PRE-FRAIL - Decoding and Preventing Frailty After Robotic-assisted Surgery: Investigating Biomarkers and Clinical Outcomes in Urinary Tract Cancer Patients

- Findings from a retrospective cohort study -

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Preface

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Abstract

Background and Objective: Bladder cancer primarily affects older, comorbid, and frail patients, making radical cystectomy a high-risk procedure with potential for major complications. Previous studies using 2D CT analyses have suggested correlations between body composition and postoperative outcomes, but readmissions, a secondary concern, may also place additional strain on healthcare resources. This study explores whether 3D AI-based analysis of preoperative CT scans can use body composition (CTBC) parameters to predict patients at higher risk of complications or readmission in patients undergoing robotic-assisted radical cystectomy at AaUH in 2020-2025.

Methods: This study included 134 patients with bladder cancer (BC) undergoing robotic-assisted radical cystectomy. Logistic univariate regression was used to assess the association between CTBC-parameters and major complications (defined by a Clavien–Dindo classification at or above grade 3), or readmission rate. Finally, LASSO regression and ROC curves were performed.

Results: In relation to major complications, univariable-adjusted logistic regression showed no significant associations between CTBC parameters and major complications. Consequently, the LASSO regression and the corresponding ROC yielded an AUC of 0.5.
In the univariable adjusted logistic regression for readmissions, intramuscular adipose tissue index (IMATI) was found to be associated with readmission [OR, 1.11; 95% CI, 1.03-1.21; $P = 0.01$]. No association was found between readmission rate and the remaining measured CTBC-parameters. Additionally, the LASSO regression and the corresponding ROC curve yielded an AUC of 0.676.

Conclusion: This study found no associations between CTBC-parameters and major complications. LASSO found an AUC of 0.5, which correlates to random chance. Furthermore, IMATI was statistically associated with readmission. However, LASSO regression and the corresponding ROC yielded an AUC of 0.676, which was deemed clinically insignificant. A larger sample size may be necessary to find a possible association and predictive variables between 3D-measured CTBC-parameters and major complications or readmission in BC patients undergoing robotic-assisted cystectomy.

Contents

Introduction

Due to improved healthcare, nutrition, and technology, the elderly population is increasing globally [1]. According to 2019 data, the number of people aged 65 years and older has increased from 0.35 billion to 0.78 billion over the past 30 years. It is predicted to reach 1.55 billion in 2050 [2]. As life expectancy increases, the incidence and prevalence of age-related diseases such as cancer increase simultaneously [3, 4]. This includes urological cancers, where the median age of diagnosis is above 70 years [5].

Urological cancers (UC) consist of several diseases, the three most common being bladder, kidney, and prostate cancer. UCs make up 2.6 million of the 19 million worldwide reported cancer incidents annually [6]. In Denmark, a total of 917 new cases of invasive bladder cancer were registered in 2024. Of these cases, 31% were surgically treated with cystectomy, 28% received irrigation treatment with the Bacillus Calmette–Guérin (BCG) intravesical instillation, and 11% received radiation therapy [7, 8]. Treatment of these diseases includes surgery, radiation, and chemotherapy [9]. The standard surgical approach to bladder cancer (BC) with curative intent is radical cystectomy (RCx), where a male patient's bladder, prostate, and seminal vesicles are removed. For females, the bladder and reproductive organs are removed [9].

Elderly BC patients constitute a very heterogeneous group, and have a widely accepted heightened risk of postoperative complications due to increased possibilities of more complex health statuses, comorbidities, polypharmacy, and cognitive impairment [10]. This ultimately results in a population that is generally more frail and carries an increased risk of surgery-related complications [11]. These complications may range from insignificant bleeding and infections to multi-organ failure and mortality. The most widely used measure of post-surgical complications is the Clavien-Dindo Scale (CDC), which grades complications from I to V [12]. Furthermore, a CDC grade of III and above implies a major complication, where additional invasive treatment is required.

Due to remarkable medical advances over the last 20 years, BC patients now have better treatment options. Routine use of advanced imaging increases the detection of cancers at an early stage [13]. In particular, the implementation of robot-assisted surgeries improves the surgical outcomes of localised UC [14]. Danish national cancer guidelines ensure that surgical treatment of suspected BC begins within 7-16 days from referral [15]. However, following these guidelines leaves little time for the surgeon to assess whether the patient is a RCx candidate. When assessing possible RCx candidates, the surgeon performs routine preoperative assessments with anaesthetic support based on the American Society of Anesthesiology (ASA), the Charlson Comorbidity Index (CCI), medical history, physical examination and laboratory tests. In addition, a cancer-diagnostic abdominal computed tomography (CT) scan is performed to clinically assess tumour localisation and possible metastases. Ultimately, these assessments should provide insight for the surgeon to make the decision if surgery could be an appropriate treatment option for the individual patient.

The combination of advanced age, comorbidities, and increased frailty requires a qualified preoperative assessment to identify elderly patients who potentially carry a higher risk of peri- and postoperative complications. Unfortunately, no universally agreed upon screening or diagnostic tool for frailty exists, but the 11-item modified Frailty Index is the most studied in RCx patients [16]. Therefore, the systematic use of validated preoperative risk assessment and screening tools for elderly patients undergoing surgery needs further investigation and implementation [17].

Several studies have used Artificial Intelligence (AI)-based or fully automated image analysis to calculate body composition [18]. The advantage of AI is that it is fast and efficient compared to manual image analysis. Furthermore, AI can analyse three-dimensional (3D) images, whereas conventional methods use cross-sectional or two-dimensional (2D) images. Consequently, it becomes possible, in the example of an abdominal CT scan, to measure 3D body composition through the entire lumbar vertebral region (L1-L5). In contrast to conventional assessment, where it is only practically applicable to measure in a single image or cross-sectional area in the mid-lumbar region (L3). This ultimately makes it plausible that AI-based analysis yields data that better reflects the patient's true body composition [19, 20].

When examining body compositions based on CT scans, it is possible to use many different variables. The most obvious and studied variables include the quantity and quality of skeletal muscle, adipose tissue distribution (consisting of visceral adipose tissue quantity, subcutaneous adipose tissue quantity, and intramuscular adipose tissue quantity), and bone density [18, 21].

Studies have found that sarcopenia in patients undergoing abdominal surgery is related to a worse postoperative outcome [18, 22]. Simultaneously, sarcopenia is highly underdiagnosed as it is clinically difficult to evaluate weight loss and muscle mass, especially in obese patients [16]. Furthermore, skeletal muscle quantity and quality scores commonly correlate with frailty, readmissions, and postoperative mortality and morbidity. Assessment of these parameters through CT body composition software provides objective measurements of patient frailty that are not otherwise clinically apparent. This approach may complement existing risk stratification tools, identifying high-risk patients undergoing major cancer surgery [18, 23, 24].

In summary, when BC patients are considered eligible for RCx, a preoperative cancer diagnostic abdominal CT scan is performed. Correlating this to the extensive scientific evidence, that CT body composition is associated with a higher post-operative risk, the following question arises:

Can AI-based CT body composition measurements utilising a preoperative CT scan predict which BC patients undergoing robot-assisted RCx are at higher risk of major postoperative complications and readmission?

The aim of this study is to examine whether CT-derived body composition measures are associated with major postoperative complications (Clavien–Dindo grade III or higher) or hospital readmission, thereby assessing their potential relevance for inclusion in a prediction model.

Methods

Study Design

This retrospective cohort study investigates muscle-invasive urinary bladder cancer (MIBC) patients undergoing robotic-assisted radical cystectomy (RCx) from October 1st 2020, until November 1st 2025, at the Department of Urology, Aalborg University Hospital (AaUH). Data is collected from the Nordic Cystectomy study (NorCys-trial) along with AI-segmentation of existing preoperative CT scans of patients who underwent RCx.

Hypothesis and aim

- Lower skeletal muscle volume, higher adipose tissue volumes and lower bone density are associated with expiriencing major complications (CDC $\geq$ III) and re-hospitalisation in RCx patients

Objectives

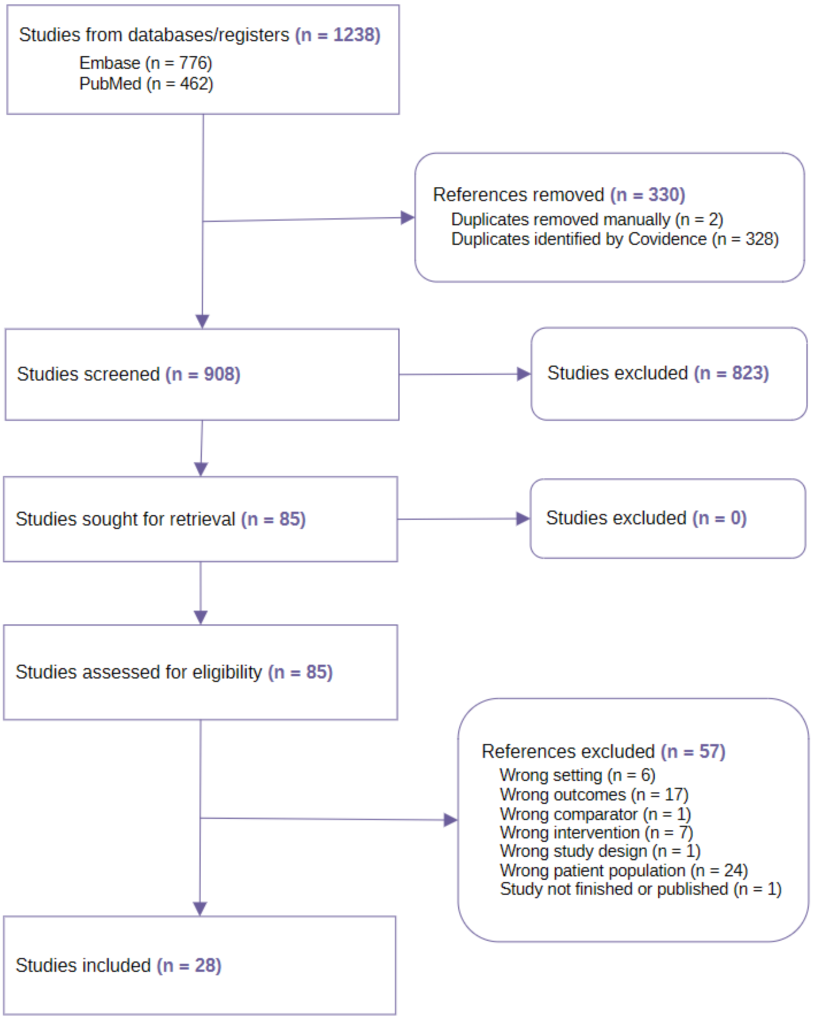
- **Primary:** Assessment of associations using logistic regression
- **Seconday:** Inclusion of all preoperative variables in a prediction model

The following sections include settings, study population, inclusion and exclusion criteria, study outcomes and a statistical analysis section. This study only includes relevant data from the NorCys-trial.

Literature Search

This study sourced the current literature via PubMed and Embase databases. Eligible studies were title/abstract- and full text screened in duplicate using Covidence, a tool for systematic literature reviewing. Furthermore, this study introduces articles and sources through cross-references and Google Scholar searches. Below is a PRISMA that illustrates the literature search (Figure 1).

Figure 1: Study Screening and Inclusion Flowchart



Study Setting

The NorCys-trial is a collaboration project between all expert centres performing radical surgery for the treatment of bladder cancer in the Nordic countries, with patient data being collected starting October 5th 2020 [25]. Currently, the project is still ongoing. Data extraction is performed from accessible electronic health records and is stored into a local REDCap database. Both this project group and research nurses in the Department of Urology at AaUH participate in data extraction.

Study Population

BC patients who undergo RCx in the Department of Urology at AaUH with a completed follow-up period as of November 17th 2025. This study uses only data from complete cases, meaning participants with preoperative CT scans suitable for AI-based CTBC-analysis with accessible follow-up data.

Inclusion Criteria

- Patients with $T_{1\text{-}4}N_XM_0$ BC diagnosis undergoing RCx at AaUH in the period of 2020-2025, who were included in the NorCys-trial

Exclusion Criteria

- Patients with a preoperative abdominal CT scan with intravenous (IV) contrast, not suitable for analysis, or taken earlier than 90 days prior to surgery
- Patients undergoing conversion from robotic-assisted laparoscopic to open procedure surgery
- Patients < 50 years of age
- Incomplete post-operative 90-day follow-up
- Non-related major surgery within 90 days postoperatively

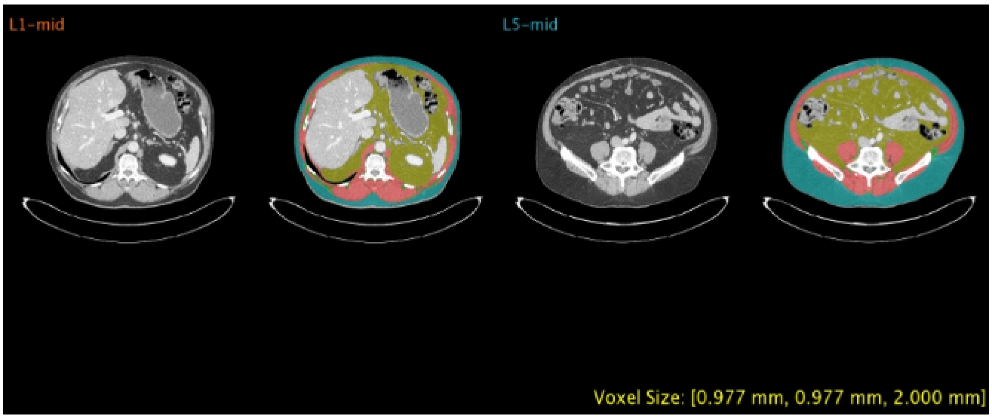
Source Data Documentation

The subjects' electronic health records, including clinical charts, laboratory measures, subject files, and imaging diagnostics, will provide relevant data.
The NorCys-trial will provide the main data points for this study; this trial is therefore unable to control for pre-trial bias.
Demographic and preoperative data include: Age, gender, tobacco use history, alcohol use history, date of preoperative CT-scan, date of surgery, date of discharge, weight, height, ASA score, EGOC-PS, CCI score, relevant bloodwork, and whether a patient had neoadjuvant chemotherapy (Table 1).

CT Body Composition Analysis

The Data Analysis Facilitation Suite (DAFS) program from Voronoi Health Analytics Incorporated (Vancouver, Canada) performs the CTBC analysis. Using DAFS, accurate measurements of the volume and morphology of each anatomical structure are possible to obtain automatically. On the basis of a relevant axial IV contrast-series CT scan, the DAFS software curates the Digital Imaging and Communications in Medicine (DICOM) images into 3-dimensional volumes. The software processes these curated volumes via non-linear machine-learning algorithms to provide multi-slice segmentation of multiple organs and tissues and vertebral bone annotations from each image (Figure 2).

Figure 2: Illustration of Data Analysis Facilitation Suite (DAFS) software presenting 2D areas and 3D volumes of the region of interest, the lumbar abdominal section in the body.



Tissue	Cross-sectional Area (cm^2)	Volume (cm^3)	Mean Intensity	Index
Skeletal Muscle	138.83	1777.05	37.09	
Subcutaneous Adipose Tissue	168.12	2151.95	-108.56	
Visceral Adipose Tissue	289.59	3706.77	-95.84	
Intramuscular Adipose Tissue	8.51	108.94	-58.41	

*Cross-sectional area for a tissue is averaged over all the slices containing that tissue within L1mid-L5mid
*Segmentations are generated using an anatomical DAFS-protocol (not using fixed thresholds).

DAFS Body Report | © 2024 Voronoi Health Analytics Inc. | 997 Seymour St #250, Vancouver, BC, Canada

The reference for analysis in the axial view spans from vertebrae L1 to L5. Skeletal muscle volume (SMV), subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), intramuscular adipose tissue (IMAT), and total adipose tissue (FAT) were scaled to slab height in centimetres to control for natural variation in body structure, creating indices (cm^3/cm). Lastly, bone density was measured using Hounsfield Units (HU) (Table 2).

Outcome measures

The primary outcome is major postoperative complications, and the secondary outcome is readmission. Via consensus from articles investigating urological surgical postoperative complications, this study uses the Clavien-Dindo Classification (CDC) [12]. Readmission is defined as a patient being readmitted to a hospital within the North Denmark Region within 90 days postoperatively (Table 3).

Clavien-Dindo Classification (CDC)

Major postoperative complications were defined using the Clavien-Dindo Classification (CDC) [12]. CDC grades complications via the type of treatment needed, ranging from minor deviations from the normal postoperative course (grade I) to life-threatening events and death (grade V).

- **Grade I** complications include any deviation from the normal postoperative course not requiring surgical, endoscopic, or radiological intervention.
- **Grade II** includes complications requiring specific bed-side treatments beyond those for Grade I complications (e.g. blood transfusions and total parenteral nutrition).
- **Grade III** involves complications requiring surgical, endoscopic, or radiological intervention, with:
  - IIIa (treatments requiring local anaesthesia)
  - IIIb (treatments requiring general anaesthesia)
- **Grade IV** complications are potentially life-threatening and require intensive care unit (ICU) management, with:
  - IVa (treatments of single-organ dysfunction)
  - IVb (treatments of multi-organ failure)
- **Grade V** represents patient death.

This trial included complications and readmissions occurring up to 90 days postoperatively. In addition, a major complication was defined by an outcome of a CDC grade 3 or higher.

Statistical Methods

Predictive Modelling with Non-Parametric Continuous Measures

This study defined CTBC parameters as continuous variables to determine the predictive power of numerical values, eliminating the need for data to be normally distributed when using the methods below. Apart from descriptive tables, histograms for each CTBC parameter will be presented to provide a graphical representation of this study's independent variables.

Univariate Logistic Regression

Univariate logistic regression was performed to examine the association between each individual preoperative variable and the binary outcome variables (major complications and readmissions). For each preoperative variable, a separate univariate logistic model was fitted to estimate an odds ratio (OR) with corresponding 95% confidence intervals (CI). Due to clinical consensus and literature suggesting that age, gender, smoking status, and BMI are possible confounders, the individual CTBC parameters were adjusted accordingly. [26, 27, 18, 28, 29, 30, 31]. A P-value of ≤ 0.05 was deemed statistically significant for detecting the effects or associations between CTBC and the risk of severe postoperative complications.

LASSO

To create a predictive model, the statistical analysis of data in this study uses the Least Absolute Shrinkage and Selection Operator (LASSO) regression.
This manages potential multicollinearity and performs variable selection. Using LASSO, challenges due to an eventual low number of events per variable (EPV) can be surpassed. This method adds an L1 penalty to the standard linear regression, which shrinks unimportant variable coefficients to zero, effectively selecting a simpler and more interpretable model. Cross-validation determines the optimal penalty parameter (λ). This method enables the possibility to utilise all preoperative variables, surpassing the risk of overfitting, contrary to a simple multivariable regression model.
After relevant variable selection via LASSO regression, the selected variables will be the predictors utilised in a corresponding ROC curve.

ROC

The Receiver Operating Characteristic (ROC) analysis plots sensitivity and specificity across a range of threshold values, resulting in an area under the curve (AUC) calculation as a summary measure of model accuracy.
A ROC curve analysis evaluates the performance of the binary predictive model. The ROC curve illustrates the trade-off between sensitivity (true positive rate) and one minus specificity (false positive rate) across a range of classification thresholds. The AUC calculation provides a single measurement of the model's discriminative ability, where a higher AUC indicates better classification performance.

Judicial and Scientific Ethics Approvals

Scientific ethics approval was obtained from the institutional review board and The National Committee on Health Research Ethics (NVK). Hospital management Paragraph 30-approval and Hospital management approval have been obtained for this study. The NVK scientific ethics approval is necessary because this study reanalyses the patients' cancer-diagnostic CT scans [32].

Results

This section presents patient selection, baseline demographic characteristics, independent variables, and outcome measures (Tables 1–4). CT body composition (CTBC) parameters constituted the primary independent variables in this study. Their associations with each outcome—major postoperative complications and hospital readmission—were evaluated using both unadjusted and adjusted univariate regression analyses, shown in Tables 5 and 6. Finally, the Least Absolute Shrinkage and Selection Operator (LASSO) regression model coefficient paths and their corresponding Receiver Operating Characteristics (ROC) curves are provided for each outcome (Figure 4).

Participants

In total, 186 bladder cancer (BC) patients who were cystectomised at Aalborg University Hospital from 2020 to 2025, and included in the NorCys-trial, were potentially eligible for inclusion. When applying the defined exclusion criteria, 52 patients were excluded:

- 5 patients were under the age of 50.
- 8 patients had no suitable CT scans available.
- 34 patients had a preoperative CT scan dated older than 90 days prior to surgery.
- 1 patient was converted to open surgery.
- 2 patients had major surgery due to other diseases within 90 days postoperatively.
- 2 patients were lost to follow-up.

Descriptive Data

Study population characteristics

Of the 134 patients included, 100 were males (75%), and 34 were females (25%) with a mean age of 71.7 years (±7.4 years). When reviewing smoking status and alcohol consumption, 104 (78%) were ever smokers and 36 (27%) were ever excessive users of alcohol. Their average BMI was 26.7 kg/m^2 (±4.4 kg/m^2). During the preoperative clinical comorbidity evaluation, 27 (20%) had a CCI assessment > 2. Furthermore, 8 (6%) had an ECOG-PS > 1, and 40 (30%) had an ASA score > 2. During clinical TNM staging, 97 (72%) had a clinically invasive tumour stage of two or above (T2+ disease), while 19 (14%) had nodal invasion (N+ disease). Regarding additional oncological treatment, 33 (25%) received neoadjuvant chemotherapy (NAC). Looking into their blood work, 58 (43%) were anaemic, 26 (19%) had elevated Creatinine levels, and 19 (14%) had hypoalbuminemia.
Patient characteristics stratified by inclusion status are presented in Table 1.

Table 1: Patient characteristics stratified by inclusion status (included vs. excluded patients).

Variable	Included N = 134	Excluded N = 52
Demographics		
Age, years, (mean ± SD)	71.7 (7.4)	69.4 (10.4)
Gender, n (%)		
Male	100 (75%)	38 (73%)
Female	34 (25%)	14 (27%)
BMI, kg/m^2, (mean ± SD)	26.7 (4.4)	26.9 (4.3)
Smoking status, n (%)		
Ever smoked	104 (78%)	43 (83%)
Never smoked	30 (22%)	9 (17%)
Alcohol status, n (%)		
Ever excessive use	36 (27%)	16 (31%)
Never excessive use	98 (73%)	36 (69%)
Preoperative clinical data		
CCI, n (%)		
CCI > 2	27 (20%)	17 (33%)
CCI ≤ 2	107 (80%)	35 (67%)
ECOG-PS, n (%)		
0	86 (64%)	35 (67%)
1	40 (30%)	11 (21%)
2+	8 (6.0%)	6 (12%)
ASA Score, n (%)		
1	24 (18%)	5 (9.6%)
2	70 (52%)	27 (52%)
3+	40 (30%)	20 (38%)
Neoadjuvant Chemotherapy, n (%)	33 (25%)	15 (29%)
Preoperative Bloodwork†		
Hemoglobin, mmol/L, (mean ± SD)	8.0 (0.9)	8.1 (1.0)
Anaemia, n (%)	58 (43%)	23 (45%)
Serum Albumin, g/L, (mean ± SD)	38.1 (3.5)	38.6 (3.5)
Hypoalbuminemia, n (%)	19 (14%)	7 (14%)
Serum Creatinine, mol/L, (mean ± SD)	88.6 (29.8)	102.7 (56.8)
Elevated Serum Creatinine, n (%)	26 (19%)	15 (29%)
Clinical TN-staging (Preoperative Assessment)		
TX, n (%)	0 (0%)	1 (1.9%)
T0/Tis/Ta/T1, n (%)	37 (28%)	27 (52%)
T2+, n (%)	97 (72%)	24 (46%)
NX, n (%)	3 (2.2%)	1 (1.9%)
N0, n (%)	112 (84%)	41 (79%)
N+, n (%)	19 (14%)	9 (17%)

† Cut points are indicated as the following: *Anaemia*: hemoglobin below the sex-specific reference interval (women < 7.3 mmol/L; men < 8.3 mmol/L); *Hypoalbuminemia*: serum albumin below the lower limit of the age-specific reference interval (18–39 years, < 36 g/L; 40–69 years, < 36 g/L; ≤ 70 years, < 34 g/L); *Elevated creatinine*: serum creatinine above the sex-specific reference interval (women > 90 µmol/L; men > 105 µmol/L).
Abbreviations: *SD* standard deviation; *BMI* body mass index; *CCI* Charlson comorbidity index; *ECOG-PS* Eastern Cooperative Oncology Group Performance Status; *ASA* American Society of Anesthesiologists.

Missing Data

No patients included in this study had missing data.

CTBC Parameters

Looking into the scaled CTBC parameters for included patients (Table 2), the mean skeletal muscle volume index (SMVI) was 136.7 cm^3/cm (±31.0), the mean visceral adipose volume index (VATI) was 176.9 cm^3/cm (±106.9), the mean subcutaneous adipose volume index (SATI) was 175.6 cm^3/cm (±84.5), the mean intramuscular adipose volume index (IMATI) was 12.3 cm^3/cm (±6.3), the mean total adipose volume index (FATI) was 377.6 cm^3/cm (±176.5), and the mean bone density was 308.9 Hounsfield units (HU) (±46.0).

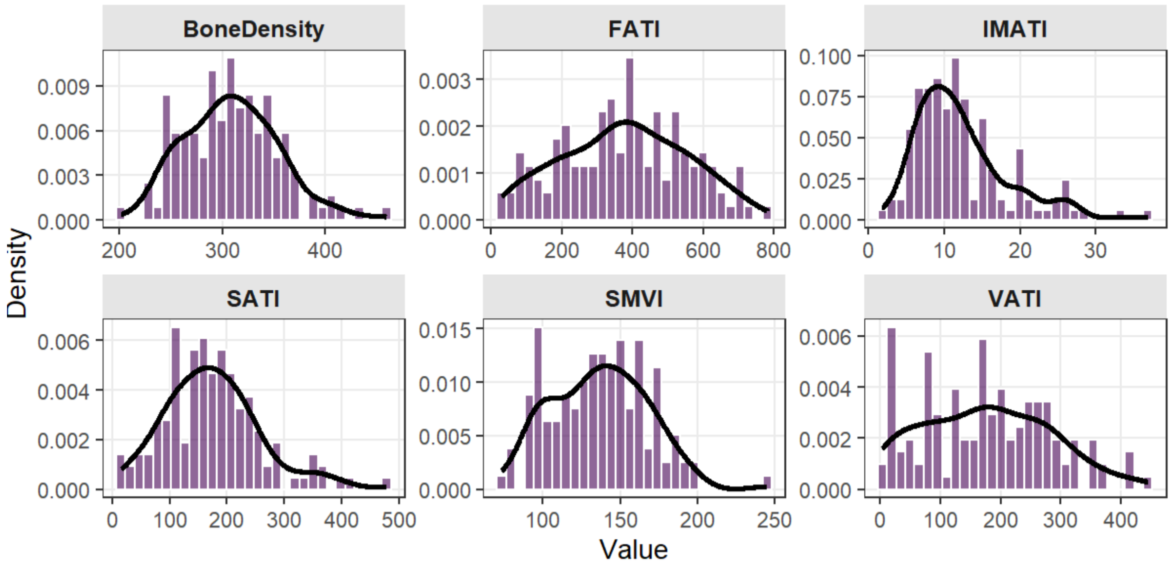
Table 2: CT body composition variables within included patients.

Variable	Included N = 134
SMVI, cm^3/cm, (mean ± SD)	136.7 (31.0)
VATI, cm^3/cm, (mean ± SD)	176.9 (106.9)
SATI, cm^3/cm, (mean ± SD)	175.6 (84.5)
IMATI, cm^3/cm, (mean ± SD)	12.3 (6.3)
FATI, cm^3/cm, (mean ± SD)	377.6 (176.5)
Bone Density, HU, (mean ± SD)	308.9 (46.0)

Abbreviations:
FVI fat volume index; *IMATI* intramuscular adipose tissue index; *HU* Hounsfield units; *SATI* subcutaneous adipose tissue index; *SMVI* skeletal muscle volume index; *VATI* visceral adipose tissue index.

Examining the distributions of the different CTBC parameters within the entire cohort of included patients(Figure 3), it can be determined that these parameters were roughly normally distributed, with the exception of IMATI, which was skewed left. However, there seemed to be a sufficient variance in the distribution of values.

Figure 3: Distribution of CT Body Composition Parameters (Histograms)



Abbreviations: *FVI fat volume index; IMATI intramuscular adipose tissue index; HU Hounsfield units; SATI subcutaneous adipose tissue index; SMVI skeletal muscle volume index; VATI visceral adipose tissue index.*
X-axis: *FATI, IMATI, SATI, SMVI, and VATI: Volumes scaled to slab height (cm^3/cm); BoneDensity measured in HU*
Y-axis: *Probablity density (1/unit)*

Outcome Data

Outcome Events

During the 90-day follow-up period, 54 (40%) of the included patients experienced major complications, while the readmission rate was 53 (40%).

Table 3: Outcomes stratified by inclusion status (included vs. excluded patients).

Variable†	Included N = 134
Major Complication, n (%)§	54 (40%)
Readmission, n (%)	53 (40%)

†: Measured postoperatively, either during admission or during the 90-day follow-up period.
§: Defined by the modified Clavien-Dindo classification system grade IIIa-V.

Examining the different types of major complications (Table 4), a total of 21 patients experienced complications needing treatment in local anaesthesia, e.g. ultrasound-guided drainage of intra-abdominal fluid collection (CDC grade IIIa). Complications requiring treatment in general anaesthesia, e.g. re-operation due to ileus (CDC grade IIIb) were seen in 11 patients. Single-organ failure requiring intensive care (CDC grade IVa) occurred in 12 patients, while multi-organ failure requiring urgent intensive care occurred in 4 patients (CDC grade IVb). Fatal complications (CDC grade V) were observed in 7 patients.

Table 4: Postoperative complications within 90 days classified by the modernised Clavien-Dindo system

Grade	Number and description
IIIa	5 - Pelvic abscess
	5 - Lymphocele
	2 - Intra-abdominal abscess
	2 - Hydronephrosis
	1 - Anastomosis defect
	1 - Anastomosis leakage
	1 - Ascites
	1 - Dysfunctional drainage
	1 - Invasive tumor adherence
	1 - Melaena
	1 - Uroplania
IIIb	3 - Ileus
	3 - Fascial dehiscence
	2 - Intraabdominal bleeding
	1 - Pelvic abscess
	1 - Bleeding ulcer
	1 - Anastomosis defect
IVa	5 - Miscellaneous medical complications†
	2 - Ileus
	2 - Intraabdominal bleeding
	1 - Anastomosis defect
	1 - Bricker bladder necrosis
	1 - Deep vein (iliac) thrombosis
IVb	4 - Sepsis
V	2 - Intestinal perforation
	1 - Sepsis
	1 - Anastomosis defect, sepsis
	1 - Ileus
	1 - Apoplexia
	1 - Lower extremity ischemia

† *"Miscellaneous medical complications"* include lactate acidosis, hypotension, hypokaliemia, pain and somnolence.

Main Results

Associations Between CTBC and Major Complications

In unadjusted univariate regression analysis, no statistically significant associations with the outcome of experiencing major complications were found with CTBC variables. Furthermore, no statistically significant associations were found when adjusting for confounders (Table 5).

Table 5: Univariate analysis for evaluation of the associations between tested parameters and major complications

Predictors	Major complication Clavien-Dindo grade IIIa-V			
	Univariate		Adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CT Parameter Indices†				
SMVI	1.01 (1.00-1.02)	0.3	1.01 (0.98-1.03)	0.6
SATI	1.00 (1.00-1.01)	0.2	1.00 (1.00-1.01)	0.4
VATI	1.00 (1.00-1.00)	0.5	1.00 (0.99-1.00)	0.6
IMATI	1.04 (0.99-1.10)	0.2	1.03 (0.96-1.11)	0.4
FVI	1.00 (1.00-1.00)	0.2	1.00 (1.00-1.00)	>0.9
Bone density (HU)	1.00 (0.99-1.00)	0.2	0.99 (0.99-1.00)	0.2

†: Units in cm^3/cm unless otherwise stated.
Adjusted values are adjusted for age, gender (female/male), BMI and smoking status (never smoked/ever smoked).
Abbreviations: *OR* odds ratio; *CI* confidence interval; *FVI* fat volume index; *IMATI* intramuscular adipose tissue index; *SATI* subcutaneous adipose tissue index; *SMVI* skeletal muscle volume index; *VATI* visceral adipose tissue index; *HU* Hounsfield units.

Associations Between CTBC and Readmissions

In unadjusted univariate regression analysis, there was a statistically significant association between intramuscular adipose tissue index (IMATI) and readmission (OR 1.07; (95% CI 1.01-1.13; *P*=0.024). When adjusting for confounders, the univariate logistic regression still found a statistically significant association with IMATI (OR 1.11; (95% CI 1.03-1.21; *P*=0.010) (Table 6).

Table 6: Univariate analysis for evaluation of the associations between tested parameters and readmission

Predictors	Readmission			
	Univariate		Adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CT Parameter Indices†				
SMVI	0.99 (0.98-1.01)	0.3	1.01 (0.99-1.03)	0.3
SATI	1.00 (1.00-1.01)	0.4	1.00 (0.99-1.01)	0.7
VATI	1.00 (1.00-1.00)	0.8	1.00 (1.00-1.01)	0.2
IMATI	1.07 (1.01-1.13)	**0.024**	1.11 (1.03-1.21)	**0.010**
FVI	1.00 (1.00-1.00)	0.6	1.00 (1.00-1.01)	0.4
Bone Density (HU)	1.00 (0.99-1.00)	0.2	1.00 (0.99-1.00)	0.3

†: Units in cm^3/cm unless otherwise stated.
Adjusted values are adjusted for age, gender (female/male), BMI and smoking status (never smoked/ever smoked).
Abbreviations: *OR* odds ratio; *CI* confidence interval; *FVI* fat volume index; *IMATI* intramuscular adipose tissue index; *SATI* subcutaneous adipose tissue index; *SMVI* skeletal muscle volume index; *VATI* visceral adipose tissue index; *HU* Hounsfield units.

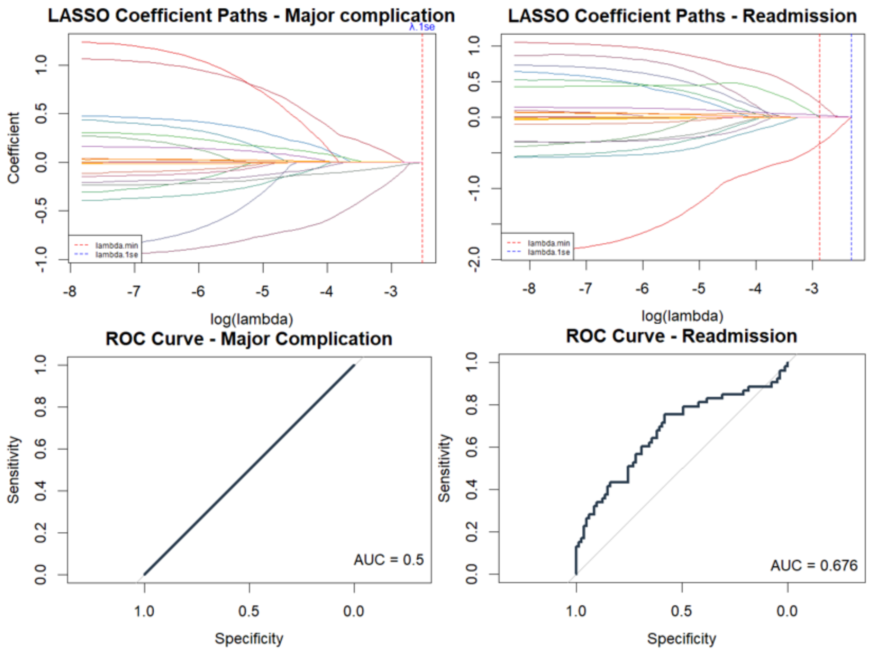
LASSO and ROC for Major Complications

Preoperative variables with the potential to predict major postoperative complications (CDC $\geq$ III) were investigated using the Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis. The resulting LASSO regression selected no variables. The corresponding Receiver Operating Characteristic (ROC) curve, with a measured area under the curve (AUC), evaluated the precision of LASSO-selected preoperative values in predicting major complications. The AUC was 0.5 (Figure 4).

LASSO and ROC for Readmissions

Preoperative variables with the potential to predict readmissions were investigated using LASSO regression analysis. The LASSO regression selected four variables: male gender, female gender, never smoked and IMATI (Figure 4). The resulting ROC curve with a measured AUC evaluated the precision of LASSO-selected preoperative values in predicting readmissions. The AUC was 0.676.

Figure 4: LASSO regression coefficient paths and ROC curve for the primary and secondary outcomes.



***LASSO coefficient paths**: The selection of the penalty in the LASSO model used 10-fold cross-validation with the minimum criteria (lambda.min). The relationship curve between partial likelihood deviation (binomial deviation) and log (lambda) was plotted. Dotted vertical lines were drawn at the optimal values by using the minimum criteria (lambda.min; red) and the 1 standard error (SE) of the minimum criteria (lambda.1se; blue).*
***ROC Curves**: Sensitivity and specificity across a range of threshold values, resulting in an area under the curve (AUC) calculation as a summary measure of model accuracy.*

Discussion

This study aimed to investigate whether AI-analysed CT body composition (CTBC) could be used to predict major postoperative complications or readmissions within 90 days post-operatively in BC patients undergoing cystectomy. To explore this, univariate logistic regressions were performed, both unadjusted and adjusted, along with LASSO regression and corresponding ROC models for each outcome. In the following sections, the results of the study, strengths and limitations, and future perspectives are further discussed.

Interpretation of Results

In the following sections, the interpretation of univariate logistic regression along with the prediction models is discussed regarding the outcomes of major complications and readmissions, respectively.

Univariate Regression

When evaluating Table 5, this study did not find any statistically significant associations between CTBC parameters and experiencing a major complication.
Furthermore, the results did not significantly change when adjusting for age, gender, BMI and smoking status. These results are unexpected, provided previous studies have shown significant relationships between CTBC parameters and major complications [33, 18, 22]. For example, Sharma et al. [22] did find a significant negative correlation between major complications and skeletal muscle index and a significant positive correlation between intramuscular adipose tissue and major complications.

Discussing Table 6, a statistically significant association between higher intramuscular adipose tissue index (IMATI) and readmission was found as the only predictor, both unadjusted and adjusted for age, gender, BMI and smoking status. An OR of 1.11 (95% CI 1.03-1.21) suggests a progressive increase in intramuscular adipose tissue is associated with higher odds of being readmitted in the 90-day postoperative period. This would correlate with the clinical reasoning that intramuscular adipose tissue accumulation, which naturally increases with accumulated adipose tissue, is associated with frailty and postoperative complications. However, it is noted that the subcutaneous adipose tissue index (SATI), visceral adipose tissue index (VATI) and total fat volume index (FATI) do not show this association. Fumagalli et al. [18], using 3D measurements, found a significant correlation between 30-day readmission and muscle quantity, muscle quality adipose tissue distribution. In this study's cohort, a similar association with muscle quality was observed: higher IMATI predicted readmission, whereas SMVI did not. This suggests the possibility that the significant IMATI finding may be attributable to this cohort being incidentally different with respect to IMATI, while not differing meaningfully in the other parameters. Nevertheless, the alignment of these IMATI results with earlier evidence suggests that AI-derived measures of muscle quality may still hold relevance for future research.

This study's findings are mostly inconsistent with previous studies. This may be related to the small sample size of 134 included patients, and therefore, a possibility of limited variance in CTBC parameters between groups with and without complications or readmissions. Furthermore, our study's AI model operated in 3D and therefore generated volumetric measurements, whereas most previous studies relied on 2D axial CT slices and reported area-based metrics. This could yield different strengths of association with clinical outcomes, and the two metrics are not necessarily interchangeable.

Prediction Models (LASSO and ROC)

As an extension of the univariate regression, LASSO regressions and corresponding ROC curves were performed for both outcomes (90-day major complication and readmission) on all preoperative variables and CTBC variables seen in Tables 1 and 2. This is rooted in the reasoning that the large number of variables could possibly cause an overfitting of a simple multiple regression model, given the low number of events per variable.

The LASSO regression for major complications did not identify any predictors, which is consistent with the results of the univariate analyses. Consequently, the ROC analysis yielded an AUC of 0.50, indicating that the model had no discriminative ability and performed no better than random chance.
Several factors may explain this. Firstly, although the event rate was relatively high, the overall sample size remained limited, reducing the model's ability to detect meaningful associations. Secondly, the variability of the CTBC measures may have been insufficient for LASSO to distinguish a stable signal from noise, leading the algorithm to shrink all coefficients toward zero. Together, these factors suggest that the study was underpowered to detect associations between CTBC and postoperative outcomes.

The LASSO model for readmission identified IMATI, gender, and smoking status as predictors, and the resulting ROC curve yielded an AUC of 0.676, suggesting a very limited clinical usability [34]. However, several of the estimated associations—such as a higher readmission risk among never-smokers—were clinically counterintuitive. These patterns are likely explained by the substantial imbalance in subgroup representation; only 25% of the cohort were women and 22% were never-smokers. Such sparsity limits the model's ability to reliably estimate effects. It increases the risk of unstable or directionally inconsistent coefficients, particularly in penalised regression where variable selection is sensitive to small fluctuations in the data. The modest AUC further suggests that the model may have captured noise rather than true underlying risk factors. Consequently, the observed associations should be interpreted with caution and are unlikely to reflect genuine clinical relationships.

Applied Methods for Measuring CT Body Composition

Many previous studies have relied on 2D cross-sectional imaging, most commonly the single axial slice at the third lumbar vertebra (L3) as a surrogate for total muscle or adipose mass or using the psoas muscle area as an indicator of muscle mass [35, 22, 36]. These measurements are often standardised by patient height (e.g., skeletal muscle index), enabling comparisons across populations. While this approach is widely used, it may introduce uncertainties in data, as natural variation in body composition differs with each individual. Furthermore, minor variations in slice location, patient positioning, or segmentation technique can introduce variability in 2D-derived metrics [37].
In contrast, the 3D approach, producing volume-based data, used in this study, provides a more comprehensive assessment of the total body composition. By integrating data across the L1-L5 abdominal section rather than relying on a single slice, 3D analysis may better reflect total abdominal muscle and adipose tissue and may reduce measurement error. However, 3D segmentation is more computationally intensive and is still less standardised across studies. Consequently, 2D and 3D metrics are not directly interchangeable, and absolute values derived from volumetric imaging cannot simply be compared to slice-based thresholds.

Another important methodological consideration is the differing definitions of sarcopenia across relevant literature [38]. Many previous studies classified patients as sarcopenic or non-sarcopenic based on predetermined cut-off values derived from 2D L3 muscle indices [39]. In the present study, no binary definition of sarcopenia was applied. Instead, SMVI was treated as a continuous variable. This approach avoids cut-off points and may better preserve information for modelling, but it also makes direct comparison with studies using categorical definitions challenging.

Overall, these methodological differences highlight important considerations for comparing this study's results with previous research. Inconsistent imaging techniques, measurement conventions, and sarcopenia definitions across studies create substantial differences, which may limit external validity and hinder clinical translation. Establishing standardised imaging protocols and consensus definitions will likely be necessary before AI models in this domain can be reliably applied across clinical departments.

Strengths and Limitations

The strength of this study lies mainly in the methodology. As previously discussed, the use of 3D segmentation may provide a more precise approximation of a patient's CTBC, along with a LASSO-regression efficiently eliminating multiple unnecessary predictors amongst many different preoperative variables. Furthermore, the inclusion criteria chosen were not too restrictive, as they were tailored to capture the most typical population of patients with bladder cancer, who were undergoing robot-assisted radical cystectomy, possibly providing a better internal and external validity. It was deemed that there was minimal selection bias.

The most common clinical practice is to provide the preoperative CT-scan no earlier than 90 days before surgery. However, the 90-day span could introduce considerable changes in body composition from the date of the scan to the date of the surgery, especially when treating patients suffering from muscle-invasive bladder cancer. More representative data would potentially be obtained, provided the scan could be performed closer to the surgery date.

Lastly, one of the most critical limitations of this study consists of its retrospective setting. As a result of this setting, this study could not evaluate potential biases during the NorCys-trial. Consequently, during actual registration of data, selection bias and information bias could exist. The NorCys-data does not include concrete clinical frailty assessment scores like the Clinical Frailty Scale (CFS) or physical screenings. Instead, it consists of Eastern Cooperative Oncology Group (ECOG) performance status, the Charlson Comorbidity Index (CCI) and the American Society of Anesthesiologists (ASA) score. This study set out to investigate frailty via postoperative major complications and readmissions using preoperative CT body composition analysis. However, these variables were unable to predict frailty comprehensively, whereas a predetermined frailty assessment could have strengthened the prediction model.

Future Perspectives

As previously discussed, the limited sample size could be a factor underlying the absence of significant associations in this study. This may explain, for example, why SMVI did not correlate with postoperative complications or readmission, despite evidence from previous studies suggesting such a relationship [18, 22, 40]. However, expanding the cohort through collaboration with additional Danish centres beyond Aalborg University Hospital could address this limitation. By utilising these, the number of patients and events would increase, thereby improving statistical power and potentially enabling more efficient detection of meaningful predictive signals. Additionally, expanding the sample size could also provide an opportunity to investigate novel definitions of sarcopenia in a 3D volumetric context. This approach may facilitate more consistent comparisons across studies, particularly as AI-based segmentation becomes increasingly efficient and accurate in quantifying this metric.

Furthermore, the NorCys-trial also includes postoperative data at approximately 4 and 12 months. These longitudinal data offer an opportunity to examine whether specific preoperative parameters are associated with subsequent declines in muscle mass or other body composition metrics. Exploring such patterns could help identify patients at risk of poorer long-term recovery and guide more tailored postoperative follow-up or rehabilitation.

Lastly, there is a growing focus on identifying frail patients who may benefit from preoperative optimisation, as demonstrated by studies such as the Comprehensive Geriatric Assessment for Optimisation in Cystectomy (COMPETENCE) study performed within Danish urology departments [41]. If validated in larger cohorts, the method of using AI-based CTBC analyses may contribute to this clinical effort by automatically detecting patients at an elevated risk of experiencing postoperative sequelae.

Conclusion

This study aimed to determine whether CT body composition variables are statistically associated with major complications or readmission rates in patients with bladder cancer undergoing robotic-assisted cystectomy at AaUH between 2020 to 2025. Furthermore, the aim was to examine whether CTBC measures were statistically associated with experiencing major postoperative complications (CDC $\geq$ III) or hospital readmission, and assessing their potential relevance for inclusion in a prediction model.

Using univariable adjusted logistic regression, no significant associations were found between CTBC parameters and major complications. Consequently, the LASSO regression and the corresponding ROC curve did not yield a usable predictive model.
In the univariable adjusted logistic regression for readmissions, only IMATI (P=0.01) OR=1.11 (95% CL: 1.03-1.21) was found to be significantly associated with readmission among the CTBC-parameters. Furthermore, LASSO regression and the corresponding ROC curve estimated an AUC=0.676, which was deemed insignificant in terms of clinical use.

The lack of significant associations between CTBC parameters and major complications or readmissions was possibly due to the limited sample size, which could have limited the variability between groups and reduced the study's ability to detect true differences. Future studies should apply the same methodology in a larger cohort, where a significant association may be detected.

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