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UROLOGY - REVIEW

Frailty as a prognostic indicator in the radical cystectomy population: a review

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Abstract

Radical cystectomy and urinary diversion are the current gold standard of management for patients with muscle-invasive bladder cancer. While it is a common urologic procedure, it is associated with significant patient morbidity and mortality. Complications associated with the operation are often frequent, although minor, and significantly impact functional outcomes as well as patient quality of life. Frailty is emerging as a new preoperative prognostic indicator to help determine which patients are at greatest risk of poor outcomes and postoperative complications after treatment. In this review, we summarize the current known literature analyzing frailty as a significant prognostic risk factor of short-term and long-term outcomes after radical cystectomy and urinary diversion in the treatment of muscle-invasive bladder cancer.

Keywords Frailty · Bladder cancer · Radical cystectomy · Prognostic indicator · Complications

Introduction

Urothelial carcinoma is the second most common genitourinary malignancy and is slated to account for 17,670 deaths and 80,470 diagnoses in 2019 [1]. Approximately, 20–25% of these patients are diagnosed with high-grade, muscle-invasive bladder cancer (MIBC), a highly malignant and aggressive disease [2]. The gold standard for treatment for MIBC is radical cystectomy (RC) with pelvic lymph node dissection (PLND) and urinary diversion. Neoadjuvant chemotherapy, usually with gemcitabine/cisplatin (GC) or methotrexate/vinblastine/doxorubicin/cisplatin (MVAC), has also been shown to prolong overall survival [3].

While RC and urinary diversion are the best evidence-based treatment for MIBC, it carries a high postoperative complication rate. At least one perioperative complication is experienced by almost two-thirds of patients undergoing an RC in the treatment of MIBC, while more than 10% experience a high-grade complication based on data from large-scale series [4]. Complications include, but are not limited to, intestinal anastomotic leak, urinary extravasation, intestinal obstruction, infection, bleeding, deep vein thrombosis, and erectile dysfunction [5]. The prevalence of these complications greatly increases the risk of surgery. The 90-day readmission rate for patients undergoing RC has also been shown to be as high as 30%, with the most common cause of readmissions being dehydration, urinary tract infections, and wound-related complications including wound infection [6].

Due to the high morbidity and mortality associated with RC and urinary diversion surgery, a method to screen patients preoperatively needs to be implemented to help better understand and identify the patient population at risk for poor outcomes and complications with specific attention to frailty. Frailty is a geriatric syndrome characterized by weakness, weight loss, and low activity that is associated with adverse health outcomes [7]. It can be defined as a biologic syndrome of decreased physiologic reserve and resistance to stressors causing vulnerability to adverse outcomes [8]. Theories regarding the pathophysiology of frailty are multiple including cumulative declines across multiple biological systems, vulnerability to stressors and decreased physiological reserves yielding a limited capacity to maintain homeostasis, release of pro-inflammatory cytokines contributing to a dysregulated inflammatory state, or dysregulation of apoptosis with deficits in repair of specific tissues (muscle, nerves, bone, etc.) [9, 10]. This literature review summarizes the known studies on frailty, or a physiologically perceived

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fragility or vulnerability, as a new prognostic criterion to help delineate and stratify high-risk patients likely to have worse outcomes after RC in the treatment of bladder cancer.

Materials and methods

A comprehensive literature review was performed at the end of April 2019 within the PubMed database using the keyword search phrases "cystectomy" and "frailty" with no date restriction. Initially, twenty-three articles were identified after the initial literature search; however, ten studies were subsequently excluded. Four of the articles identified were pre-existing literature reviews, one article was not in English (i.e., German), one article was an editorial/author response, one article was a case report of an elderly cystectomy patient who experienced improved clinical endpoints after participation in a comprehensive, multimodal prehabilitation program, and the other three articles were not relevant, discussing medical comorbidities as a predictor of short- and long-term complications after RC, racial disparities in treatment outcomes in patients with early stage bladder cancer, and hyperthermia in the treatment of non-muscle-invasive bladder tumors, respectively. The remaining thirteen articles are included in our literature review below and stratified based on the definition of frailty into the following categories: (1) sarcopenia and weight loss, (2) frailty index from the original 70-item Canada Study of Health and Aging Frailty Index (including the simplified [5-factor], modified [11-factor], and full version based on the American College of Surgeons [ACS] National Surgical Quality Improvement Program [NSQIP] data), and (3) Fried Frailty Criteria (FFC). Our findings, including a review of the results, are summarized below.

Results

Thirteen relevant articles on frailty as a prognostic indicator in the RC population were identified via PubMed search and stratified according to the definition of frailty used as noted above. Four studies defined frailty based on sarcopenia and weight loss, eight studies used the simplified, modified, or full version of the frailty index based on known validated factors from NSQIP data, and one study used the FFC. Each study and its pertinent findings are discussed below.

Frailty based on sarcopenia/weight loss

Sarcopenia is defined as the loss of skeletal muscle mass and function and can serve as an indicator of frailty. It has been associated with a poor quality of life and physical disability with inability to perform daily tasks of living [11]. Malignancy is a known risk factor for the development of sarcopenia. A common methodology used to measure sarcopenia is the lumbar skeletal muscle index (LSMI), which is easily calculated by measuring the surface area of the psoas muscle using a cross-sectional, axial image at L3 on a computed tomography (CT) scan of the abdomen/pelvis. Four studies have previously examined the association of sarcopenia and weight loss with the outcomes of RC and urinary diversion in the treatment of bladder cancer patients (Table 1).

Mayr et al. analyzed sarcopenia as a potential preoperative predictor for 90-day mortality and postoperative complications after RC and urinary diversion in a single-center retrospective study of 327 patients undergoing RC for bladder cancer [12]. LSMI was measured using psoas area on preoperative abdominal CT to assess for sarcopenia and complications were recorded and graded within 90 days after RC for bladder cancer. In the study population, 108 (33%) patients were classified as sarcopenic and experienced significantly more complications than non-sarcopenic patients. On multivariate analysis, an American Society of Anesthesiologists (ASA) Physical Status Classification System score of 3 or 4, the presence of clinical metastatic disease, and sarcopenia based on LSMI measurements were shown to be independent predictors of 90-day mortality. Sarcopenia was also independently associated with high-grade (Clavien ≥ IIIb) complications when correcting for age, body mass index (BMI), ASA score, and type of urinary diversion.

Psutka et al. retrospectively evaluated sarcopenia as a predictor of cancer-specific survival (CSS) and OS among 205 patients with urothelial cancer of the bladder undergoing RC [13]. International consensus definitions of LSMI < 55 cm^2/m^2 for men and < 39 cm^2/m^2 for women were used to define sarcopenia. In the study population, 141 patients (68.8%) were found to be sarcopenic. Patients with sarcopenia were older but were otherwise similar to patients without sarcopenia with respect to sex, Charlson comorbidity index (CCI), ASA score, Eastern Cooperative Oncology Group (ECOG) performance status, receipt of neoadjuvant chemotherapy, TNM stage of disease, and tumor grade. At median follow-up of 6.7 years, sarcopenic patients had significantly worse 5-year CSS (49% vs 72%) and OS (39% vs 70%) compared to patients without sarcopenia. Additionally, sarcopenia was found to be independently associated with both increased cancer-specific mortality (hazard ratio [HR] = 2.14) and all-cause mortality (HR = 1.93) on multivariable analysis.

Finally, Mayr et al. investigated the impact of sarcopenia as an independent predictor of oncological outcomes after RC for bladder cancer in a retrospective, multi-institutional study of 500 patients [14]. Similar to prior studies, LSMI was measured preoperatively on CT scan imaging. One-hundred and eighty-nine patients (37.8%) were classified as sarcopenic, and patients with sarcopenia

Table 1 Frailty based on sarcopenia/weight loss in the radical cystectomy population for bladder cancer

Study	Study size	Definition of frailty	Endpoint(s)	Result(s)
Mayr et al. [12]	327	Sarcopenia (LSMI)	90-day complications and mortality	Sarcopenia, ASA 3-4, cM + were independent predictors of 90-day mortality Sarcopenic patients had significantly more 90-day complications Sarcopenia was independently associated with Clavien ≥ IIIb complications
Psutka et al. [13]	205	Sarcopenia (LSMI)	5-year CSS and OS	Patients with sarcopenia were older. Sarcopenic patients had significantly worse 5-year CSS and OS Sarcopenia was found to be independently associated with both increased cancer-specific and all-cause mortality
Mayr et al. [14]	500	Sarcopenia (LSMI)	5-year CSS and OS	Patients with sarcopenia were older Sarcopenic patients had significantly worse 5-year CSS and OS Sarcopenia was associated independently with both increased cancer-specific and all-cause mortality
Okita et al. [15]	385	≥7.5% weight loss at one month	30-day complications and OS	Patients with significant weight loss had higher grade complications within 1 month of surgery Significant weight loss was an independent risk factor for worse OS

were older compared with their counterparts, but both groups were comparable regarding gender, comorbidity, tumor, node, metastasis (TNM) stage, and type of urinary diversion. Sarcopenic patients had significantly worse 5-year OS (38.3% vs. 50.5%) and 5-year CSS (49.5% vs. 62.3%) rates compared with patients without sarcopenia. Moreover, sarcopenia was associated independently with both increased all-cause mortality (HR = 1.43) and increased cancer-specific mortality (HR = 1.42). These results corroborate prior findings that the presence of sarcopenia can significantly lower a patient's CSS and OS after undergoing RC for bladder cancer.

Postoperative weight loss has also been associated negatively with postoperative outcomes after RC. Okita et al. retrospectively evaluated this risk factor in 385 patients who met the study search criteria that underwent RC and urinary diversion for MIBC [15]. Median postoperative weight loss was measured from baseline at one week and one month and overall survival (OS) was estimated using the Kaplan–Meier method. The authors suggested that patients with significant weight loss, defined as ≥ 7.5% weight loss at one month, had higher grade complications within 1 month and significantly shorter OS than those with postoperative 1-month weight loss of < 7.5%. Significant weight loss was also an independent risk factor for worse OS on Cox regression analysis, and type of urinary diversion, loss of serum albumin, and loss of hemoglobin were not significantly associated with weight loss.

Frailty based on NSQIP frailty index

Various frailty indices have been created and used to help determine which patients should be classified as "frail" to identify at-risk populations for complications after major abdominal surgery and guide postoperative management. One of the first indices created was the Canada Study of Health and Aging Frailty Index (CSHA) [8]. This 70-item scale included various measurements of gait, cognitive function, grip strength, nutritional status, and comorbidities to help predict morbidity and mortality in patients. As many of the factors listed in the CSHA are not routinely collected in clinical care, alternative indices were adapted from the original 70-item index, including the 11-factor modified frailty index (mFI) and the 5-factor simplified frailty index (sFI) based on NSQIP data.

The 11-item mFI, also known as the NSQIP frailty index, is an NSQIP-based 11-factor index that has been proven to adequately reflect frailty and predict mortality and morbidity [8]. These 11 factors, made of 16 variables, map to the original 70-item CSHA and include functional status, history of diabetes mellitus, congestive heart failure, hypertension requiring medication, transient ischemic attack or cerebrovascular accident, myocardial infarction, peripheral vascular disease or rest pain, cerebrovascular accident with neurological deficit, chronic obstructive pulmonary disease or pneumonia, percutaneous coronary intervention, prior cardiac surgery, angina, and impaired sensorium. The mFI

has become increasingly popular in clinical outcomes studies and has been used to predict discharge disposition, complication rates, and mortality.

A simplified 5-item frailty index (sFI) was also created based on previously described measures of frailty as a reliable tool to predict adverse outcomes postoperatively [16]. Variables in this index include a history of chronic obstructive pulmonary disease, diabetes, history of congestive heart failure, hypertension requiring medication, and overall functional status.

Eight studies have previously evaluated the association of the mFI or sFI with regard to outcome measurements in RC patients such as discharge disposition, complications, mortality/survival, and health care resource utilization (Table 2). Pearl et al. identified patients treated with radical cystectomy for bladder cancer using the NSQIP database from 2011 to 2014 [17]. Patients were classified as robust (mFI = 0), pre-frail (mFI = 0.09–0.18), or frail (mFI ≥ 0.27), and the primary endpoint was discharge disposition (defined as home, skilled nursing facility, and rehabilitation dichotomized as home versus non-home). Among 4330 patients, 32.8% were robust, 65.1% were pre-frail, and 2.2% were frail. Overall, 86.2% were discharged home, 4.4% were discharged to a rehabilitation facility, and 9.4% were discharged to a skilled nursing facility (SNF). Frail patients were found to be significantly more likely to be discharged to non-home care independent of major complications post-surgery.

A similar study by Suskind et al. was conducted identifying 20,974 patients aged 65 years and older in the NSQIP database from 2011 to 2013 who had undergone any commonly performed inpatient urologic procedure using the mFI to assess for frailty [18]. Overall, 5.5% ($n = 1144$) of urologic cases resulted in discharge to skilled or assisted living facility, with RC and transurethral resection of bladder tumor (TURBT) accounting for the highest percentage (16.3%). Twenty-five percent of patients undergoing urology procedures were frail (mFI ≥ 0.18), including 9.8% of patients discharged to a facility. After adjustment for other variables including year, age, race, type of anesthesia, smoking status, recent weight loss, and whether or not the procedure was elective, frailty was strongly associated with discharge to a facility (odds ratio [OR] = 3.1; 95% confidence interval (CI) = 2.5–3.8).

The mFI and sFI have also been shown to be a useful prognostic indicator in predicting complications and mortality in patients with bladder cancer undergoing RC. In a study by Chappidi et al. 2679 cystectomy patients identified through the NSQIP database from 2011 to 2013 were analyzed to determine the impact of mFI on Clavien–Dindo (CD) 4 and 5 complications as well as overall mortality [19]. The mFI groups were determined by the number of risk factors per patient (0, 1, 2, and ≥ 3). Out of the 2679 patients identified, 31% ($n = 843$) had an mFI of 0, 44% ($n = 1176$) had an mFI of 1, 21% ($n = 555$) had an mFI of 2, and 4% ($n = 105$) had an mFI ≥ 3. A CD complication was experienced by 59% ($n = 1585$) of patients. Patients classified as mFI ≥ 2 had a significantly higher rate of CD grade 4 or 5 complications (14.6% vs. 8.3%, $p < 0.001$) and overall mortality rate (3.5% vs. 1.8%, $p = 0.01$) in the 30-day postoperative period. Independent predictors of CD grade 4 or 5 complications on multivariate analysis included age > 80 years (OR: 1.58), mFI = 2 (OR: 1.84), and mFI ≥ 3 (OR: 2.58).

Finally, Taylor et al. evaluated the impact of frailty (measured by the sFI) on health care resource utilization (HRU) and post-surgical morbidity/mortality after major urologic oncology surgery using subjects from the 2012 to 2016 NSQIP database [20]. HRU was defined as discharge to continued care facility, unplanned readmission, or prolonged length of stay (greater than 75th percentile) after RC. Increasing HRU was associated with greater frailty (sFI: 0 = 16.7%, 1 = 21.9%, 2 = 28.3%, and 3 or more = 35.4%). An increase in sFI was also independently associated with more complications and more high-grade complications 30 days after surgery and, for subjects who underwent RC, an increase in sFI was associated with higher mortality (sFI: 0 = 0.8%, 1 = 1.5%, 2 = 2.2%, and 3 or more = 3.9%).

Both the mFI and the sFI have been compared in prior published literature to other, more established variables that have been extensively studied and may also be predictive of clinical outcomes after RC. The mFI and the sFI have been analyzed in prior studies as a predictor of post-surgical morbidity and mortality after RC in direct comparison with these other known measurements in various populations of bladder cancer patients.

For example, an alternative, commonly used variable to predict clinical outcomes after RC is the Charlson Comorbidity Index (CCI) and the modified Charlson Comorbidity Index (mCCI), which sought to predict the risk of death within 1 and 10 years of hospitalization for patients with comorbid conditions, including myocardial infarction, chronic lung disease, liver disease, and diabetes mellitus [21]. CCI by itself is not a measurement of frailty, but is another variable that may serve as a useful prognostic indicator of treatment-related complications and survival-related endpoints after RC and urinary diversion.

NSQIP has similarly created a surgical risk calculator as an alternative to frailty to determine the likelihood of postoperative complications by providing a customized risk assessment for each patient based on the operation they are undergoing, demographic information, and preoperative comorbidities [22]. It has been shown to help estimate the incidence of experiencing postoperative complications including readmission, serious morbidity, a return to the operating room, and discharge destination. The NSQIP surgical risk calculator, therefore, serves as an alternative variable in predicting clinical outcomes after RC.

Table 2 Frailty based on frailty index in the radical cystectomy population for bladder cancer

Study	Study size	Definition of frailty	Endpoint(s)	Result(s)
Pearl et al. [17]	4330	mFI	Discharge disposition	Patients defined as frail (mFI ≥ 0.27) were more likely to be discharged to non-home care independent of postoperative complications
Suskind et al. [18]	1638	mFI	Discharge disposition	Frailty (mFI ≥ 0.18) was independently associated with discharge to a facility
Chappidi et al. [19]	2679	mFI	Mortality, grade 4 or 5 complication rate (30-day)	Patients classified as mFI ≥ 2 had a significantly higher rate of 30-day grade 4 or 5 complications and overall mortality rate Independent predictors of grade 4 or 5 complications in the 30-day postoperative period included age > 80 years, mFI = 2, and mFI ≥ 3
Taylor et al. [20]	946	sFI	Health care resource utilization	Increase in sFI was independently associated with prolonged length of stay, more discharges to continued care, and unplanned readmission
Lascano et al. [27]	N/A	mFI	Mortality, grade 4 complication rate (30-day)	Patients with an mFI > 0.20 were more likely to have a CD 4 complication or mortality within 30 days of surgery mFI was comparable or superior to CCI but inferior to ASA in predicting 30-day mortality or CD 4 events When mFI was augmented with ASA, the new index was superior to other risk stratification tools separately.
Sathianathen et al. [28]	5516	sFI, mFI	Major (grade ≥ 3) complications (30-day), discharge disposition	sFI ≥ 3 was an independent predictor of 30-day major complications after RC sFI outperformed ASA in predicting major complications in the 30-day postoperative period but was similar to mFI and NSQIP risk calculator Significant correlation between sFI and discharge disposition
Woldu et al. [29]	346	mFI	1-month complication rates, 3-month readmission rates, hospitalization length, hospitalization costs	There was a weak association of all frailty indices with major complications, but no significant differences when stratifying the results according to mFI, CCI, or ASA Length of hospitalization and associated costs correlated with mFI
Meng et al. [30]	1516	mFI	Adverse events (minor, severe, infectious, any), extended length of hospital stay, discharge to a higher level of care, and mortality	Most predictive comorbidity or demographic criteria for any adverse event after RC was mCCI, BMI, and gender Overall performance was poor for all indexes Combining BMI and mCCI resulted in incremental improvement

The ASA has a scoring system to assess the preoperative physical status of a patient to determine if the patient can tolerate anesthesia and surgery. Unlike frailty, stratification of patients in the ASA scoring system is based primarily on functional limitations, presence of systemic diseases, number of body systems involved, and if the chronic disease is controlled [23]. An ASA score of 1 describes a normal healthy patient while an ASA score of 5 describes a patient not expected to survive without the procedure.

The Adult Comorbidity Evaluation (ACE) scale also uses medical comorbidities, including myocardial infarction, respiratory diseases, end-stage renal disease, stroke, and rheumatic diseases, to classify patients into grades based on severity [24]. It has been previously studied in predicting postoperative morbidity in patients with bladder cancer undergoing surgery. For example, Atallah et al. conducted a study of 49 patients aged ≥ 75 years undergoing open RC and urinary diversion for bladder cancer [25]. Preoperative associated morbidities were collected and graded according to ASA score, the ACE scale, and the CCI. The most commonly associated conditions in the study population were smoking, renal insufficiency, and arterial hypertension. Incidence of early and late complications was 49% and 16%, respectively, with 4 deaths occurring during early follow-up and 25 deaths occurring during late follow-up. The incidence of postoperative morbidity and mortality after RC was not related to ASA, ACE, or CCI. Preoperative malnutrition, renal insufficiency, higher need of perioperative blood transfusions, and prolonged ileus, however, were identified as risk factors of short-term postoperative morbidity while late complications after RC seemed to be related to low body weight.

Finally, ECOG developed an index (ECOG performance status) based on a patient's level of functioning, which includes their ability to take care of themselves, daily activity, and physical ability such as walking and working [26]. Patients are graded from a scale of 0–5 with 0 being fully active and 5 being deceased. Karnofsky (Karnofsy performance status) uses a similar scale except graded from 0 (dead) to 100 (normal with no complaints or evidence of disease). These performance scales also represent alternative prognostic criteria when compared to frailty.

Despite these multiple different methods being used currently in the clinical setting to predict short-term morbidity and long-term oncological outcomes after RC in addition to the many different variations or versions of the frailty index, there is no defined consensus which is superior or more accurate in predicting oncological or morbidity-related endpoints. As noted above, since there are multiple different frailty indices as well as other prognostic variables available for use, comparisons amongst them are valuable to assess their overall accuracy and efficacy in predicting complications and mortality after surgery. The remaining four articles compared the previously described frailty indices with other known prognostic criteria based on endpoints such as discharge disposition, complication rates, hospitalization costs, length of stay, and overall mortality.

A retrospective study was conducted by Lascano et al. evaluated the predictive ability of the mFI on mortality and CD 4 complications within 30 days in patients undergoing cystectomy, prostatectomy, nephrectomy, and nephroureterectomy identified in NSQIP from 2005 to 2013 [27]. In 41,681 patients who were undergoing surgery for presumed urologic malignancy, patients with an mFI > 0.20 were more likely to have a CD 4 complication (OR = 3.7) or mortality (OR = 5.95) in the 30-day postoperative period after adjusting for race, sex, age, smoking history, and procedure. When compared to ASA and CCI, the mFI was shown to be inferior to ASA and superior or comparable to CCI in predicting 30-day CD 4 events or mortality. When the mFI was combined with ASA, it was superior to all other prognostic variables separately.

Sathianathen et al. analyzed 5516 patients undergoing radical cystectomy for bladder cancer from the NSQIP database from 2007 to 2015 to assess the validity of the simplified five-item frailty index (sFI) [28]. Using multivariate logistic regression analysis, sFI was compared to the mFI, NSQIP risk calculator, and the ASA score as a predictor of major (CD ≥ 3) complications within 30 days of surgery. The incidence of 30-day major complications after RC was 10.7%. Patients with an sFI ≥ 3 had a significantly higher likelihood of experiencing a major complication after surgery (OR = 3.22). While the sFI was comparable to mFI and NSQIP risk calculator, its outperformed ASA in predicting major complications and correlated with discharge destination. These results were consistent in the subgroup of patients aged 65 years and older, in whom predictive methods are often inaccurate.

Another study by Woldu et al. determined the validity of mFI when compared to CCI and ASA as risk stratification tools [29]. In a single-institutional study of 346 patients who underwent RC for bladder cancer, the authors analyzed these prognostic parameters in addition to standard clinicopathologic and treatment variables as predictors of 1-month complication rates, 3-month readmission rates, hospitalization length, and hospitalization costs. The overall complication rate was 56.6%, the major (CD ≥ 3) complication rate was 19.4%, and the readmission rate was 27.9% in this cohort. There were no significant differences in the rate of major complications within 30 days of RC when stratifying the results according to the mFI, CCI, or ASA class. Length of hospitalization and associated costs, however, correlated with the mFI alone. The authors concluded, therefore, that NSQIP frailty indices provided little additional predictive ability over the ASA classification and the CCI score.

Lastly, Meng et al. determined the predictive ability of mFI compared to the mCCI after RC for bladder cancer in relation to minor adverse events, severe adverse events, infectious adverse events, any adverse event, extended length of hospital stay, discharge to a higher level of care, and mortality [30]. Data from 1516 patients undergoing elective RC for bladder cancer were extracted from 2005 to 2011 in the NSQIP database, and the endpoints noted above were assessed using area under the curve (AUC) analysis from the receiver operating characteristic curves. The most predictive comorbidity index for any adverse event was the mCCI (AUC = 0.511), and the most predictive demographic factor was BMI (AUC = 0.519) and gender (AUC = 0.519). Although the overall performance for all predictive indexes was poor, combining BMI with the mCCI resulted in incremental improvements in discriminative ability for perioperative adverse outcomes after RC. Similar to the Woldu et al. study noted above, the authors stated that the mFI provided little additional prognostic ability over the mCCI score in standard clinical practice.

Frailty based on fried frailty criteria

Another standardized tool that has been used to measure frailty as a prognostic criterion after RC in bladder cancer is the Fried Frailty Criteria (FFC) (Table 3). The FFC, derived from the Cardiovascular Health Study, has also been reported to correlate with worse postoperative outcomes after major surgery [31]. FFC includes factors such as shrinking, physical endurance, weakness, slow walking speed, and low physical activity. Burg et al. evaluated 123 patients ≥ 65 years (median age = 74) undergoing RC for bladder cancer [32]. Patients were preoperatively assessed and classified using the FFC (grip strength, gait speed, exhaustion, physical activity, shrinking) in addition to other prognostic factors including CCI, ASA, Katz Index of Independence in Activities of Daily Living, Karnofsky performance scale, ECOG performance status, and Center for Epidemiological Studies Depression scale, which includes symptomatology such as restless sleep, poor appetite, and loneliness. Thirty-day and 90-day postoperative complications were recorded as endpoints for this study. Fifty-nine patients (48.0%) had ≥ 1 complication within 30 days after surgery and 72 patients (58.5%) within 90 days. A higher Center for Epidemiological Studies Depression scale (OR: 1.08) and shrinking (OR: 3.79), defined as ≥ 10 lb of unintentional weight loss in the past year, were independent predictors for increased postoperative 30-day complications after RC, while increased physical activity (OR: 0.84) was independently associated with less 90-day complications after surgery. Intermediate or full frailty measured by the FFC was associated with high-grade 30-day (OR: 4.87) and 90-day (OR: 3.01) complications along with ECOG performance status ≥ 3 (OR: 45, and OR: 17.85, respectively). The authors, therefore, concluded that frailty defined by the FFC was predictive of high-grade complications after RC, while individual components were predictive of having any complication.

Discussion

As noted above, frailty is emerging as a useful prognostic tool in predicting patients at risk for postoperative complications after RC for bladder cancer. As described in many of the above studies, frailty can significantly impact outcomes such as postoperative morbidity, mortality, length of stay, and cost of care. As the population ages, the incidence of bladder cancer will continue to rise, and urologists and oncologists will encounter the dilemma of treatment decisions in a significantly elderly and frail group. Since RC is associated with significant loss of function both short-term and long-term, an index/measurement tool to predict frailty would be highly useful in predicting the quality of life trade-off for each individual patient that would occur with surgery. It would also aid in the development of a personalized risk/benefit calculator to determine the next best course of treatment. For example, a study conducted by Shariat et al. reported that elderly, "frail" patients have a poorer response to intravesical Bacillus Calmette Guerin (BCG), RC, and perioperative chemotherapy compared to their younger

Table 3 Frailty based on fried frailty criteria in the radical cystectomy population for bladder cancer

Study	Study size	Definition of frailty	Endpoint(s)	Result(s)
Burg et al. [32]	123	FFC	30-day and 90-day postoperative complications	Center for Epidemiological Studies Depression Scale and shrinking were associated with 30-day complications after RC Physical activity was protective for 90-day complications Intermediate or full frailty was associated with high-grade 30-day and 90-day complications as well as ECOG performance status ≥ 3 FFC was predictive of high-grade complications after RC

counterparts [33]. It is, therefore, essential to determine each individual patient's frailty, functional status, independence (with regard to activities of daily living), and the potential psychological effects that RC may have both short-term and long-term prior to treatment decisions.

While the number and types of frailty definitions showing promise as a prognostic indicator in the RC population are growing, limitations exist. These include lack of objective measurements included in their calculations, lack of proper testing, and lack of standardization across studies. A wide variety of frailty measurements have been reported based on different criteria including sarcopenia/weight loss, mFI, sFI, or the FFC. While they have all shown various degrees of predictive value in postoperative morbidity and mortality after RC in the bladder cancer population, there is no consistency regarding their use across multiple studies or institutions. Furthermore, these frailty indices often examine different endpoints, different databases, and different patient populations, often with special attention to a specific age group or disease stage, limiting its generalized applicability to other RC cohorts.

Additionally, as noted above, reported studies can sometimes disagree on the definition of variables used to determine frailty. Sarcopenia (i.e., muscle wasting), for example, was defined in the Psutka et al. study to be an LSMI of < 55 cm^2/m^2 for males and < 39 cm^2/m^2 for females [13]. Other studies evaluating sarcopenia in the RC population, however, have defined sarcopenia as an LSMI of < 42.2 cm^2/m^2 for males and < 33.9 cm^2/m^2 for females [34]. This difference could be secondary to the specific study population analyzed or due to lack of external validation of ideal cutoff points based on multiple, prior, large-scale trials in the bladder cancer population. Similarly, the factors listed in these studies to define frailty such as severity of comorbidities, nutritional status, cognitive function, and gait measurements lack consensus on appropriate cutoff values in addition to being more subjective in nature. Objective measurements of frailty with pre-defined, standardized definitions need to be developed to optimize testing of their prognostic abilities after RC, which could further their credibility and validity as a prognostic marker across multiple institutions and patient populations. The current lack of standardization makes it difficult to generalize frailty to a wide population of RC patients and determine their usefulness and predictive ability, especially in the growing setting of multimodal management including neoadjuvant systemic therapy.

Lastly, the majority of the articles examining frailty after RC and urinary diversion are population-based, single-cohort studies which analyze the indices retrospectively as a predictor of endpoints. A prospective trial of one or more frailty measurements should be considered in the RC population to appropriately test their significance and to minimize bias from other prognostic criteria. Prospective studies would also allow for the evaluation of prehabilitation therapy as a way to prepare the body for surgery by either reducing or reversing frailty in bladder cancer patients undergoing RC to improve postoperative morbidity. Carli et al. analyzed the impact of a multimodal prehabilitation program on the postoperative recovery of a 85-year-old male patient with muscle-invasive urothelial carcinoma of the bladder associated with hydronephrosis scheduled to undergo elective radical cystoprostatectomy and ileal conduit diversion [35]. The patient had a past medical history of poorly controlled type II diabetes, anemia, chronic renal failure, and glaucoma. He was deemed to be frail secondary to multiple criteria including a Fried score of 5 (mildly frail), 15% body weight loss, weak grip strength, severe depression and moderate anxiety, poor nutritional status [patient-generated subjective global assessment (PG-SGA) = B], and low functional walking capacity [6-min walking test (6MWT) = 210 m]. He was enrolled in a 4-week multimodal prehabilitation program including moderate aerobic and resistant exercises, nutritional counseling with whey protein supplementation (20 g/day), and relaxation exercises. His postoperative course was largely uneventful, with the exception of hyperglycemia and hypomagnesemia. The patient was discharged on postoperative day 7 and returned home to continue the program for an additional 8 weeks. Measurements of 6MWT, Health-Related Quality of Life (via SF-36 questionnaire), physical activity, and Hospital Anxiety and Depression Scale (HADS) conducted at baseline, before RC, and at 4 and 8 weeks after surgery revealed a progressive remarkable improvement before surgery that continued after surgery until last follow-up. This case report, the authors suggested, provided evidence of the benefits of comprehensive, multimodal prehabilitation programs in reducing postoperative morbidity and mortality in bladder cancer patients undergoing RC and urinary diversion, especially in those that are deemed to be frail and at high risk for postoperative complications.

Conclusions

The quality of life and psychosocial concerns for patients undergoing RC and urinary diversion for bladder cancer need to be weighed against the cancer-related benefits of surgery. Determining patients at greatest risk for postoperative complications, morbidity, and mortality is crucial in determining what treatment modalities should be offered primarily and whether RC should be reserved for low-risk patients. Frailty has emerged as a valuable predictor of postoperative outcomes and is growing in use. The measurements of frailty mentioned above are useful tools that need to be utilized and integrated into the preoperative assessment and treatment planning of bladder cancer patients

undergoing surgery. Multimodal prehabilitation programs that could potentially improve or reverse frailty prior to RC also need to be considered and applied on a large scale to optimize clinical outcomes.

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