The Change of Urea to Creatinine Ratio is Associated With Postoperative Complications and Skeletal Muscle Wasting in Pancreatic Cancer Patients Underwent Pancreatoduodenectomy

Kaipeng Duan
The First Affiliated Hospital of Soochow University
Mengting Gong
The First Affiliated Hospital of Soochow University
Xin Gao
The First Affiliated Hospital of Soochow University
Luxin Wei
The First Affiliated Hospital of Soochow University
Dongming Zhu
The First Affiliated Hospital of Soochow University
Jin Zhou (zhoujinsdfyy@126.com)
The First Affiliated Hospital of Soochow University

Research

Keywords: Muscle wasting, urea to creatinine ratio, complications, pancreatoduodenectomy

Posted Date: August 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-60525/v1

Abstract

Background

Surgical Patients with depleted skeletal muscle mass tend to have a worse outcome in the perioperative period, but the muscle mass is difficult to quantify. Here, we aimed to evaluate the relationship of perioperative change of serum urea to creatinine ratio (CUCR) with postoperative complication and skeletal muscle mass in pancreatic cancer patients underwent pancreatoduodenectomy (PD).

Methods

Pancreatic cancer patients underwent PD were included retrospectively. We analyzed the association of serum urea, creatinine, and urea to creatinine ratio (UCR) between patients with and without major postoperative complications. In a subset of patients with serial CT scans, we tested the correlation of the CUCR and the changes of CT-derived skeletal muscle area (SMA). Furthermore, the capacity of complication prediction of CUCR and CT-derived parameter were compared in these patients.

Results

We included 321 surgical patients from January 2014 to July 2020. Patients were grouped with high- and low CUCR according ROC curve (cut-off: 71.3 for male and 67.4 for female). Patients with high CUCR (n=175) have higher complication rate (30.3% vs. 21.1%, p=0.002), including POPF (23.4% vs. 15.1%, p=0.017), infection rate (16.0% vs. 11.0%, p=0.043) and longer postoperative days to discharge (16.7±6.5, vs. 12.1±4.2, p=0.031). Multivariable logistic regression demonstrated CUCR was an independent predictor for complications in these patients, independent of age, sex and BMI. In a subset patients with serial 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).

Conclusion

Perioperative CUCR is an independent predictor for postoperative complications in pancreatic cancer patients underwent PD procedure. Elevated CUCR is a reflection of skeletal muscle wasting in postoperative surgical patients.

Introduction

Pancreatic cancer is one of the leading causes of death in the world, 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 to be the only curative option [2]. For tumor located in the head of the pancreas, pancreatoduodenectomy (PD) was the main procedure for surgical treatment. This invasive and complicated surgery has a high rate of complications, such as postoperative pancreatic fistula (POPF), abdominal infection and bleeding, thus increasing the financial burden and reducing the quality of life [3, 4]. Therefore, identifying the subjects with high risk of postoperative complications seems

pragmatic to address this issue. Recently, body composition analysis has been demonstrated to stratify patients effectively in critical and surgical patents [5-8]. Especially, among pancreatic cancer patients, reduced skeletal muscle mass or density was associated with higher surgical site infection and shortened 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 kind of data may be lost if the patients had no CT scans or did the test in another hospital. Thus, exploiting a more general and stable laboratory indicator to represent skeletal muscle condition seems necessary 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 liver from its precursor amino acid, which may come from exogenous intake and muscle protein degradation. However, the relative long half-time may confine its usage in timely evaluating the metabolic status and muscle condition [12]. Creatinine is the final product of creatine, which is mainly located in muscle tissue and converted into creatinine at a stable rate. Creatinine is released into circulation and exclusively excreted by the kidney. With normal renal function, serum creatinine concentration 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 critical ill population [10, 16]. But the role of creatinine on major abdominal surgery remains to be evaluated. Hence, we tested whether the changes of urea to creatinine ratio (CUCR), as a reflection of muscle catabolism, was related to postoperative complications in pancreatic patients underwent PD. Meanwhile, the relationship between CUCR and CT-derived muscle wasting was examined in our study.

Methods

Patients and data

In this retrospective study, we analyzed the laboratory data and clinical outcomes from 321 pancreatic cancer patients who underwent PD in a tertiary hospital (The First Affiliated Hospital of Soochow University) from January 2014 to July 2020. Inclusion criteria were age of 18 years or older, receiving PD procedure and diagnosed with pancreatic ductal adenocarcinoma (PDAC) by postoperative pathology. Exclusion criteria were with renal or other organ failure, 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 need specific treatment, such as upgrading antibiotics, secondary closure and additional drainage. Second outcome included 28-day mortality, length of postoperative hospitalization. This study was approved by our hospital's medical ethical committee and since it concerned an analysis of anonymized laboratory and clinical data, all 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, prealbumin, albumin, urea, creatinine and urea to creatinine ratio (UCR) (concentrations in mmol/L). Estimated glomerular filtration (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with serum creatinine, sex, and age as input variables [19]. Skeletal muscle area (SMA) was assessed in a subset of patients with both preoperative and postoperative 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 changes of SMA in perioperative period.

Surgical procedure and perioperative management

All patients received Whipple or pylorus-preserving PD procedure 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 closed 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 parenteral nutrition was used as a supplementary part according to the patients' condition. Other management included proton pump inhibitor, antibiotics, anti-coagulation and encouraged early mobilization.

Statistics

Data were expressed as mean and standard deviation (SD) when normally distributed or median and interquartile range (IQR) when skewed. For normally distributed categorical or continuous variables, chi-square test or ANOVA were utilized to determine variances between groups respectively, and Kruskal-Wallis test for continuous variables not normally distributed. ROC curve analysis was used to define the CUCR values best fit to predict complications in female and male patients separately. Univariable analyses were conducted in a set of selective factors as continuous variables. Then, multivariable regression analyses cumulatively included adjustment for sex (model 1), age (model 2), and BMI (model 3).

A dynamic alteration of UCR was compared between patients with and without postoperative major complications. Trajectories of daily blood test results were displayed as rolling medians with 95% confidence interval of the median. Spearman correlation coefficient was employed to the characterized the association between CUCR and abdominal SMA alteration derived from CT scans. The diagnostic capability of CUCR and abdominal SMA on major complication was compared in ROC curves.

SPSS Statistics 22.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Values were reported as mean ± standard deviation (SD) or median and 25–75% interquartile range (IQR). All statistical tests

were two-sided. A $p < 0.05$ was considered statistically significant.

Results

During the study period, a total of 495 patients underwent PD procedure, of which 362 patients were diagnosed with pancreatic cancer from postoperative pathology. Thirty-two patients were with renal or other organ dysfunctions, and seven were excluded because of incomplete data. Therefore, 321 patients were eligible for final analysis. Furthermore, a subgroup of 71 patients with both digital pre- and postoperative abdominal CT scans was analyzed to examine the relationship between skeletal muscle information and clinical markers. Figure 1 was the consort diagram showing the inclusion process.

Patient characteristics

Patient characteristics were presented in table 1, grouped by high or low CUCR values. The cut-off value of CUCR was determined by ROC curves in predicting postoperative complications (cut-off 71.3 for male and 67.4 for female). Of all these patients, the mean age and BMI were 59.5±13.9 years and 22.6±3.7, respectively. The postoperative creatinine and urea in the table 1 were referring to those tested about one week after surgery. Serum creatinine has shown a reduction after surgery, from 69.4 ± 25.8 umol/L to 49.3 ± 26.1 umol/L ($p < 0.05$), whereas serum urea has presented with an increase from 5.7 ± 2.7 mmol/L to 7.9 ± 2.9 mmol/L ($p < 0.05$). The rate of major complication was 26.2%, including 19.6% for POPF and 13.7% for infection. The postoperative time to discharge and 28-day mortality were 14.6±6.2 days and 2.80%, respectively.

One hundred and seventy-five subjects had high CUCR, with a higher mean age ($p=0.033$), and higher CRP level ($p=0.041$). The sex ratio, BMI, nutritional risk score and systemic comorbidity were comparable in two groups. There was also no significant difference in the main blood test between the two groups. Of note, high CUCR group has a higher complication rate (30.3% vs. 21.1%, $p=0.002$), higher POPF (23.4% vs. 15.1%, $p=0.017$), higher infection (16.0% vs. 11.0%, $p=0.043$) and longer postoperative days to discharge (16.7±6.5, vs. 12.1±4.2, $p=0.031$).

Table 1
Characteristics of included patients grouped by CUCR.

Contents	Low CUCR group (n=146)	High CUCR group (n=175)	All Patients (n=321)	p
Male (%)	71 (48.1%)	92 (53.5%)	163 (51.3%)	0.322
Age	58.7 ± 11.7	62.3 ± 14.2	59.5 ± 13.9	**0.033**
BMI	23.1 ± 3.4	22.2 ± 4.1	22.6 ± 3.7	0.619
NRS2002	2.7 ± 1.6	2.9 ± 1.7	2.8 ± 1.9	0.167
Systemic comorbidity (n, %)	56(38.4%)	70(40.0%)	107(39.2%)	0.412
hypertension	39(26.7%)	48(27.4%)	87(27.1%)	0.337
Diabetes mellitus	26(17.8%)	33(18.8%)	46(18.4%)	0.532
Others	11(7.5%)	15(8.6%)	43(8.1%)	0.417
Preoperative Creatinine (umol/L)	76.2 ± 23.4	65.1 ± 29.2	69.4 ± 25.8	0.521
Preoperative Urea (mmol/L)	6.6 ±2.4	5.3 ± 3.1	5.7 ± 2.7	0.124
Urea to Creatinine Ratio (UCR)	75.1 (35.2-89.1)	78.3 (30.1-96.5)	77.5 (33.7-93.6)	0.781
eGFR (mL/min/1.73m^2)	93.32 ± 8.1	96.14 ± 10.5	95.05 ± 9.4	0.375
Albumin (g/L)	38.5 ± 4.2	37.8 ± 3.9	38.2 ± 4.1	0.172
Hemoglobin (g/L)	117.2 (98.2-131.2)	112.5 (96.2-125.3)	114.1 (97.2-128.4)	0.343
Postoperative CRP (mg/L)	8.1 (3.3-10.1)	11.3 (2.1-16.4)	7.7 (2.7-10.6)	**0.041**
Postoperative creatinine (umol/L)	54.3 ± 21.6	45.7 ± 27.4	49.3 ± 26.1 *	0.021
Postoperative urea (mmol/L)	7.8 ± 2.4	8.1 ± 3.4	7.9 ± 2.9 *	0.324
Postoperative UCR	124.1 (56.4-147.2)	137.2 (58.2-167.3)	129.5 (57.2-156.1) *	**0.017**
CUCR (%)	56.6 (19.1-92.7)	89.2 (47.2-154.2)	73.3 (24.2-134.5)	**<0.001**
Cancer Stage: (n, %)				
I	19 (13.0%)	28 (16.0%)	43 (14.6%)	0.264
II	57 (39.0%)	66 (37.7%)	123 (38.3%)	0.432
III and IV	70 (48.0%)	81 (46.3%)	151 (47.0%)	0.785

IPNT (d)	3.2 ± 2.1	3.5 ± 2.3	3.3 ±2.4	0.351
ACD(kcal/d)	812 ± 235	797 ± 265	806 ± 286	0.612
APD(g/kg/d)	1.17 ± 0.22	1.22 ± 0.19	1.19 ± 0.25	0.532
Major complications (n, %)	31 (21.2%)	53(30.3%)	84(26.2%)	**0.002**
POPF	22(15.1%)	41(23.4%)	63(19.6%)	**0.017**
Nosocomial infection	16(11.0%)	28(16.0%)	44(13.7%)	**0.043**
Length of hospitalization (d)	17.5 ± 7.3	21.2 ± 8.1	18.5 ± 7.9	0.125
Postoperative time to discharge (d)	12.1 ± 4.2	16.7 ± 6.5	14.6 ± 6.2	**0.031**
28-day mortality (n,%)	4 (2.74%)	5 (2.86%)	9 (2.80%)	0.676
CUCR: change of urea to creatinine ratio. BMI: body mass index. UCR: urea to creatinine ratio. CRP: C-reactive protein. IPNT: initial parenteral nutrition time, ACD: average calorie delivery, APD: average protein delivery. POPF: postoperative pancreatic fistula. * indicates $p < 0.05$, compared with corresponding preoperative data.				

Trajectories of laboratory tests in patients with and without major complications

The dynamic changes of UCR were depicted in figure 2. Data was allocated to four time points: baseline (preoperative value), postoperative 1-3 days, 4-7 days and 8-12 days. The complication group (CDC≥3) has a significant higher UCR at the third and fourth time points (102.1, 87.2-139.2 vs. 94.3, 68.1-118.3, $p<0.05$; 162.7, 117.9-190.0 vs. 104.6, 87.2-129.3, $p<0.01$), while the first two time points showed no difference. In patients with major complications, we also showed the trajectory relative alteration of several routine blood markers, including prealbumin, albumin, urea, creatinine and UCR (figure 3). Compared to preoperative values, prealbumin, albumin and creatinine showed a reduction trend, and creatinine displayed with a relative lagging change than prealbumin and albumin. Urea and UCR were demonstrated with an arch-shape elevation than baseline value. Particularly, UCR showed a more distinct increase than urea.

Association between CUCR and postoperative complications

At univariable analysis, major complication was 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 multivariable logistic

regression analyses, after adjusted for sex, age and BMI, only CUCR remains significant in associated postoperative complication (OR 1.89, 95%CI 1.52-2.14, p=0.015). (Table 2)

Table 2
Logistic regression analysis of postoperative complications.

	Univariable		Model 1		Model 2		Model 3	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
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**

CUCR was analyzed as continuous data. Model 1 adjusted for sex. Model 2 adjusted for sex, age. Model 3 adjusted for sex, age and BMI.

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

In a subset of 71 patients, digital pre- and postoperative abdominal CT scans were obtained. Preoperative CT was examined within one week of surgery, and postoperative CT was examined between one to two weeks 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 cm^2 (145 - 181) to 140 cm^2 (126 - 167), and L4-psoas by 16%, from 31 cm^2 (24 - 45) to 26 cm^2 (15 - 36). The median CUCR in these patients was 76.8% increase (31.6-131.7). Through spearman correlation analysis, 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).

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

Discussion

In this retrospective study, we for the first time found the perioperative CUCR was associated with postoperative major complications in pancreatic cancer patient underwent PD, independent of important covariates and confounders. Meanwhile, the CUCR was correlated well with the change of SMA derived from CT scans and can be used as clinical parameter for complication prediction.

It was appealing to risk stratify surgical and critical patients and target those who might benefit the most. Traditionally, performance status and nutritional status were the widely adopted approaches [21–24]. However, the former is relatively subjective and the latter lacks unified standard. BMI was considered to be a prominent factor affecting patient short- and long-term status [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]. But sarcopenic or obese patients may also have normal BMI. Therefore, body composition analysis is increasingly gained attention in nutritional assessment and risk stratification [29]. Martin et al demonstrated 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]. Our present study also revealed baseline skeletal mass has a diagnostic potency in postoperative complication (Fig. 5). However, data acquisition of skeletal muscle or body composition requires CT or special instrument, which limited its clinical application.

Patients with skeletal muscle wasting may display with various phenotypes, such as reduced BMI, cachexia, frailty and deranged biochemical indicator. Two large observational studies have revealed 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-come mortality in AKI patients [34]. Since urinary creatinine is closely related serum creatinine and its production, it has been reported early low urinary creatinine excretion was a strong risk factor for both short- and long-term mortality in ICU patients without renal dysfunction [16].

Our study has shown serum creatinine concentration reduced by 29.0%, from 69.4 ± 25.8 umol/L to 49.3 ± 26.1 umol/L, and urea concentration increased by 38.6%, from 5.7 ± 2.7 mmol/L to 7.9 ± 2.9 mmol/L, a week after PD in all patients. What potential pathophysiology underlies these changes? 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 tightly-linked relationship between serum and intramuscular creatine content [13], the early reduction of serum creatinine in our study may result from the altered metabolism and bioenergetic failure in skeletal muscle. The elevating of urea lasted more than ten days after surgery. We considered this was the reflection of skeletal muscle catabolism and amino acid liberation. Thus combining the two divergent markers might distinguish patients with different catabolism extent.

ROC curves shown the cut-off values of CURC in predicting postoperative complication were 71.3 for male and 67.4 for female, respectively. The high CURC group showed higher rate of complication, including POPF and nosocomial infection, and longer span of postoperative time to discharge. Further multivariable analysis revealed the CUCR was the only risk factor for complication after adjusted by sex, age and BMI confounders. This result was consistent with previous studies. In patients with acute kidney injury (AKI), a raised urea to creatinine ratio has been demonstrated to be a risk factor for survival [36, 37]. A large retrospective study reported elevated urea to creatinine ratio was significantly associated with prolonged persistent critical illness after trauma [10]. These changes are an indication of skeletal muscle wasting [32]. As we observed the CURC was correlated well with the change of SMA in L3 level and psoas derived CT-scans. This was in line with the results of Haines' research which focused on critical trauma patients. They have found 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 urea to creatinine ratio at the time of second CT negatively correlated with these muscle areas [10].

What mechanism contributed to the muscle wasting observed in our patients? Systemic inflammation as reflected by elevated CRP levels may have a crucial role in the process. Mechanism studies have shown several cytokines, including TNF-α, IL-1β, and NF-κB activation can cause severe muscle wasting [38–41]. Besides, a close and direct relationship has established between intramuscular inflammation and anabolic signaling [35]. Particularly, in these 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 for muscle wasting [39, 41–43].

In the present study, we demonstrated the dynamic change of several indicators for metabolism and nutrition. Of particular interest, the turning point occurred around 8–12 days after surgery. This metabolic trajectory is akin to those 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 can hardly be reversed by nutrition support [35, 45, 46]. About one week later, the late phase ensues when anabolism increases and there is 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. Among these indicators, UCR displayed with a more distinctive change. Hence, it may be referable in the clinical practice, but this required further researches.

In the ROC curve, CUCR and CSMA had a comparable potency in predicting postoperative complication, which is superior to that of BSMA. This result indicates the wasting process is more detrimental than the baseline nutritional conditions. Meanwhile, the higher UCR in patients with CDC $\geq$ 3 in two weeks after

surgery also support this assumption. Indeed, other than CT scan, several methods can be used to quantify the change of skeletal muscle mass [29]. Repeated ultrasonography shows promising results in detecting muscle wasting in several studies [47, 48]. However, tissue edema and interobserver reliability should be taken into consideration when interpret the results [49]. Bioelectrical impedance analysis (BIA) is another non-invasive and easy method to gain insight into body composition [50]. But the accuracy is affected when patients is with large fluids shifts. Therefore, a simpler and reliable test to measure muscle wasting is on demand in the future.

Our present study does have some intrinsic limitations. First, the retrospective research precluded the absolute unification of testing time in perioperative period, hence we employed time interval. Second, even though the initial time and contents of PN show no significant difference, the serum urea and creatinine level could be affected by hypovolemia, bleeding and renal function. Third, the serial CT scans were only available in a subset of included patients, which weakened the association between CUCR and muscle wasting in the study. Finally, we only compared the routine test and short-term outcome in these PD patients. Analysis on histological and molecular markers as well as long-term outcome are required in the future research.

Conclusion

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

Abbreviations

PD: pancreatoduodenectomy; CUCR: change of serum urea to creatinine ratio; UCR: urea to creatinine ratio; SMA: skeletal muscle area; POPF: postoperative pancreatic fistula; PDAC: pancreatic ductal adenocarcinoma; CDC: Clavien-Dindo Classification; BMI: body mass index; CRP: C - reactive protein; L3: third lumbar; BSMA: baseline skeletal muscle area; CSMA: the change of skeletal muscle area; AUC: areas under the curve; PN: parenteral nutrition; IPNT: initial parenteral nutrition time, ACD: average calorie delivery, APD: average protein delivery.

Declarations

Acknowledgments

The authors declare that they have no competing interests. This research was supported by National Natural Science Foundation (81700788).

Funding

This research was supported by National Natural Science Foundation (81700788).

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author’s contributions

Conceived and designed the study: Dongming Zhu, Jin Zhou. Kaipeng Duan. Data collection and analysis: Kaipeng Duan, Mengting Gong, Xin Gao. Drafting the article: Kaipeng Duan, Luxin Wei. Final approval of the version to be submitted: all authors.

Competing interests

The authors declare that they have no competing interests. This research was supported by National Natural Science Foundation (81700788).

Consent for publication

All images in this manuscript are entirely unidentifiable and do not include any personal details, therefore no consent for publication was obtained

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University. The need for informed consent was waived because of the retrospective nature of the study using only data obtained from standard care.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. Cancer J Clin. 2019;69(1):7–34.
2. Spadi R, Brusa F, Ponzetti A, Chiappino I, Birocco N, Ciuffreda L, Satolli MA. Current therapeutic strategies for advanced pancreatic cancer: A review for clinicians. World J Clin Oncol. 2016;7(1):27–43.
3. van der Gaag NA, Harmsen K, Eshuis WJ, Busch ORC, van Gulik TM, Gouma DJ. Pancreatoduodenectomy associated complications influence cancer recurrence and time interval to

death. European journal of surgical oncology: the journal of the European Society of Surgical Oncology the British Association of Surgical Oncology. 2014;40(5):551–8.

4. Sugiura T, Uesaka K, Ohmagari N, Kanemoto H, Mizuno T. Risk factor of surgical site infection after pancreaticoduodenectomy. World journal of surgery. 2012;36(12):2888–94.
5. Weijs PJ, Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, Beishuizen A. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Critical care. 2014;18(2):R12.
6. Toledo DO, Carvalho AM, Oliveira A, Toloi JM, Silva AC, Francisco de Mattos Farah J, Prado CM, Silva JM, Jr. The use of computed tomography images as a prognostic marker in critically ill cancer patients. Clinical nutrition ESPEN. 2018;25:114–20.
7. Sandini M, Bernasconi DP, Fior D, Molinelli M, Ippolito D, Nespoli L, Caccialanza R, Gianotti L. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. Nutrition. 2016;32(11–12):1231–7.
8. Jang M, Park HW, Huh J, Lee JH, Jeong YK, Nah YW, Park J, Kim KW. Predictive value of sarcopenia and visceral obesity for postoperative pancreatic fistula after pancreaticoduodenectomy analyzed on clinically acquired CT and MRI. European radiology. 2019;29(5):2417–25.
9. van Dijk DP, Bakens MJ, Coolsen MM, Rensen SS, van Dam RM, Bours MJ, Weijenberg MP, Dejong CH, Olde Damink SW. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. Journal of cachexia sarcopenia muscle. 2017;8(2):317–26.
10. Haines RW, Zolfaghari P, Wan Y, Pearse RM, Puthucheary Z, Prowle JR. Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma. Intensive care medicine. 2019;45(12):1718–31.
11. Efron PA, Mohr AM, Bihorac A, Horiguchi H, Hollen MK, Segal MS, Baker HV, Leeuwenburgh C, Moldawer LL, Moore FA, et al. Persistent inflammation, immunosuppression, and catabolism and the development of chronic critical illness after surgery. Surgery. 2018;164(2):178–84.
12. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth. 2000;85(4):599–610.
13. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiological reviews. 2000;80(3):1107–213.
14. Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: the Heart and Soul Study. Circulation. 2010;121(11):1295–303.
15. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clinical journal of the American Society of Nephrology: CJASN. 2008;3(2):348–54.
16. Hessels L, Koopmans N, Gomes Neto AW, Volbeda M, Koeze J, Lansink-Hartgring AO, Bakker SJ, Oudemans-van Straaten HM, Nijsten MW. Urinary creatinine excretion is related to short-term and

long-term mortality in critically ill patients. Intensive care medicine. 2018;44(10):1699–708.

17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205–13.
18. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8–13.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
20. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. **A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care**. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 2008, 33(5):997–1006.
21. Zampieri FG, Iwashyna TJ, Viglianti EM, Taniguchi LU, Viana WN, Costa R, Correa TD, Moreira CEN, Maia MO, Moralez GM, et al. Association of frailty with short-term outcomes, organ support and resource use in critically ill patients. Intensive care medicine. 2018;44(9):1512–20.
22. Zampieri FG, Bozza FA, Moralez GM, Mazza DD, Scotti AV, Santino MS, Ribeiro RA, Rodrigues Filho EM, Cabral MM, Maia MO, et al. The effects of performance status one week before hospital admission on the outcomes of critically ill patients. Intensive care medicine. 2017;43(1):39–47.
23. Hutagalung R, Marques J, Kobylka K, Zeidan M, Kabisch B, Brunkhorst F, Reinhart K, Sakr Y. The obesity paradox in surgical intensive care unit patients. Intensive care medicine. 2011;37(11):1793–9.
24. Mogensen KM, Robinson MK, Casey JD, Gunasekera NS, Moromizato T, Rawn JD, Christopher KB. Nutritional Status and Mortality in the Critically Ill. Critical care medicine. 2015;43(12):2605–15.
25. Abhyankar S, Leishear K, Callaghan FM, Demner-Fushman D, McDonald CJ. Lower short- and long-term mortality associated with overweight and obesity in a large cohort study of adult intensive care unit patients. Critical care. 2012;16(6):R235.
26. Pickkers P, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. Critical care medicine. 2013;41(8):1878–83.
27. Sakr Y, Alhussami I, Nanchal R, Wunderink RG, Pellis T, Wittebole X, Martin-Loeches I, Francois B, Leone M, Vincent JL, et al. Being Overweight Is Associated With Greater Survival in ICU Patients: Results From the Intensive Care Over Nations Audit. Critical care medicine. 2015;43(12):2623–32.
28. Hartrumpf M, Kuehnel RU, Albes JM. The obesity paradox is still there: a risk analysis of over 15 000 cardiosurgical patients based on body mass index. Interact Cardiovasc Thorac Surg. 2017;25(1):18–24.

29. Looijaard W, Molinger J, Weijs PJM. Measuring and monitoring lean body mass in critical illness. Curr Opin Crit Care. 2018;24(4):241–7.
30. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013;31(12):1539–47.
31. Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Twisk JW, Oudemans-van Straaten HM, Weijs PJ. Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. Critical care. 2016;20(1):386.
32. Cartin-Ceba R, Afessa B, Gajic O. Low baseline serum creatinine concentration predicts mortality in critically ill patients independent of body mass index. Critical care medicine. 2007;35(10):2420–3.
33. Udy AA, Scheinkestel C, Pilcher D, Bailey M, Australian, New Zealand Intensive Care Society Centre for O, Resource E. The Association Between Low Admission Peak Plasma Creatinine Concentration and In-Hospital Mortality in Patients Admitted to Intensive Care in Australia and New Zealand. Critical care medicine. 2016;44(1):73–82.
34. Mildh H, Pettila V, Korhonen AM, Karlsson S, Ala-Kokko T, Reinikainen M, Vaara ST, Group FS. Three-year mortality in 30-day survivors of critical care with acute kidney injury: data from the prospective observational FINNAKI study. Ann Intensiv Care. 2016;6(1):118.
35. Puthucheary ZA, Astin R, McPhail MJW, Saeed S, Pasha Y, Bear DE, Constantin D, Velloso C, Manning S, Calvert L, et al. Metabolic phenotype of skeletal muscle in early critical illness. Thorax. 2018;73(10):926–35.
36. Uchino S, Bellomo R, Goldsmith D. The meaning of the blood urea nitrogen/creatinine ratio in acute kidney injury. Clinical kidney journal. 2012;5(2):187–91.
37. Rachoin JS, Daher R, Moussallem C, Milcarek B, Hunter K, Schorr C, Abboud M, Henry P, Weisberg LS. The fallacy of the BUN:creatinine ratio in critically ill patients. Nephrology dialysis transplantation: official publication of the European Dialysis Transplant Association - European Renal Association. 2012;27(6):2248–54.
38. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine Signaling in Skeletal Muscle Wasting. Trends Endocrinol Metab. 2016;27(5):335–47.
39. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nature reviews Drug discovery. 2015;14(1):58–74.
40. Cai D, Frantz JD, Tawa NE Jr, Melendez PA, Oh BC, Lidov HG, Hasselgren PO, Frontera WR, Lee J, Glass DJ, et al. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell. 2004;119(2):285–98.
41. Duan K, Chen Q, Cheng M, Zhao C, Lin Z, Tan S, Xi F, Gao T, Shi J, Shen J, et al. Hypothalamic activation is essential for endotoxemia-induced acute muscle wasting. Scientific reports. 2016;6:38544.

42. Bonaldo P, Sandri M. Cellular and molecular mechanisms of muscle atrophy. Dis Models Mech. 2013;6(1):25–39.
43. Braun TP, Zhu X, Szumowski M, Scott GD, Grossberg AJ, Levasseur PR, Graham K, Khan S, Damaraju S, Colmers WF, et al. Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis. The Journal of experimental medicine. 2011;208(12):2449–63.
44. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clinical nutrition. 2019;38(1):48–79.
45. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Guiza FG, Wouters PJ, Mesotten D, Van den Berghe G. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Critical care medicine. 2013;41(10):2298–309.
46. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, Meersseman P, Derese I, Mesotten D, Wouters PJ, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. The Lancet Respiratory medicine. 2013;1(8):621–9.
47. Puthucheary ZA, Phadke R, Rawal J, McPhail MJ, Sidhu PS, Rowlerson A, Moxham J, Harridge S, Hart N, Montgomery HE. Qualitative Ultrasound in Acute Critical Illness Muscle Wasting. Critical care medicine. 2015;43(8):1603–11.
48. Selva Raj I, Bird SR, Shield AJ. Ultrasound Measurements of Skeletal Muscle Architecture Are Associated with Strength and Functional Capacity in Older Adults. Ultrasound Med Biol. 2017;43(3):586–94.
49. Mourtzakis M, Parry S, Connolly B, Puthucheary Z. Skeletal Muscle Ultrasound in Critical Care: A Tool in Need of Translation. Annals of the American Thoracic Society. 2017;14(10):1495–503.
50. Kuchnia A, Earthman C, Teigen L, Cole A, Mourtzakis M, Paris M, Looijaard W, Weijs P, Oudemans-van Straaten H, Beilman G, et al. Evaluation of Bioelectrical Impedance Analysis in Critically Ill Patients: Results of a Multicenter Prospective Study. JPEN Journal of parenteral enteral nutrition. 2017;41(7):1131–8.

Figures

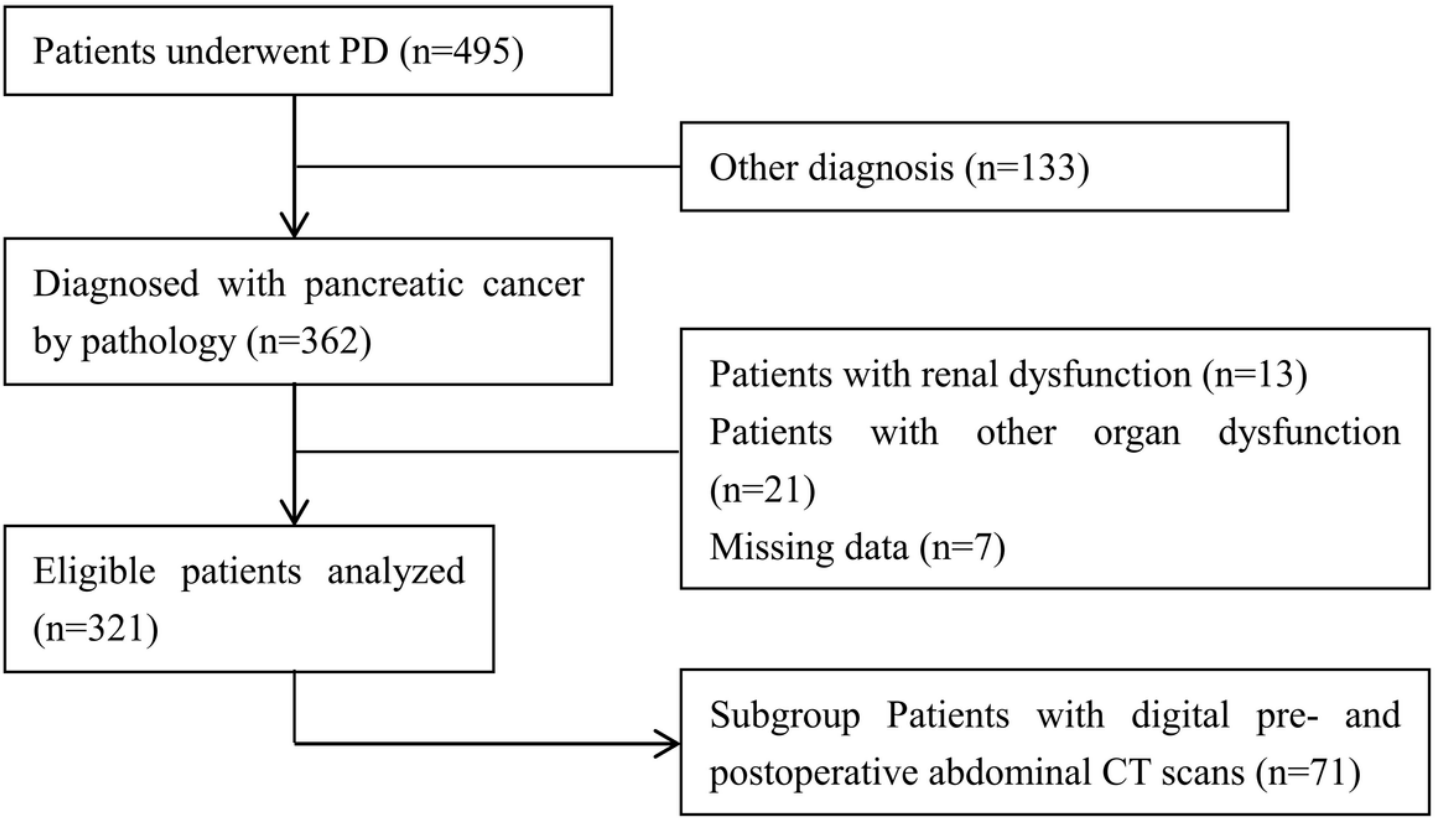

Figure 1

Flowchart of patients included into the analysis.

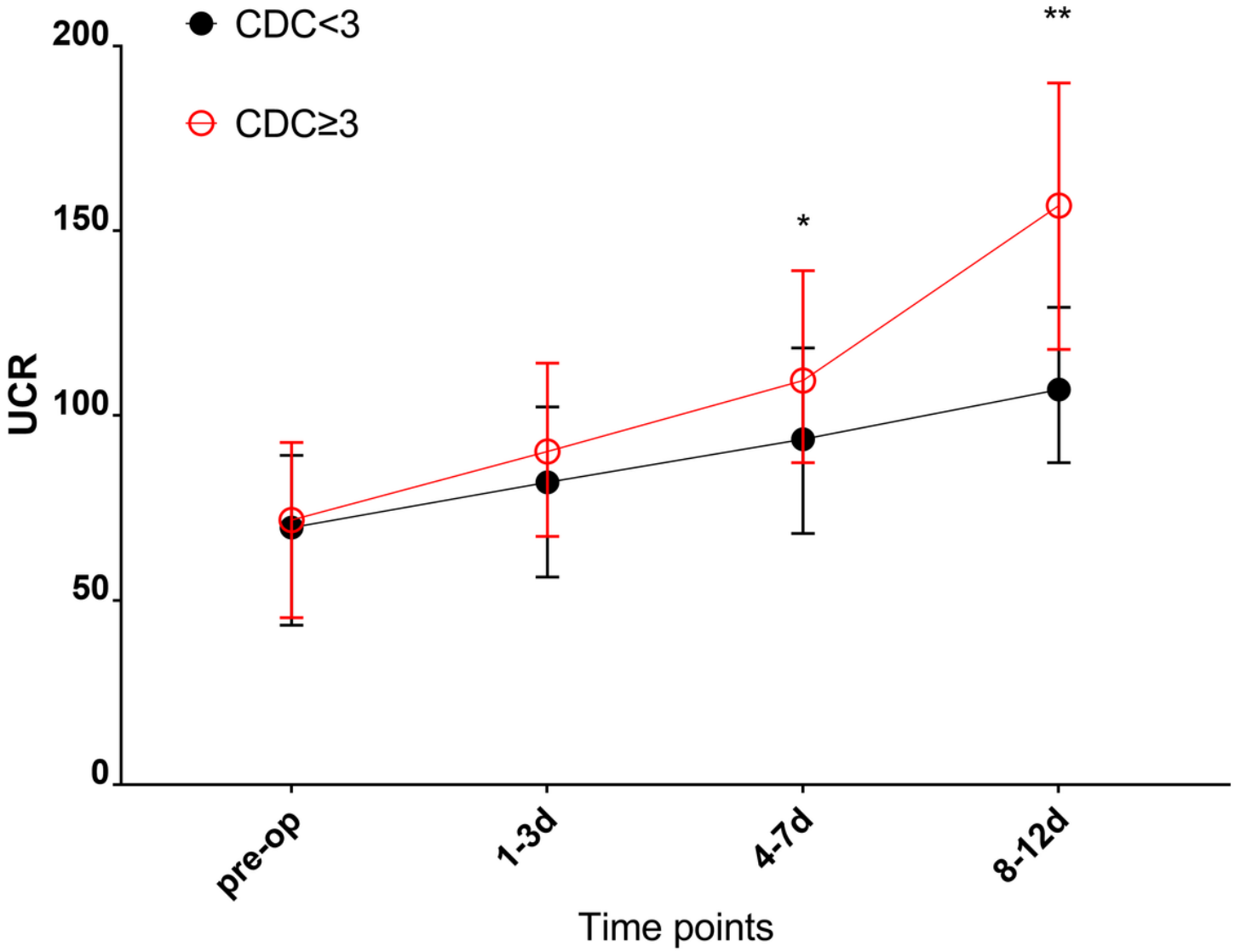

Figure 2

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.

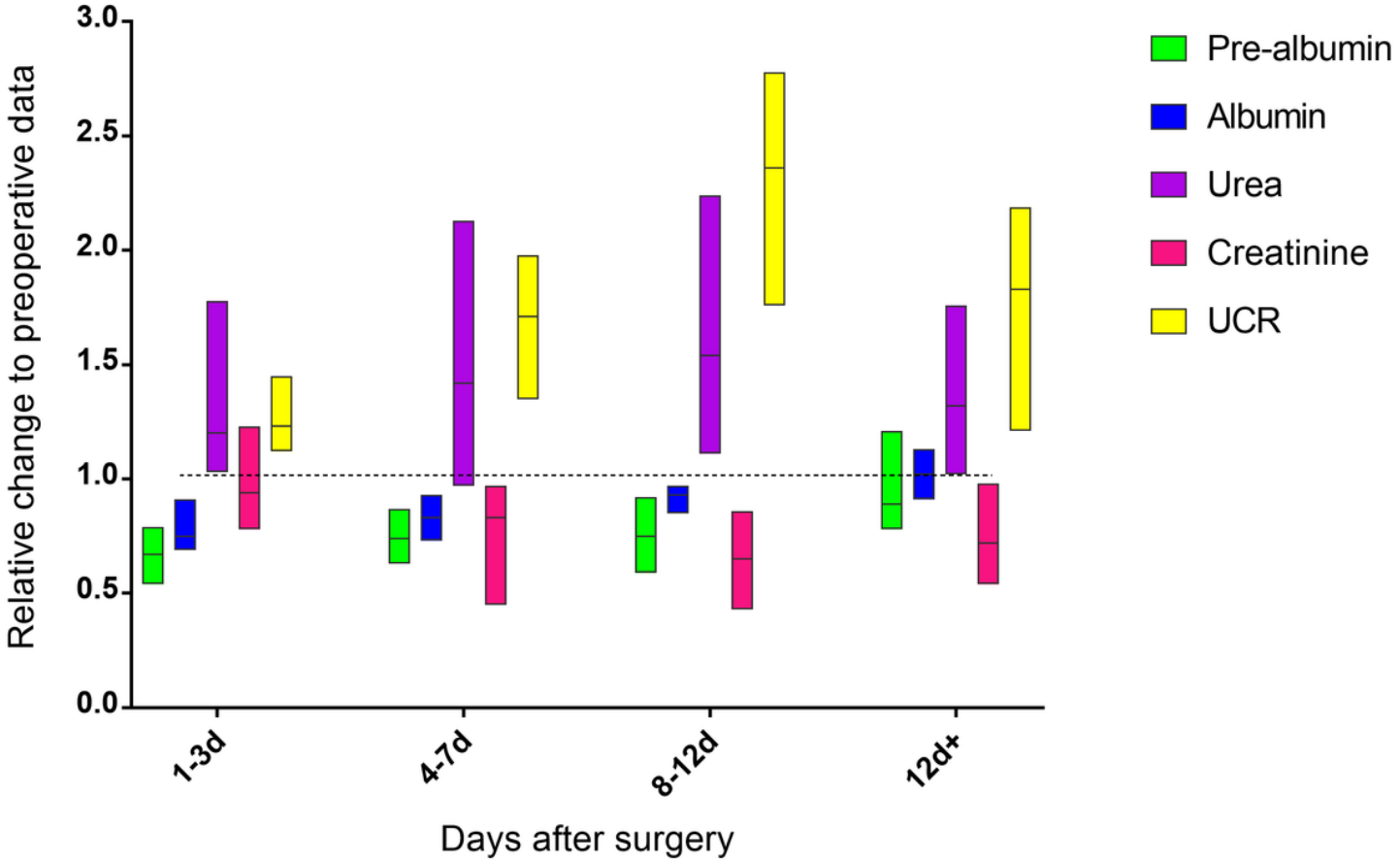

Figure 3

The postoperative trajectory alteration of blood markers in patients with major complications (data were depicted as median and 25-75% IQR).

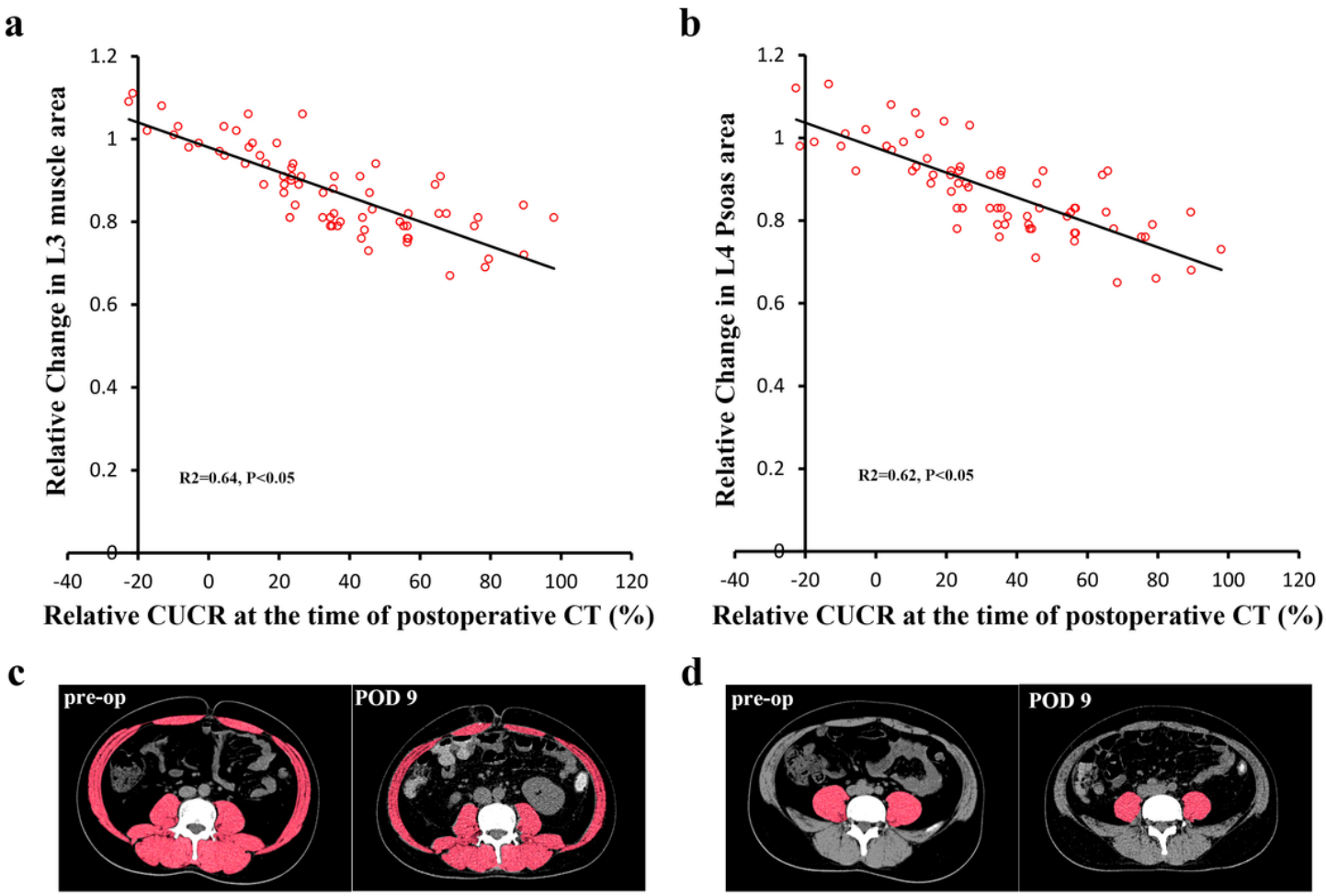

Figure 4

Correlation between CUCR and CT-derived muscle area change. In a subset group (n=71) with pre- and postoperative 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.

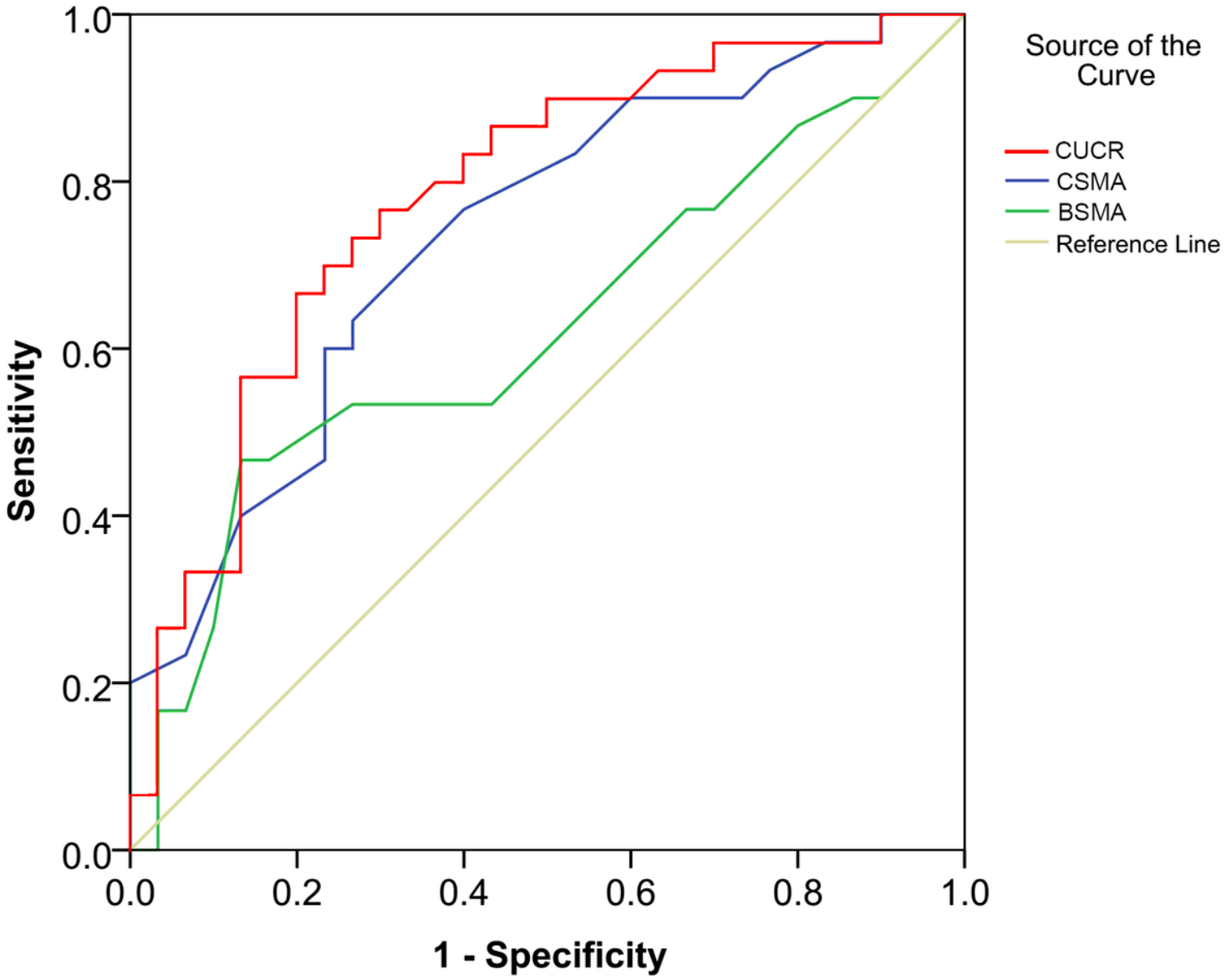

Figure 5

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, the change of urea to creatinine ratio. CSMA, the change of skeletal muscle area. BSMA, the baseline skeletal muscle area.