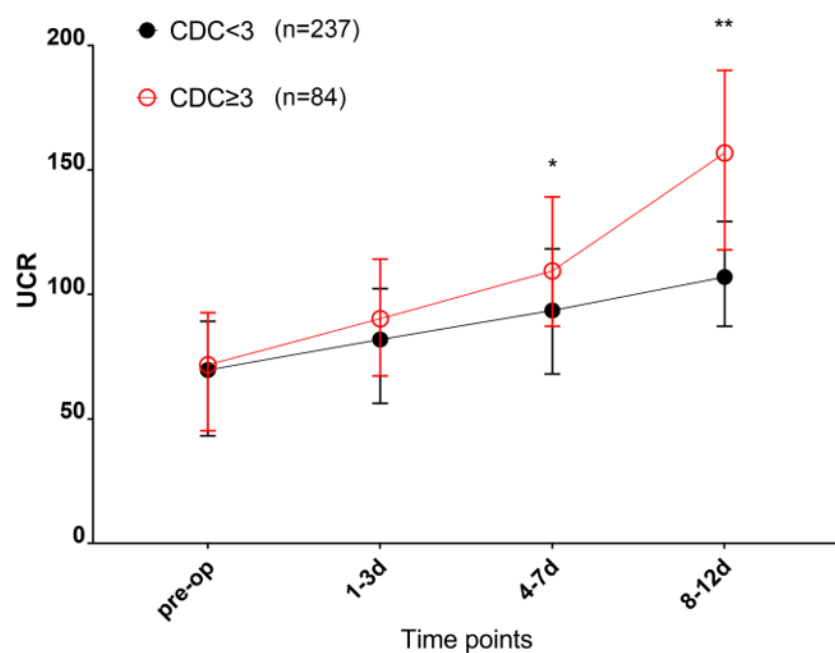


Figure 1. Dynamic changes of UCR in patients with (red) and without (black) major complications. The concentration of urea and creatinine was mmol/L. * indicates $p<0.05$; ** indicates $p<0.01$. UCR: urea to creatinine ratio.

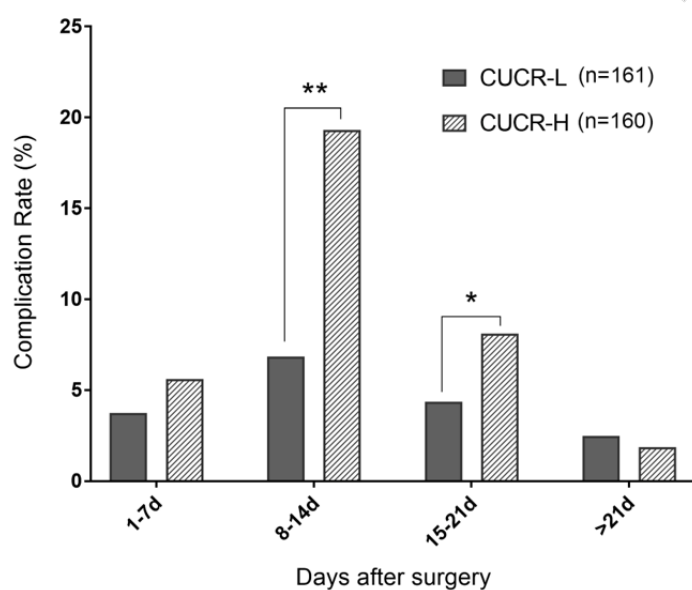


Figure 2. Temporal distribution of complication onset time in CUCR-L and CUCR-H group. CUCR-L group: patients with CUCR value below the median in a week after PD. CUCR-H group: patients with CUCR value above the median in a week after PD. * indicates $p<0.05$; ** indicates $p<0.01$.

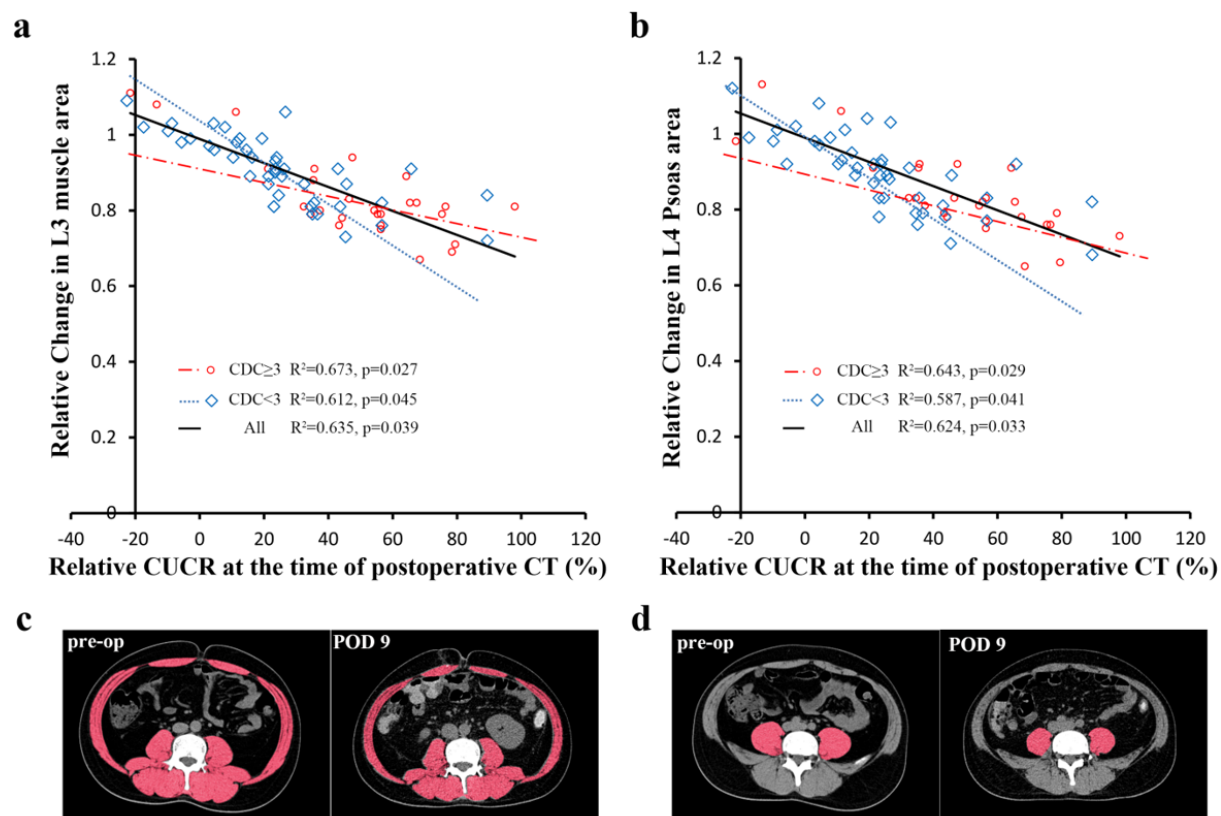


Figure 3. Correlation between CUCR and CT-derived muscle area change. In a subset group ($n=71$) with both pre- and postoperative abdominal CT scans, spearman correlation was utilized to show the relationship between CUCR and the relative change of muscle area in L3 (a) or psoas area in L4 (b). The CUCR was calculated from pre- and postoperative data nearest to the time of the corresponding CT scan. Representative CT image slides show the perioperative change of skeletal muscle area in L3 (c) and the psoas area in L4 (d). The muscle tissue was marked in red. CUCR: the change of urea to creatinine ratio; Pre-op: preoperatively; POD 9: postoperative day 9.

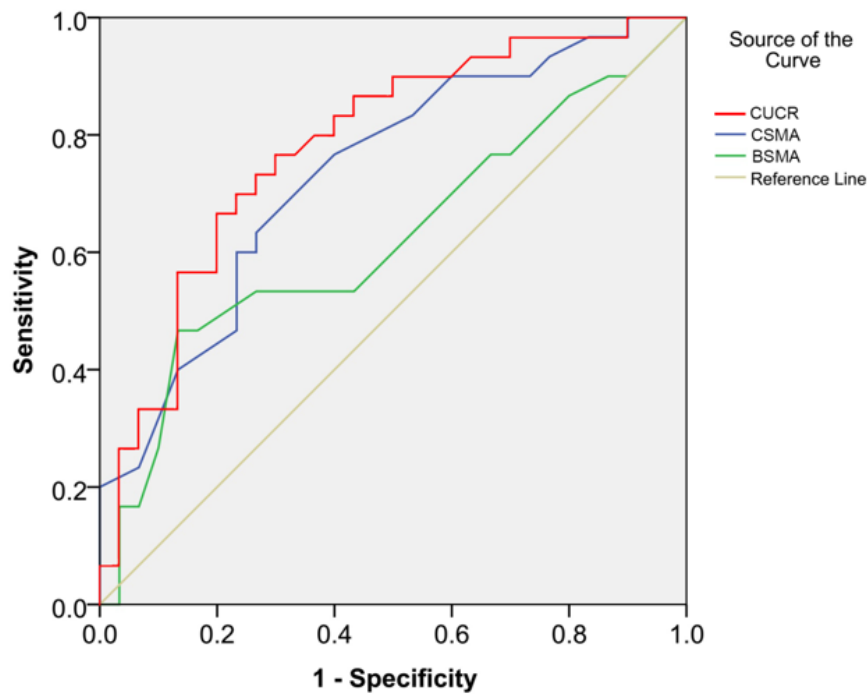


Figure 4. ROC curves for the prediction of complication from CUCR, CSMA and BSMA. The AUC was 0.781, 0.735 and 0.622, respectively. The sensitivity was 0.767, 0.633 and 0.533 respectively. The specificity was 0.700, 0.733 and 0.733 respectively. CUCR, change of urea to creatinine ratio. CSMA, the change of skeletal muscle area. BSMA: the baseline skeletal muscle area.