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

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Research

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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 pancreateoduodenectomy (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, pancreateoduodenectomy (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).
| 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/1.73m²)                   | 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 |
### Table

|                | Group 1 | Group 2 | Group 3 | p-value |
|----------------|---------|---------|---------|---------|
| **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 |
| Albumin          | 0.77 (0.65-0.92) | 0.021 | 0.83 (0.71-0.97) | 0.039 |
| CRP              | 1.19 (0.95-1.31) | 0.123 | 1.12 (0.94-1.41) | 0.189 |
| Creatinine       | 0.92 (0.82-1.04) | 0.043 | 0.89 (0.71-1.12) | 0.040 |
| UCR              | 1.21 (0.21-1.63) | 0.071 | 1.41 (1.12-1.74) | 0.031 |
| Change of Creatinine | 0.87 (0.75-1.07) | 0.029 | 0.76 (0.54-0.89) | 0.021 |
| CUCR             | 2.31 (1.87-2.92) | 0.000 | 2.65 (1.91-3.21) | 0.000 |

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 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 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 area (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 ≥ 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**

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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.

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**Figures**
Figure 1

Flowchart of patients included into the analysis.

Patients underwent PD (n=495)

Diagnosed with pancreatic cancer by pathology (n=362)

Eligible patients analyzed (n=321)

Other diagnosis (n=133)

Patients with renal dysfunction (n=13)
Patients with other organ dysfunction (n=21)
Missing data (n=7)

Subgroup Patients with digital pre- and postoperative abdominal CT scans (n=71)
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.