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Original Article

Preoperative frailty and outcome in patients undergoing radical cystectomy

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Objective

To determine the value of preoperative frailty screening in predicting postoperative severe complications and 1-year mortality in patients undergoing radical cystectomy (RC).

Patients and Methods

Prospective cohort single-centre study in patients undergoing RC from September 2016 to December 2017. Preoperative frailty screening was implemented as standard care and was used to guide shared decision-making during multidisciplinary team meetings. Frailty screening consisted of validated tools to assess physical, mental and social frailty. Patients were considered frail when having two or more frailty characteristics.The primary endpoint was the composite of a severe complication (Clavien–Dindo Grade III–V) within 30 days and 1-year all-cause mortality. The secondary endpoints included any complication (Clavien–Dindo II–V), length of stay, readmission within 30 days, and all-cause mortality. Logistic regression analysis and the concordance statistic (c-statistic) were used to describe the association and predictive value of preoperative frailty screening.

Results

A total of 63 patients were included; 39 (61.9%) were considered frail. Preoperative frailty was associated with a seven-fold increased risk of a severe complication or death 1 year after RC [adjusted odds ratio (OR) 7.36, 95% confidence interval (CI) 1.7–31.8; 22 patients]. Compared to the American Society of Anesthesiologists (ASA) score and Charlson Comorbidity Index, frailty showed the best model performance (Nagelkerke R^2 0.20) and discriminative ability(c-statistic 0.72, $P < 0.01$) for the primary endpoint. After adding frailty to the conventional ASA risk score, the c-statistic improved by 11% ($P < 0.01$). Overall survival was significantly worse in frail patients (23.2 months, 95% CI 18.7–30.1) vs non-frail patients (32.9 months, 95% CI 30.0–35.9; $P = 0.01$).

Conclusions

Frail patients undergoing RC are at high risk of postoperative adverse outcomes including death. Preoperative frailty screening improves preoperative risk stratification and may be used to guide patient selection for RC.

Keywords

bladder carcinoma, frailty, radical cystectomy, risk assessment, #BladderCancer, #blcsm

Introduction

Bladder cancer is frequently diagnosed worldwide and a common cause of death. Approximately 30% of all newly diagnosed patients present with muscle-invasive bladder cancer (MIBC) [1]. Radical cystectomy (RC) is the 'gold standard' for patients with MIBC and patients with recurrent high-risk non-MIBC (NMIBC) [2,3]. Although RC is a common urological surgical procedure, postoperative morbidity and mortality rates remain high [4–6]. Especially frail patients with multiple comorbidities seem to suffer from adverse outcomes [7–9].

Frailty is an age-related state of functional decline, characterised by weight loss, muscle wasting and reduced functional capacity. Frailty has been associated with postoperative complications, disability, loss of health-

related quality of life (HRQL), and decreased cancer survival [8]. With the ageing of the population, the incidence of bladder cancer will continue to rise, and physicians will encounter the dilemma of treatment decisions in older and frailer patients. Increasing complexity in the management of frail patients undergoing RC and concerns about adverse outcomes demand accurate preoperative risk assessment.

Current traditional risk assessment tools, e.g. the American Society of Anesthesiologists (ASA) score or the Charlson Comorbidity Index (CCI) score, are used to guide selection of surgical candidates. However, these predictors focus primarily on medical comorbidities and do not take frailty characteristics into account. There is an unmet need for a preoperative risk stratification tool, with specific attention for frailty, to identify patients at high risk of poor outcomes. The purpose of the present prospective study was to determine the predictive value of preoperative frailty screening on short- and long-term postoperative outcomes in patients undergoing RC.

Patients and methods

Design

The present study was a single-centre prospective cohort study. In 2016, the St. Antonius Hospital, a large teaching hospital and regional referral centre for uro-oncological surgery, implemented frailty screening as standard care for patients scheduled for RC. The results were discussed in a multidisciplinary team (MDT) meeting, with representatives of the departments of Anaesthesiology and Intensive Care, Urology, Internal Medicine, Medical Oncology and Geriatrics [10]. As patients were treated according to standard local guidelines, the need for informed consent was waived by the local Review Board of the Ethics Committee (Medical research Ethics Committee United, number W17.139). The study was performed in accordance with the principles of the Declaration of Helsinki.

Patients

All patients who were scheduled for RC between September 2016 and December 2017 in the St. Antonius hospital were eligible for inclusion. All patients were routinely discussed in a urological oncology MDT to determine treatment strategy. Each surgical procedure was performed according to standard clinical practice by two experienced urologists.

Preoperative Frailty Screening

Preoperative frailty screening was performed directly after routine preoperative assessment by an anaesthesiology or internal medicine resident. Frailty screening was supervised by an anaesthesiologist dedicated to preoperative screening and consisted of validated tools to assess physical, mental and social frailty. Analysis of physical frailty included nutritional status [Mini Nutritional Assessment (MNA)], gait speed [Timed to Get up and Go Test (TUGT)], polypharmacy (five or more medicines), daily functioning (NAGI scale) and grip strength [11–13]. Screening for mental frailty included an assessment of cognition [six-item Cognitive Impairment Test (6-CIT)] and HRQL [Short Form 12 (SF-12)] [14,15]. To assess social frailty we evaluated a patient's living situation and social support system. Frailty characteristics were considered 'normal' or 'abnormal' according to predefined cut-off points based on the literature. Patients were considered frail when two or more frailty characteristics were present.

Clinical Characteristics and Data Collection

During routine preoperative assessment, baseline characteristics, medical history and laboratory tests were routinely collected. MIBC was defined as a clinical T Stage of ≥T2. To assess the overall weight of comorbidities, the age-adjusted CCI and the ASA classification scores were calculated for each patient [16]. Data were registered in an electronic database [RedCAP (Research Electronic Data Capture), Vanderbilt University, hosted by St. Antonius hospital].

Endpoint Definitions

The primary endpoint was the composite of a severe complication (Clavien–Dindo Grade III–V) within 30 days after RC or death after 1 year. The secondary endpoints were any complication (Clavien–Dindo Grade II–V), length of stay, readmission within 30 days after RC, and all-cause mortality. The primary and secondary endpoints were extracted from electronic medical reports. Mortality was collected from the municipal Personal Records Database.

Statistical Analysis

Data are presented as frequencies and percentages for categorical data, and as median with first and third quartile [interquartile range (IQR)] or mean with standard deviation (SD) for continuous data. Normal distribution of the variables was assessed with visual inspection of the histograms and quantile–quantile plots. Differences between frail and non-frail patients were tested using chi-square test for dichotomous or categorical variables and Mann–Whitney *U*-test or Student's *t*-test for independent continuous variables.

The association between separate risk scores, individual frailty characteristics and the endpoints were analysed with univariable logistic regression. Because age and tumour stage (MIBC vs NMIBC) were a priori expected to be related with the endpoints and the investigated risk scores, all models

were adjusted for those variables resulting in adjusted odds ratios (ORs) with 95% CIs.

To assess the discriminatory ability of separate risk scores and the added value of frailty, the concordance statistic (c-statistic) was used. The c-statistic is an index of predictive discrimination, with a value of 0.5 indication random prediction, and a value of 1 indicating perfect prediction. Overall model performance was reported by Nagelkerke R^2. Nagelkerke R^2 ranges from 0 to 1, with higher values indicating better model performance.

Kaplan–Meier curves were used for survival analysis. Differences in Kaplan–Meier curves between frail and non-frail patients were analysed with log-rank tests. Finally, Cox regression analysis was used to adjust for muscle invasiveness, because patients with MIBC have a poor prognosis compared to patients with NMIBC.

A $P < 0.05$ was considered statistically significant. All data analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS®) for Windows, version 22 (IBM Corp., Armonk, NY, USA).

Results

Population and Outcome

A total of 64 patients were scheduled for RC and underwent preoperative frailty screening. One patient was excluded, because RC was abandoned after reassessment of the cancer stage by the pathologist. The final cohort consisted of 63 patients, with a median (IQR) age of 67 (61–74) years. Two patients (3.2%) had surgery for non-oncological diseases: one patient had chronic bladder pain syndrome, and another patient had iatrogenic ureteric injury after rectal amputation.

Of all the oncological patients, 61.9% was diagnosed with MIBC. Five patients (7.9%) received neoadjuvant chemotherapy and 24 patients (38.1%) underwent a robot-assisted laparoscopic RC with intracorporeal urinary diversion. In all other patients, a complete open surgical procedure was performed. In all, 21% (13/63) of patients was classified as ASA ≥3, and the median (IQR) CCI score was 5 (4–6). Baseline characteristics of frail and non-frail patients are presented in Table 1. Overall, 22 patients (34.9%) had a severe complication or died (Clavien–Dindo Grade III–V) at ≤1 year of RC. Any complication occurred in 42/63 patients (66.7%). Fascial dehiscence (five of 10 patients) or other acute abdominal signs (caused by rectal, small bowel or urostoma lesions in three of 10 patients) were the most common reasons for re-operation. The operation technique (laparoscopic vs open) was not associated with the occurrence of a severe complication ($P = 0.34$). More than half of the patients (58.7%) were diagnosed with an infection, including eight (eight of 37) patients with urosepsis. Urosepsis was the most common reason for readmission to the intensive care

Table 1 Baseline characteristics ($N = 63$).

Characteristic	Frail patients	Non-frail patients	*P*
Number of patients	39	24	
Age, years, mean (SD)	69 (8)	62 (8)	<0.01
Male gender, *n* (%)	30 (76.9)	18 (75)	0.86
BMI, kg/m^2, mean (SD)	25.5 (3.5)	26.4 (3.6)	0.36
Age-adjusted CCI score, mean (SD)	5 (1.5)	4 (1.1)	<0.01
ASA classification, *n* (%)			
1	5 (12.8)	10 (41.7)	<0.01
2	21 (53.8)	14 (58.3)	
≥3	13 (33.3)	0 (0)	
Comorbidities, *n* (%)			
Cardiovascular disease	23 (59)	16 (41)	<0.05
Pulmonary disease	8 (20.5)	0 (0)	<0.05
Diabetes mellitus	4 (10.3)	2 (8.3)	1.00
Renal failure (GFR <60 mL/min/1.73m²)	7 (17.9)	1 (4.2)	0.14
Stroke	4 (10.3)	1 (4.2)	0.64
Intoxication, *n* (%)			
Current smoking	18 (46.2)	2 (8.3)	<0.01
Alcohol use*	11 (28.2)	4 (16.7)	0.30
cT Stage, *n* (%)			
MIBC	26 (66.7)	13 (54.1)	0.42
NMIBC	14 (35.9)	13 (54.2)	
Lymph node positive	9 (23.1)	3 (12.5)	0.35
Non-oncological	1 (2.6)	1 (4.2)	1.00
Neoadjuvant chemotherapy, *n* (%)	4 (10.3)	1 (4.2)	0.64
Type of RC, *n* (%)			
Robot-assisted	14 (35.9)	10 (41.7)	0.65
Open	25 (64.1)	14 (58.3)	

cT, clinical T Stage. Woman >2 and men >3 units/day.

Table 2 Frailty characteristics (*N* = 63).

Variable	Score range	Cut-off point for frailty	Median (IQR)	Frail patients, *n* (%)
Age	0–inf	≥75 years	67 (61–74)	14 (22.2)
6-CIT	0–28	≥6	0 (0–2)	5 (7.9)
SF-12 PCS (*N* = 54)	0–100	<50	51.5 (42.2–55.7)	26 (48.1)
SF-12 MCS (*N* = 54)	0–100	<50	47.4 (42.6–51.3)	37 (68.5)
NAGI	0–7	≥3	0 (0–0)	4 (6.3)
MNA	0–30	≤7	11 (9–11)	8 (12.7)
TUGT	0–inf	≥10 s	8.6 (7.58–9.80)	13 (20.6)
Grip strength	0–inf	Age dependent	–	20 (31.7)
Polypharmacy	0–inf	≥5 drugs	3 (1–5)	20 (31.7)
Anaemia	0–11	<8 mmol/L	8.6 (7.6–9.1)	19 (30.6)
Living alone	Yes-no	–	–	20 (31.7)
At home with home care	Yes-no	–	–	6 (9.5)
No social support system	Yes-no	–	–	0 (0)

inf, infinity; MCS, Mental Component Summary; PCS, Physical Component Summary.

Table 3 Postoperative outcomes (*N* = 63).

Variable	Frail patients (*N* = 39)	Non-frail patients (*N* = 24)	*P*
Severity of complications, *n* (%)			
Clavien–Dindo Grade II	16 (41)	12 (50)	0.30
Clavien–Dindo Grade III	4 (10.3)	3 (12.5)	
Clavien–Dindo Grade IV	4 (10.3)	0 (0)	
Clavien–Dindo Grade V	3 (7.7)	0 (0)	
Re-operation, *n* (%)	9 (23.1)	1 (4.2)	0.07
Unplanned ICU admission, *n* (%)	7 (17.9)	0 (0)	0.04
Length of stay, days, median (IQR)	14 (11–27)	13 (11–16)	0.21
30-day mortality, *n* (%)	3 (7.7)	0 (0)	0.28
Readmission within 30 days, *n* (%)	5 (12.8)	3 (12.5)	1.00
Required new home care or residential care after RC, *n* (%)	29 (74.4)	19 (79.2)	0.66
1-year mortality, *n* (%)	12 (30.8)	1 (4.2)	0.01
2-year mortality, *n* (%)	18 (46.2)	4 (16.7)	0.02

ICU, intensive care unit.

unit, and readmission within 30 days after discharge, with one-third (22/63) of the patients dying within 2 years of RC.

Preoperative Frailty

Table 2 presents the prevalence of preoperative frailty characteristics in the study population.

The age of the study population ranged from 45 to 82 years, 3.2% (two of 63) of patients were octogenarians. One or more frailty characteristics were present in 52 (82.5%) patients. Physical frailty was more common (51 patients, 81%) than mental or social frailty (38 patients, 60.3% and no patients, respectively). Multi-domain frailty was present in 39 (61.9%) patients.

Physical frailty consisted primarily of impaired grip strength, anaemia or polypharmacy. Of the anaemic patients, two of 19 (10.5%) were diagnosed with severe anaemia (haemoglobin level of ≤6 mmol/L) and one of 19 (5.3%) developed anaemia after neoadjuvant chemotherapy.

The median (IQR) number of prescriptions was 3 (1–5) and 20 (31.7%) patients had five or more prescribed medications. Mental frailty was characterised by loss of HRQL; more than half of the patients reported a HRQL below the population mean. None of the patients were considered frail on the social domain. Although 20% of the patients lived alone, all patients had a strong social support system. Overall, 39 patients (61.9%) were considered frail (with two or more frailty characteristics).

Preoperative Frailty and Outcome

A severe complication or death after 1 year was more common in frail patients (48.7% vs 12.5% in non-frail patients, $P < 0.01$) (Table 3). After adjustment for age and muscle invasiveness, preoperative frailty was associated with a seven-fold increased risk of a severe complication or death after 1 year (Table 4). Compared to the ASA and CCI scores, frailty showed the best model performance and discriminative ability for the primary endpoint. After adding frailty to the conventional ASA risk score, the discrimination slope increased by 11% (c-statistic 0.75, $P < 0.01$). Individual frailty characteristics were not associated with the primary or secondary endpoints. Of all frailty characteristics, polypharmacy showed the best model performance (Nagelkerke R^2 0.08).

After a median (IQR) follow-up of 26 (14–31) months, overall survival was worse in frail patients, at a mean of 23.2 months (95% CI 18.7–30.1) vs 32.9 months (95% CI 30.0–35.9) for non-frail patients ($P = 0.01$; Fig. 1). Overall survival was worse for patients with MIBC (22.8 months, 95% CI 18.2–27.5) compared to patients with NMIBC (32.3 months, 95% CI 28.9–35.8) ($P < 0.01$). Frailty remained associated with worse overall survival after adjustment for muscle invasiveness (adjusted hazard ratio 3.2, 95% CI 1.1–9.4; $P = 0.04$).

Table 4 Results of risk scores and components of the preoperative frailty screening on the prediction of severe complications and 1 year all-cause mortality.

Model	OR (95% CI)*	*P*	Nagelkerke R^2	c-statistic*	*P*
Single risk score					
ASA score (<3, ≥3)	4.28 (1.13–16.17)	0.03	0.12	0.64	0.07
CCI score (<5, ≥5)	1.53 (0.45–5.19)	0.49	0.03	0.57	0.37
Frailty model (<2, ≥2)	7.36 (1.70–31.84)	<0.01	0.20	0.72	<0.01
ASA + frailty model	3.58 (1.52–8.41)	<0.01	0.22	0.75	<0.01
Frailty characteristics					
Polypharmacy	2.72 (0.88–8.45)	0.08	0.08	0.63	0.09
Anaemia	1.39 (0.44–4.40)	0.57	0.03	0.59	0.27
6-CIT	1.28 (0.20–8.37)	0.80	0.02	0.56	0.47
TUGT	2.55 (0.70–9.33)	0.16	0.06	0.62	0.12
Hand grip strength	1.89 (0.63–5.73)	0.26	0.05	0.59	0.27
NAGI	1.95 (0.25–15.14)	0.52	0.03	0.57	0.35
MNA	2.05 (0.46–9.25)	0.35	0.04	0.60	0.20
SF-12 PCS	1.83 (0.63–5.31)	0.27	0.05	0.61	0.17
SF-12 MCS	0.43 (0.15–1.26)	0.12	0.07	0.63	0.10
Living alone	0.98 (0.32–3.00)	0.97	0.02	0.55	0.50

MCS, Mental Component Summary; PCS, Physical Component Summary. *All models were adjusted for age and muscle invasiveness.*

Discussion

The present study determined the value of preoperative frailty screening to predict postoperative severe complications and 1 year all-cause mortality in patients undergoing RC. Frailty was commonly present and associated with a seven-fold increased risk of severe postoperative adverse outcomes, including 1-year mortality. Furthermore, preoperative frailty screening improved risk prediction for severe complications or death 1 year after RC, and may be useful for preoperative shared decision-making in patients scheduled for RC.

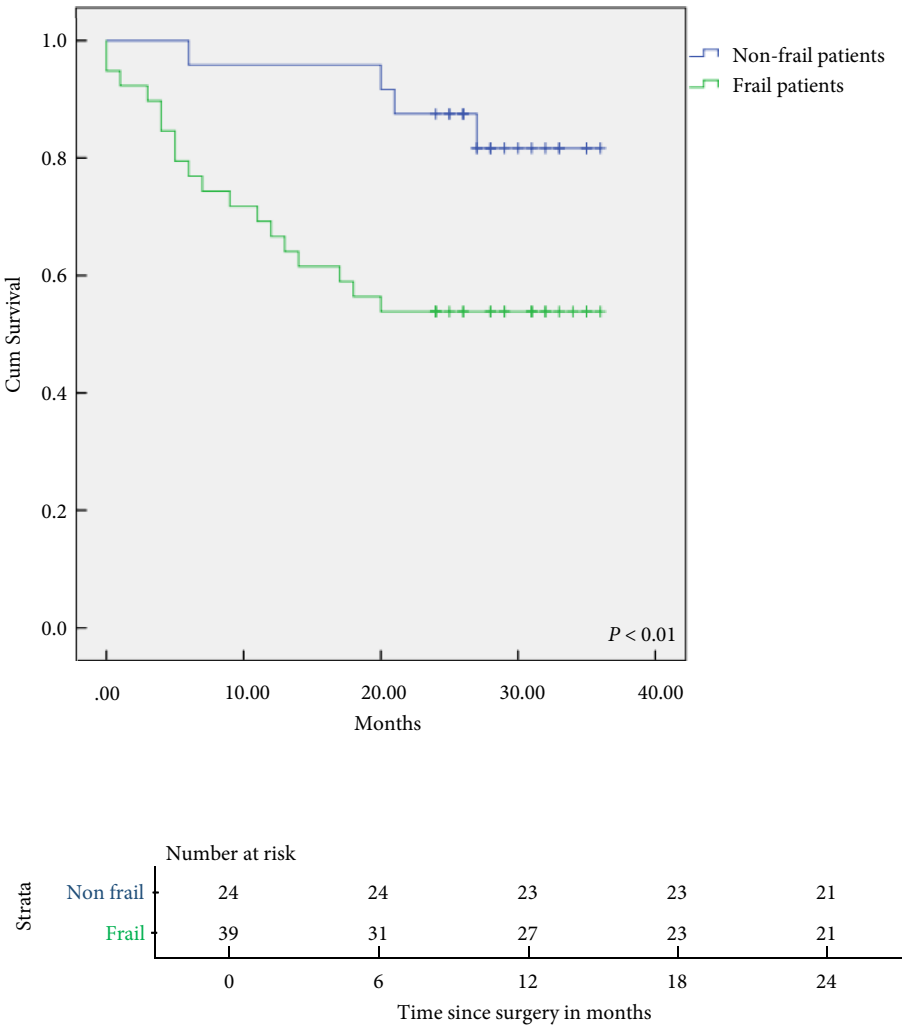
Although RC provides the best long-term oncological prognosis in MIBC and recurrent high-risk NMIBC, surgical morbidity and mortality are high. Especially in frail patients, RC has been associated with poor postoperative outcomes [7–9,17–19].

Contemporary series from high-volume centres report complication rates that range from 25% to 80%, with major complications occurring in approximately one-third of patients [4,5]. Furthermore, comparable results of 30-day mortality (2–4%) and long-term mortality (5-year overall survival 42–58%) were observed in several other studies [6,19,20]. As found in our present study, frailty is common in patients scheduled for RC [8]. In our present cohort, most patients had at least one frailty characteristic and two-thirds of patients were frail in two out of three domains. This can be expected in a population that is characterised by older age and multi-morbidity. Patients with bladder cancer have the highest median age at time of diagnosis in all types of cancers and a median of eight chronic comorbidities, compared to a median of four in the general population [21]. As older age and comorbidities are often associated with frailty, it seems essential to take frailty characteristics into account in order to make the right treatment decisions in the growing cohort of patients undergoing RC.

A majority of the patients is willing to undergo surgical treatment for bladder cancer when risk of adverse outcome is acceptable. Information on expected changes in daily functioning and HRQL after RC is more likely to influence preoperative decision-making than the often limited cancer-related overall survival. However, this type of outcome data in frail patients with bladder cancer is currently lacking, which makes risk stratification complicated. Besides that, preoperative risk management consists of traditional risk assessment tools, such as the ASA or the CCI scores and do not take frailty characteristics into account, leading to an underestimation of perioperative risk. The majority of the studies that examine frailty in patients undergoing RC are population-based, single-centre historical cohort studies [8]. Most studies use the simplified Frailty Index or the Modified Frailty index, which are solely based on functional status and comorbidities [7,17,18,22]. Prospective studies that cover all frailty domains (physical, mental and social), such as our present study, are scarce. In one prospective study of 123 patients with bladder cancer, the Fried Frailty Criteria were predictive of high-grade complications [19]. Our present study results showed that an assessment of frailty in multiple domains was strongly associated with adverse outcome, and that adding frailty to the ASA classification improved discrimination for the primary outcome by 11%.

In addition to improved preoperative risk stratification, frailty screening has the ability to identify potentially modifiable risk factors. Considering that frailty is associated with adverse outcome, it seems reasonable to focus on prehabilitation in order to reduce postoperative complications. However, it is uncertain if prehabilitation is effective in decreasing

Fig. 1 Kaplan–Meier plot of frail vs non-frail patients.



postoperative outcomes in high-risk patients. A recent randomised controlled study of 70 patients undergoing RC concluded that multimodal prehabilitation resulted in faster functional recovery after RC [23]. In contrast, preoperative exercise-based programmes failed to show significant improvement in physical and surgical outcomes [24]. Additionally, a preoperative risk profile that includes frailty may contribute to shared decision making by better informing the surgeon and patient on the risk of adverse outcomes. High-risk patients may be better candidates for bladder-sparing approaches, such as (chemo)radiation [25]. In order to optimise preoperative shared decision-making and to ensure the complexity of the management of frail patients, a MDT approach can be beneficial in the development of such patient-centred treatment plans [10]. Due to the absence of high-quality outcome data in frail patients, clinical consensus in the form of a MDT approach (experienced-based medicine) may be the best available evidence to guide patient selection for RC.

The following limitations should be considered. Although data were prospectively and consecutively collected, our sample size is limited. As a result we were unable to determine which individual frailty characteristics were most strongly associated with adverse outcome. As a full frailty screening is time consuming, a short frailty screening would improve its applicability in daily practice. Although a clear recommendation cannot be made based on our present data, we would suggest the use of screening tools that cover both the physical and mental domains of frailty. Furthermore, to avoid overfitting the multivariable analysis we were not able to add more variables such as operation technique. This also applies for the Cox regression analysis, where we adjust only for muscle invasiveness while variables such as older age, smoking and N+ stage may have influenced survival.

Finally, information on the long-term cause of death was not available, which makes it impossible to distinguish between non-cancer and cancer-related survival. However, frailty

remained associated with 1 year mortality after adjustment of tumour stage in the Cox regression analysis. Despite these limitations, the present study showed a detailed overview of our 1 year of experience in multi-domain frailty screening and adds important information on risk prediction of frail patients undergoing RC.

In conclusion, our present study confirmed that frailty is common in patients undergoing RC and strongly associated with severe complications and all-cause mortality. Preoperative frailty screening has the ability to improve risk stratification and may be used to guide patient selection for RC. However, larger prospective trials are necessary to confirm our present findings.

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Conflict of Interest

Willem Jan W. Bos: Outside the scope of the reported work: grant from Zilveren Kruis Insurance Company. All authors declare that they have no conflict of interest.

Author Contributions

Study concept and design: van der Vlies, Blaauw, Los, van Dongen, Noordzij; Acquisition of data: van der Vlies, Blaauw, Noordzij; Analysis and interpretation of data: van der Vlies, Blaauw, Noordzij; Drafting of the manuscript: van der Vlies, Blaauw, Los, Noordzij; Statistical analysis: van der Vlies, Blaauw, Noordzij; Critical revision of the manuscript for important intellectual content: van der Vlies, Los, Stijns, van Hengel, Blaauw, Bos, van Dongen, van Melick, Noordzij.

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Abbreviations: ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; HRQL, Health-Related Quality of Life; IQR, interquartile range; MDT, Multidisciplinary Team; (N)MIBC, (non-)muscle-invasive bladder cancer; MNA, Mini Nutritional Assessment; OR, Odds ratio; RC, radical cystectomy; RedCAP, Research Electronic Data Capture; SD, Standard deviation; SF-12, Short Form 12; TUGT, Timed to Get up and Go Test; 6-CIT, 6-item Cognitive Impairment Test.

