

Title:

Urinary titin as a potential biomarker of sarcopenia and its association with postoperative complications in colorectal cancer patients

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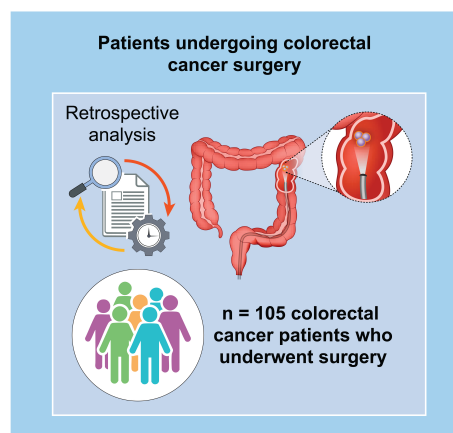
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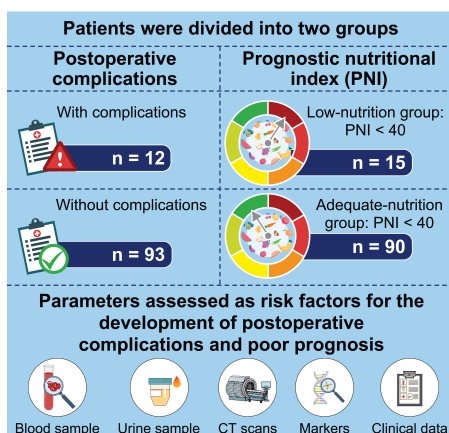
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Urinary Titin (U-Tin) - A New Indicator of Postoperative Complication in Colorectal Cancer

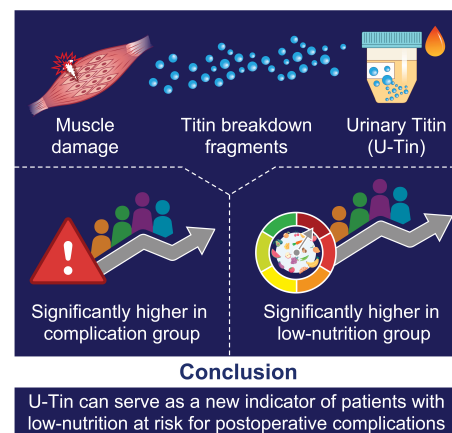
Study population



Methods



Outcomes



Urinary titin as a potential biomarker of sarcopenia and its association with postoperative complications in colorectal cancer patients

Running title: Urinary titin as an indicator in colorectal cancer

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Abbreviations: Urinary Titin (U-Tin), Psoas Volume (PV), Prognostic Nutritional Index (PNI), Lymphocyte Monocyte Ratio (LMR), Platelet Lymphocyte Ratio (PLR), Neutrophil Lymphocyte Ratio (NLR), CRP Albumin Ratio (CAR), Alkaline Phosphatase (ALP), Modified-Glasgow Prognostic Score (mGPS), Body Mass Index (BMI; kg/m²), Cholineelastase (Ch-E)

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Lay summary

Background and Purpose of the Study:

Incidences of colorectal cancer are increasing with the growing elderly population. Sarcopenia, an age-related decline in skeletal muscle mass, is associated with increased postoperative complications, making prevention and management crucial. The Prognostic Nutritional Index, a method used for nutritional assessment, has gained much attention, and it is reportedly associated with postoperative complications and sarcopenia. No direct biomarker exists for sarcopenia, prompting focus on titin, a giant elastic protein found in skeletal muscle. This study evaluated the association between colorectal cancer postoperative complications, Prognostic Nutritional Index, and psoas major muscle volume, investigating whether urinary titin could serve as a novel indicator for postoperative complications.

Methods

The study included 105 patients who underwent colorectal cancer surgery. The patients were divided into groups based on postoperative complications (presence/absence) and Prognostic Nutritional Index (≥ 40 or < 40). Urinary titin and psoas muscle volume were evaluated in all participants and risk factors were assessed statistically.

Results

Of the 105 patients, 63 were men and 42 were women, with a median age of 75 years. Twelve patients developed postoperative complications. Comparison between groups revealed a significant tendency for higher urinary titin levels in the complication group. Fifteen patients had a Prognostic Nutritional Index of < 40 , indicating a significant tendency for higher urinary titin levels in a Prognostic Nutritional Index of < 40 .

Conclusion

Urinary titin is a potential new indicator for postoperative complications following colorectal cancer surgery.

Abstract

Introduction: Studies suggest that older individuals are at risk colorectal cancer postoperative complications following colorectal cancer owing to preoperative sarcopenia, and the prevention of these complication is crucial. The Prognostic Nutritional Index is a preoperative nutritional assessment, and its association with postoperative complications and sarcopenia have been previously reported.

Purpose: A reduction in skeletal muscle mass is essential for diagnosing sarcopenia, there are no available biomarkers that evaluate this. Thus, we focused on titin, a giant elastic protein present in skeletal muscle.

Material and methods: This study was conducted as a prospective observational cohort study. A total of 105 patients who underwent colorectal cancer surgery in our department were included in the study. The patients were divided into two groups: those with and those without postoperative complications of Clavien–Dindo classification II or higher, and those with Prognostic Nutritional Index of 40 or higher or lower. Using blood samples, nutritional markers, inflammatory markers, urinary titin, and psoas volume, univariate and multivariate analyses were performed between the two groups to examine risk factors.

Results: Postoperative complication group comprised 12 patients, and comparisons between the two groups revealed a trend toward higher urinary titin in the group with complications with significant differences in univariate and multivariate analysis. The group with Prognostic Nutritional Index of <40 comprised 15 patients, and both analysis showed a trend toward higher urinary titin in the Prognostic Nutritional Index of <40 group with significant differences.

Conclusion: Urinary titin may serve as a potential marker associated with postoperative complications.

Keywords: Colorectal cancer. Postoperative complications. Sarcopenia. Urinary titin.

Key Points

Study population: The study population comprised 105 patients scheduled for colorectal cancer surgery at the Department of Gastroenterological Surgery of a

university-affiliated hospital from October 2021 to December 2023.

Methods: Patients were divided into groups with and without postoperative complications classified as Clavien–Dindo (C–D) grade II or higher for comparison. Patients were additionally divided into two groups based on Prognostic Nutritional Index (PNI) scores (≥ 40 or < 40) using 40 as the cutoff value for comparison. Correlations between urinary titin (U-Tin) and albumin levels, PV, and postoperative hospitalization duration were examined.

Results: U-Tin showed significant differences between the complication-free and complication-present groups as well as between the PNI-high and PNI-low groups. U-Tin also correlated with albumin levels, PV, and postoperative hospital stay.

Conclusion: U-Tin demonstrated potential as a new indicator of postoperative complications in colorectal cancer patients.

Introduction

With the recent increase in the elderly population, prevention and management of age-related increases in frailty, sarcopenia, and other geriatric syndromes have become imperative. Frailty refers to the general age-related changes in terms of physical, mental, and social aspects, and has been found to be a risk factor for postoperative complications and poor prognosis (1). Sarcopenia is classified as primary and secondary sarcopenia. Primary sarcopenia is solely an effect of aging, whereas secondary sarcopenia is a state of reduced muscle mass caused by reduced activity (disuse atrophy), malnutrition, organ failure, and malignancy, and constitutes a part of frailty (1, 2). Many patients with gastrointestinal cancers are believed to be malnourished and have a high prevalence of sarcopenia. Furthermore, malnutrition and sarcopenia have also been associated with postoperative complications, prolonged hospital stays, and survival period (3). Malnutrition before colorectal cancer surgery is often due to increased catabolism and decreased food intake caused by malignancy, often resulting in secondary sarcopenia. Thus, presence of sarcopenia during colorectal cancer surgery has a significant postoperative impact, making preoperative assessment of sarcopenia crucial in patients with colorectal cancer (4-6). Sarcopenia diagnosis algorithms have been reported in Asia and Europe (2, 3, 7, 8). However, the Prognostic Nutritional Index (PNI) proposed by Onodera et al. is widely used to assess the nutritional status and immunity of patients undergoing surgery, and has shown some effectiveness in predicting postoperative complications and disease outcomes (9). There are also increasing reports linking PNI and sarcopenia (10). Sarcopenia diagnosis requires measurement of skeletal muscle mass using bioelectrical impedance analysis, dual energy X-ray absorptiometry, and skeletal muscle index (SMI) using computed tomography (CT). SMI, which is commonly used for skeletal muscle evaluation in gastrointestinal diseases, is based only on the height of the third lumbar vertebra by CT. Additionally, the measurement-taking procedure is complicated and time consuming, making it difficult to accurately determine the amount of skeletal muscle. Recently, the volume of the psoas major muscle mass calculated using 3DCT has made it possible to measure skeletal muscle mass. This software is easy to use, and there is an increasing number of reports evaluating sarcopenia using skeletal muscle

mass (5). However, there are no biomarkers that evaluate skeletal muscle itself using blood or urine samples, and their emergence has been anticipated.

Titin, a giant elastic fiber protein found in skeletal muscle, spans approximately half of the sarcomere from the Z band to the M line. Specifically, the N-terminal region, which interacts with numerous proteins and contributes to functional sensitivity, structural integrity, and force transmission, is increasingly attracting attention as the first protein to be broken in skeletal muscle (11–13). Various reports describe titin measurement in determining the diagnosis and pathophysiology of muscular dystrophy and myocardial infarction with skeletal muscle damage and atrophy, suggesting that it may also be useful in understanding the status of sarcopenia (14).

Herein, we focused on titin, a giant elastic protein present in skeletal and other muscles, and examined whether urinary titin (U-Tin) and psoas volume (PV) are related to preoperative nutritional status and postoperative complications in patients with colorectal cancer, and whether U-Tin can serve as a new indicator of postoperative complications in colorectal cancer.

Methods

Patient Selection: Study population

This is a prospective cohort study and complies with the STROBE criteria. The subject sample included 105 patients were prospectively enrolled to undergo surgery for colorectal cancer from October 2021 to December 2023 at the Department of Gastroenterological Surgery of a university-affiliated hospital.

- Inclusion criteria: Patients without preoperative colon cancer–related ileus or perforation.
- Exclusion criteria: Patients with obstructive colon cancer and poor preoperative general condition.

Ethical Considerations:

This study was conducted in accordance with the Declaration of Helsinki (1975, revised 2008) and the regulations of the Japanese Ministry of Health, Labour and Welfare. This study was approved by the Research Ethics Committee of XXXX (Ethics Permit No. XXXX).

Urinary titin N-terminal fragment concentration assay:

For the spot urine (2.0 mL) measurement of U-Tin, in principle, urine samples were prospectively collected as part of the study protocol approximately 1 month before surgery. Urine samples were stored at -80°C until analysis. U-Tin was measured by titin N-Fragment Assay IBL, ELISA kit (IBL Co., Ltd., Gunma, Japan). Measured values were corrected with urinary creatinine in consideration of concentrated or diluted urine as follows: $\text{Titin-N fragment value (pmol/mg/Cr)} = \text{measured titin-N fragment value (nmol/L)} \times 100 \div \text{urinary Cr value (mg/dL)}$ (15).

To minimize U-Tin measurement variability, all samples were batch-processed using same-lot reagents and analyzed by a single blinded tester. Urine samples were centrifuged immediately after collection and stored at -80°C with one or fewer freeze–thaw cycles. U-Tin values were corrected by urinary creatinine (pmol/mg Cr) to reduce dilution effects.

Skeletal muscle mass measurement:

Skeletal muscle measurements were taken using CT images taken less than 30 days before surgery, and the PV was measured using the 3D image analysis system SYNAPSE VINCENT (FUJIFILM: V6.8.0177 Tokyo, Japan). The PNI was measured based on the PNI (O-PNI) by Onodera using the following formula: $10 \times \text{Alb (g/dL)} + 0.005 \times \text{total lymphocyte count/mm}^3$ (according to the PNI by Onodera).

Classification of Study Subjects

1 Intergroup comparison:

1)The patients were divided into two groups: those with and without postoperative complications of Clavien–Dindo (C-D) classification II or higher (16). C–D classification was determined by consensus among five gastrointestinal surgeons involved in postoperative management during the patient's hospitalization.

2)PNI was used to compare two groups of patients with PNI above and below 40, using 40 as the cutoff value.

2 Evaluation items

Sex, age, length of postoperative hospital stay, disease stage as well as blood and urine samples for U-Tin (nmol/L), PV, lymphocyte monocyte ratio (LMR), platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), CRP albumin ratio (CAR), modified-Glasgow Prognostic Score (mGPS), GFR, creatinine, total cholesterol, CRP, body mass index (BMI; kg/m²), choline elastase (Ch-E), alkaline phosphatase (ALP), urinary creatinine, and creatine kinase.

Statistical analysis

EZR (version 1.54, Saitama, Tokyo) was used for statistical analysis. Categorical data were compared using, T test, Mann–Whitney U-test, and Fisher's exact test, as appropriate. Correlations were depicted as scatter plots and analyzed using Pearson's test. Multivariate logistic regression analysis was performed using a two-variable model consisting of U-Tin and one clinically essential covariate (albumin or BMI) in order to avoid overfitting. P-value of <0.05 was considered statistically significant.

Missing data:

All clinically relevant variables, including U-Titin, PV, albumin, CRP, and PNI, had no missing values in this dataset. Therefore, no data imputation or exclusion due to missingness was required, and all analyses were conducted using complete data.

Sample size

Patients were divided into C–D classification groups of II or higher and less than II. The difference in mean U-Tin values between the two groups was 6.5, with a standard deviation of 7.4. The estimated postoperative complication rate for colorectal cancer was 8% (17).

Assuming a two-sided test with an α value of 0.05 and 80% power, the target sample size for the study was calculated to be 104 patients: 12 patients with C–D classification II or higher and 92 patients with stage I.

Sensitivity Analysis:

To evaluate the robustness of the key analysis results, sensitivity analyses were

performed.

- U-Tin was analyzed by classifying values into quartile groups.
- The outcome definition was changed from Clavien–Dindo grade II or higher to grade III or higher, and the analysis was repeated.

Internal Validation

A logistic regression model using U-Tin alone as the explanatory variable was constructed to predict postoperative complications (C–D grade II or higher). To assess potential overfitting, internal validation was conducted using 1,000 bootstrap samples. The mean difference between the Area Under the Curve (AUC) within the bootstrap samples and the AUC applied to the original dataset was estimated as the optimism bias, and the optimism-corrected AUC was then calculated.

Results

The 105 patients comprised 63 men and 42 women with a median age of 75 years (40–93), median U-Tin of 6.09 nmol/L (1.3–41.8), and median PV of 212.8 cm³ (61.8–675.9). The median duration of postoperative hospitalization was 11 days (3–87).

1) Comparison of patients with and without postoperative complications

Complications of Clavien–Dindo classification II or higher were reported in 12 cases (11%), including 8 males and 4 females.

Diseases included 4 cases of paralytic ileus, 2 cases of wound infection, 2 cases of suture failure, 1 case of cardiac failure, 1 case of pneumonia, 1 case of disseminated intravascular coagulation, and 1 case of acute subdural hematoma.

- Univariate analysis of Predictors in those with and without postoperative complications of Clavien–Dindo classification II or higher.

U-Tin ($P = 0.004$) levels were significantly higher in the group with and without postoperative complications, while PNI, Alb, Ch-E, and urinary creatinine were significantly higher in the group with complications (Table 1).

PV showed no significant difference. ($P = 0.5$)

- Multivariate analysis of predictors in Clavien–Dindo classification grade II or higher.

Only U-Tin showed a tendency to be higher in the complication group with a significant difference ($P = 0.01$) (Table 1).

2) Intergroup comparison based on Prognostic Nutritional Index (PNI) level.

There were 15 cases (13%) with PNI less than 40, including 10 men and 5 women.

- Univariate analysis of predictors for preoperative nutritional status using Prognostic Nutritional Index.

U-Tin, BMI, Total cholesterol, CRP, mGPS, WBC, Hemoglobin, Ch-E, and platelet counts showed significant differences between groups. (Table 2)

- Multivariate analysis of predictors for preoperative nutritional status using Prognostic Nutritional Index.

U-Tin values tended to be higher in the PNI of <40 group with a significant difference ($P = 0.00$) (Table 2).

3) Correlation with U-Tin

- Relationship between U-Tin and Alb

U-Tin showed a negative correlation with Alb (correlation coefficient = -0.4 , 95% confidence interval -0.5 to 0.2 , P -value = 0.0001) (Fig. 1).

- Relationship between U-Tin and PV

U-Tin showed a negative correlation with PV (correlation coefficient = -0.2 , 95% confidence interval -0.4 to 0.04 , P -value = 0.002) (Fig. 2).

- Relationship between U-Tin and length of postoperative hospital stay

U-Tin showed a positive correlation with postoperative hospital stay (correlation coefficient = 0.4 , 95% confidence interval 0.2 – 0.5 , P -value = 0.00004) (Fig. 3).

Sensitivity Analysis

When postoperative complication rates were compared across U-Tin quartiles, the highest quartile demonstrated the greatest incidence of complications at 23.1%.

Logistic regression analysis treating U-Tin as a continuous variable also showed a significant association with postoperative complications (OR 1.08, $P = 0.013$), supporting the findings from the primary analysis. Moreover, when the definition of

complications was restricted to those classified as Clavien–Dindo grade III or higher ($n = 7$), U-Tin remained significantly associated with postoperative complications (OR 1.12, $P = 0.002$), further confirming the robustness of the study results.

Internal Validation

Internal validation demonstrated that the apparent AUC of the U-Tin model was 0.63, with an estimated optimism of 0.02 calculated using the bootstrap method. This yielded an optimism-corrected AUC of 0.62. Despite the relatively small cohort, the model was considered to have a modest but meaningful level of discriminatory ability.

Discussion

In this study, we examined whether titin could serve as a new indicator to assess the risk of postoperative complications of colorectal cancer and preoperative nutritional status.

Titin is the largest of the known proteins. In humans, titin has a molecular mass of 3816 kDa, length of 1.2 μm , and is expressed in rhabdomyosarcoma (skeletal and cardiac muscle). It is a structural sarcomere protein, the contractile structural unit of rhabdomyosarcoma muscle, and is the third most abundant protein component after myosin and actin. Titin extends from the Z line through myosin to the middle of the sarcomere and fixes it like a spring from both sides (5, 18). Moreover, titin is degraded by proteolytic enzymes such as calpain and matrix metalloproteinases, and is excreted in the urine when striated muscle injury occurs (19).

Few reports of gastrointestinal diseases have analyzed the relationship between U-Tin and preoperative malnutrition or sarcopenia, and Oshida et al. reported elevated U-Tin in patients with sarcopenia and nonalcoholic fatty liver disease (20). Furthermore, Miyoshi et al. reported that U-Tin is an indicator of preoperative sarcopenia and nutritional status in patients with gastrointestinal and hepatobiliary pancreatic malignancies (15).

Furthermore, Hirayama et al. reported that PV is useful in the diagnosis of sarcopenia (21). However, in the present study, PV showed no significant difference from PNI or postoperative complications. Whereas, U-Tin and PV were shown to be correlated,

indicating that PV may be a useful means to diagnose sarcopenia.

The present study showed that in patients with colorectal cancer, higher U-Tin levels were associated with lower serum albumin, reduced plasma volume, and longer postoperative hospital stays. Furthermore, U-Tin was significantly higher in the postoperative complication group and the malnourished group in univariate and multivariate analyses. These findings suggest that U-Tin may serve as a potential biomarker for identifying patients at increased risk of postoperative complications.

Unlike diseases such as myocardial infarction and muscular dystrophy, which are directly affected by muscle damage, cancer-related sarcopenia is thought to be caused by chronic muscle damage or skeletal autolysis due to cachexia, which causes titin to be released into the urine (17).

A growing number of facilities are now offering exercise therapy and nutritional interventions to improve nutritional status and sarcopenia (22). However, much of the skeletal muscle mass loss in colorectal cancer patients is thought to be due to decreased activity level and insufficient protein supply to skeletal muscle due to poor nutritional status, and excessive exercise therapy aimed at increasing muscle mass might cause further muscle damage in malnourished, sarcopenic patients with reduced muscle mass (15). Therefore, it may be necessary to assess the muscle condition such as by measuring U-Tin before starting an appropriate exercise therapy. Additionally, it is conceivable that the introduction of exercise and preoperative nutritional therapy would further improve malnutrition and sarcopenia, and thereby reduce the risk of postoperative complications.

This study has several limitations. First, it was a single-center prospective analysis with a relatively small sample size, which limited the ability to evaluate U-Tin concentrations according to colorectal cancer stage. Future studies with larger cohorts are needed to analyze stage-specific differences in U-Tin levels.

Second, because no missing data were observed for any clinically relevant variables, the risk of bias due to missingness is considered minimal.

Additionally, although internal validation using bootstrap resampling suggested that the prediction model incorporating U-Tin alone had reasonable discriminatory ability with limited overfitting, external validation has not yet been performed. As this study

was conducted at a single institution, the generalizability of the findings remains limited.

Therefore, multicenter studies with larger and more diverse patient populations are required, particularly to standardize U-Tin measurement as a non-invasive biomarker.

Finally, the associations identified in this study should be interpreted as exploratory. U-Tin should be considered a potential biomarker rather than a definitive diagnostic indicator at this stage. Future research should focus on validating U-Tin cutoff values for identifying sarcopenia and malnutrition across broader gastrointestinal cancer populations.

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Table

Table1. Univariate and multivariate analysis of predictors for postoperative complications (Clavien–Dindo \geq II)

Variable	Univariate analysis			Multivariate analysis			
	Complications \geq II (n=12)	Complications <II (n=93)	P- value	Odds ratio	95%CI lower	95%CI upper	P- value
U-Tin	14.16 \pm 13.6	7.62 \pm 6.0	0.004	1.09	1.02	1.17	0.01
Albumin	3.3 \pm 0.8	3.7 \pm 0.6	0.04	0.10	0.005	2.2	0.1
Age	78.8 \pm 7.2	72.52 \pm 11.6	0.07				
Sex (F/M)	4/8	38/55	0.8				
PHP	23.5 \pm 13.8	11.6 \pm 4.11	0.00				
PNI	44.63 \pm 11.4	50.82 \pm 8.6	0.02				
PV	211.06 \pm 64.3	231.06 \pm 98.5	0.5				
BMI	21.9 \pm 3.0	22.5 \pm 3.4	0.5				
Prealbumin	18.40 \pm 7.6	20.2 \pm 6.3	0.4				
GFR	55.4 \pm 22.1	65.3 \pm 17.8	0.08				
CRE	1.11 \pm 0.6	0.95 \pm 0.9	0.6				
T-Chol	180.3 \pm 65.4	179.7 \pm 40.8	1.0				
CRP	2.8 \pm 1.3	2.0 \pm 0.8	0.4				
Hb	11.0 \pm 2.7	12.1 \pm 2.3	0.1				
PLT	26.6 \pm 7.9	25.3 \pm 7.8	0.6				
mGPS	0.6 \pm 0.8	0.6 \pm 0.8	0.9				
D-C (I–IV)	2.1 \pm 0.5	2.1 \pm 1.1	1.0				
Ch-E	207.4 \pm 86.3	260.3 \pm 83.4	0.04				
U-CRE	54.6 \pm 30.3	109.5 \pm 91.0	0.04				
Ck	71.3 \pm 53.9	78.6 \pm 45.9	0.6				

U-Tin showed significant differences in univariate and multivariate analyses.

Postoperative Hospitalization Period (PHP), Urinary Titin (U-Tin), Prognostic Nutritional Index (PNI), Psoas Volume (PV), Body Mass Index (BMI; kg/m²), Creatinine (CRE), Total Cholesterol (T-Chol), Glasgow Prognostic Score (mGPS), Hemoglobin (Hb), Platelet

Count (PLT), Choline esterase (Ch-E), Urinary Creatinine (U-CRE), Disease Classification (D-C), Creatine Kinase (CK), 95% CI (95% confidence interval)

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Table 2: Univariate and multivariate analysis of preoperative nutritional status using PNI

Variable	Univariate analysis			Multivariate analysis				
	PNI < 40 (n = 15)	PNI ≥ 40 (n = 90)	P-value	RCE	95% CI lower	95% CI upper	SE	P-value
U-Tin	12.2±11.5	7.7 ± 6.4	0.03	-0.4	-0.6	0.2	0.1	0.00
BMI	20.9± 3.2	22.8± 3.4	0.04	0.9	0.4	1.3	0.2	0.00
Sex (F/M)	3/12	39/58	0.76					
Age	74.9± 10.3	72.1± 12	0.4					
PHP	17.46±20.1	12.8± 7.1	1.0					
PV	205.5± 69.6	233.2±99	0.3					
GFR	64.2± 27.1	64.2±17	1.0					
CRE	1.3 ± 1.6	0.9 ± 0.7	0.09					
T-chol	124.2± 30.3	189.0±38	0.001					
CRP	3.9 ± 4.3	0.4 ± 0.6	0.001					
mGPS	1.8 ± 0.4	0.4 ± 0.6	0.00					
WBC (×10 ³)	7.9 ± 3.3	6.0 ± 1.7	0.00					
Hb	9.3 + 1.8	12.4± 2.1	0.00					
PLT	31.2± 7.3	24.5± 7.5	0.00					
Ch-E	138.1± 44.7	273.6±74	0.00					
U-CRE	87.7± 57.1	105.6±92	0.5					
D-C(I-IV)	2.5 ± 0.4	2.0 ± 1.0	0.1					

U-Tin showed significant differences in univariate and multivariate analyses.

Urinary Titin (U-Tin), Psoas Volume (PV), Body Mass Index (BMI; kg/m²), Creatinine (CRE), Total cholesterol (T-Chol), Glasgow Prognostic Score (mGPS), White Blood Cell Count (WBC), Hemoglobin (Hb), Platelet Count (PLT), Cholineelastase (Ch-E), Urinary Creatinine (U-CRE), Disease Classification (D-C), Regression Coefficient Estimates (RCE),

95%CI(95% confidence interval), Standard Error(SE)

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Figure Legends

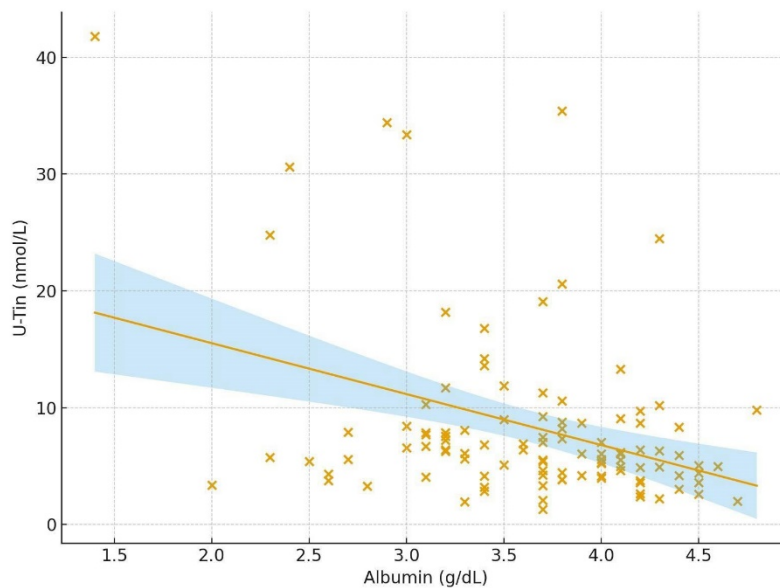


Figure 1. Correlations between U-Tin and Albumin.

U-Tin showed a negative correlation with Albumin.

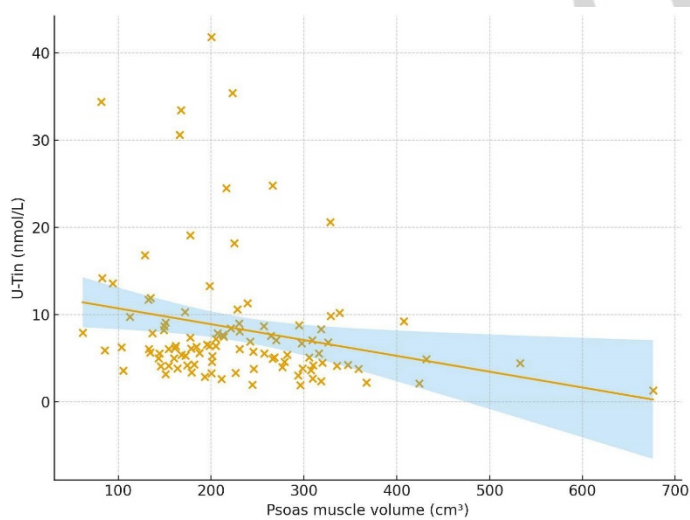


Figure 2. Correlation between U-Tin and Psoas Volume (PV).

U-Tin showed a negative correlation with Psoas Volume (PV)

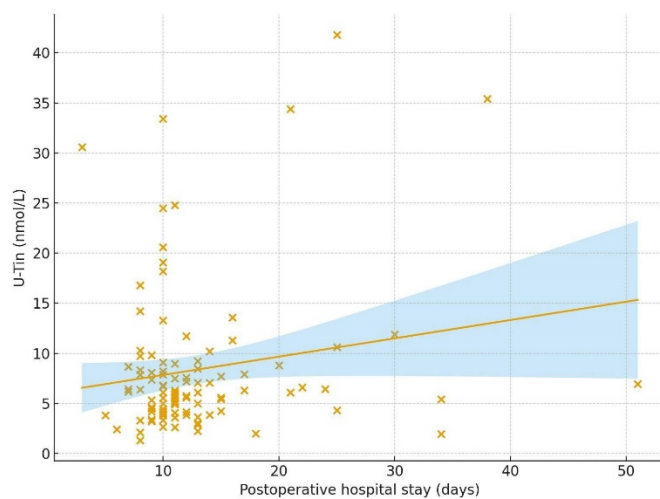


Figure 3. Correlation between U-Tin and postoperative hospitalization duration.

U-Tin showed a positive correlation with postoperative hospital stay.