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Frailty as a Marker of Adverse Outcomes In Bladder Cancer Patients Undergoing Radical Cystectomy

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Abstract

Objective—To investigate the modified frailty index (mFI) as a pre-operative predictor of post-operative complications following radical cystectomy in bladder cancer patients.

Materials and Methods—Patients undergoing radical cystectomy (RC) were identified from the National Surgical Quality Improvement Program (NSQIP) participant use files (2011-2013). The mFI was defined in prior studies with 11 variables based on mapping the Canadian Study of Health and Aging Frailty Index to NSQIP comorbidities and activities of daily living (ADL)s. Modified frailty index groups were determined by the number of risk factors per patient (0, 1, 2, 3). Univariate, χ^2 , independent sample t-test, and logistic regression analyses were performed when appropriate. A sensitivity analysis was performed to determine the mFI value at which Clavien 4 and 5 complications would reach significance.

Results—Of the 2679 cystectomy patients identified, 31% percent of patients had a mFI of 0, 44% had a mFI of 1, 21% had a mFI of 2, and 4% had a mFI 3. Overall, 59% of patients experienced a Clavien complication. When stratified at a cutoff of mFI ≥ 2 , the overall complication rate was not different (61.7% vs. 58.3%, $p=0.1319$), but the mFI2 or greater group had a significantly higher rate of Clavien grade 4 or 5 complications (14.6% vs. 8.3%, $p<0.001$) and overall mortality rate (3.5% vs. 1.8%, $p=0.0128$) in the 30-day post-operative period. The multivariate logistic regression model showed independent predictors of Clavien grade 4 or 5 complications were age >80 years old (OR, 1.58 [1.11-2.27]), mFI2 (odds ratio [OR], 1.84 [1.28-2.64]), and mFI3 (OR, 2.58 [1.47-4.55]).

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Conclusions—Among patients undergoing radical cystectomy, the mFI can identify those patients at greatest risk for severe complications and mortality. Given that bladder cancer is increasing in prevalence particularly among the elderly, pre-operative risk stratification is crucial to inform decision making about surgical candidacy.

Keywords

Bladder Cancer; Frailty; Radical Cystectomy; Perioperative Outcomes

1.1 Introduction

In 2015, 74,000 new cases of bladder cancer will be diagnosed and 16,000 deaths will occur due to this disease [1]. Bladder cancer is primarily a disease of older patients with approximately 9 out of 10 people with bladder cancer over the age of 55 and a mean age of muscle-invasive bladder cancer at diagnosis is 73 years of age [1]. It is estimated that the number of individuals over 65 in the United States will almost double in the next 35 years to more than 88 million by 2050 [2]. As a result, the burden of bladder cancer on the US healthcare system will continue to rise over the next few decades as America's population continues to age and thus increased utilization of surgery will be necessary to treat advanced cancers of the genitourinary tract.

The preferred treatment for muscle-invasive bladder cancer is radical cystectomy (RC) with pelvic lymph node dissection. However, the rates of perioperative complications ranges from 28% to 64% with 30 day mortality rates from 1.1% to 5.2% in patients undergoing this procedure [3-13]. In light of significant perioperative morbidity and mortality, it is important to identify patient-level factors which may be used in preoperative risk stratification and to help guide the decision making process about whether to proceed with radical cystectomy, as there is a subset of patients that would benefit from bladder sparing radiation therapy [14]. Furthermore, identification of modifiable risk factors may allow for interventions aimed at mitigating specific perioperative complications.

While chronologic age has been a good predictor of adverse postoperative outcomes following surgeries in various specialties, studies have identified frailty as a more accurate predictor of adverse postoperative outcomes in cohorts of patients undergoing gynecological oncology and bariatric surgery [15, 16]. Therefore, a frailty index is an objective measure that could be used for peri-operative risk stratification. Frailty can be defined as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes [17]. One of the first assessments created to assess frailty was the Fried Frailty phenotype which defined frailty to include at least 3 of the following: unintentional weight loss, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity [17]. Subsequently, a widely accepted and validated index of frailty used to operationalize the phenotype stated above was created and termed the Canadian Study of Health and Aging Frailty Index (CSHA-FI). This index incorporates 70 deficits, including symptoms, signs, disabilities, and diseases, to calculate a measure of frailty [18]. However, identifying and quantifying 70 items for each patient provides a barrier to the practical use of the CSHA-FI

in patient populations. As a result, a modified frailty index (mFI) containing 11 variables that were selected by mapping the CSHA-FI items onto the existing National Surgical Quality Improvement Program (NSQIP) preoperative variables was created, and it was first utilized in colectomy patients as a successful predictor of ICU-level complications and mortality [19]. The mFI is a modification of a comorbidity index that incorporates specific comorbidities of interest with an assessment of functional status in its calculation.

Currently there is no literature to support the use of the mFI in patients undergoing cystectomy. Therefore, our objective was to investigate the mFI as a pre-operative predictor of post-operative complications following radical cystectomy.

1.2 Patients and Methods

Approval for this research was secured from The Johns Hopkins Medicine Institutional Review Board.

1.2.1 Patient Cohort

Patients undergoing cystectomy were identified from the National Surgical Quality Improvement Program (NSQIP) participant use files (2011-2013). Briefly, the NSQIP dataset is a national prospectively maintained registry run by the American College of Surgeons (ACS). Unlike a claims-based dataset, all data are abstracted prospectively by nurses to verify clinical information. A three year interval was selected to allow for the maturation of the NSQIP dataset (which was small and undersampled prior to 2011) and to reflect a contemporaneous cohort of bladder cancer patients. Additionally, the data for readmissions and reoperations was only available after 2011.

Patients undergoing radical cystectomy (RC) for bladder cancer were identified based on Current Procedure Terminology (CPT) codes for RC (51570, 51575, 51580, 51585, 51590, 51595, 51596, and 51597) and the International Classification of Diseases (ICD9) codes for bladder cancer (188 and 188.x). This was a similar methodology to prior urologic studies using NSQIP(20). The mFI was defined as in prior studies based on mapping the Canadian Study of Health and Aging Frailty Index to NSQIP comorbidities and activities of daily living (ADL)s (see Table 1)(18). Eleven variables from the CSHA-FI were matched with the preoperative comorbidities in NSQIP to create the mFI (Table 1). Modified frailty index groups were determined by the number of risk factors per patient (0, 1, 2, 3).

1.2.2 Statistical Analysis

Primary outcomes of interest included the presence of Clavien 4 (life-threatening complication requiring ICU management) or 5 (death) complications within 30 days of surgery. Secondary outcomes of interest included having a complication of any type within 30 days of surgery, specific complications (septic shock, ventilator dependence for >48 hours, unplanned intubation, myocardial infarction [MI], acute renal failure requiring dialysis [ARF], cardiac arrest requiring cardiopulmonary resuscitation [CA], surgical site infection [SSI], deep vein thrombosis [DVT], pulmonary embolism [PE]) as well as operative time, hospital length of stay (LOS), re-operation, and re-admission within 30 days of surgery.

Univariate χ^2 and independent sample t-test were utilized to compare baseline demographic information for categorical and continuous variables as appropriate. Additional univariate analyses were performed to compare basic complication outcomes according to mFI. A sensitivity analysis was performed to determine the mFI group threshold at which the rate of Clavien 4 or 5 complications became significantly higher. A multivariate logistic regression model was then created using all variables that had $p < 0.10$ in the univariate logistic regression analysis. This multivariate model contained age, gender, race, smoking status, and the mFI score to predict the likelihood of having a Clavien grade 4 or 5 complication. All Statistical analysis was performed using SAS®, version 9.1. A p-value of < 0.05 was considered statistically significant.

1.3 Results

In total, 2679 patients were identified as having undergone radical cystectomy for bladder cancer in the National Surgical Quality Improvement Program from 2011-2013.

1.3.1 Cohort Demographics

Demographics data for this cohort is listed in Table 2. Thirty-one percent of patients had a mFI of 0, 44% had a mFI of 1, 21% had a mFI of 2, and 4% had a mFI 3. There was no significant difference in gender ($p=0.24$) or race ($p=0.2151$) between the mFI groups. Higher mFI group status was associated with a higher pre-operative BMI, pre-operative creatinine, and ASA classification (all $p < 0.001$). As the mFI group number increased, patients were more likely to be smokers with 9.6% smokers in the mFI0 group, 7.8% in the mFI1 group, 9.0% in the mFI2 group, and 33.3% in the mFI3 group ($p < 0.001$). Higher mFI group status was also associated with older age; mean age of 65.0 for mFI0, 70.1 for mFI1, 70.7 for mFI2, and 72.8 for mFI3 ($p < 0.001$).

1.3.2 Peri-operative Outcomes

Table 3 shows peri-operative outcomes stratified by an mFI cutoff greater than or equal to 2. There was a significant difference in mean operative time (352.1 vs. 353.6 min, $p < 0.01$) and length of hospital stay (10.0 vs. 11.0 days, $p < 0.01$) between groups. There was no significant difference in surgical site infections rate (5.0% vs. 5.8%, $p=0.4169$), 30-day readmission rate (20.3% vs. 21.1%, $p=0.6548$), 30-day reoperation rate (5.9% vs. 7.1%, $p=0.2563$), and overall complication rate (61.7% vs. 58.3%, $p=0.1319$) between groups. Several types of complications were more common in the mFI2 or greater group including respiratory (5.2% vs. 9.7%, $p < 0.001$), cardiovascular (2.2% vs. 4.4%, $p=0.0024$), and renal (1.7% vs. 3.2%, $p=0.0240$) complications. Notably, the mFI2 or greater group had a significantly higher rate of Clavien grade 4 or 5 complications (14.6% vs. 8.3%, $p < 0.001$) within 30 days of surgery and overall mortality rate (3.5% vs. 1.8%, $p=0.0128$).

1.3.3 Multivariate Logistic Regression Model

The multivariate logistic regression model showed age > 80 years old (OR, 1.58 [1.11-2.27]), mFI2 (odds ratio [OR], 1.84 [1.28-2.64]), and mFI3 (OR, 2.58 [1.47-4.55]) are independent predictors of the likelihood of Clavien grade 4 or 5 complications with mFI3 being the

strongest predictor (Table 4). While age groups <80 years old, mFI1 status, gender, race, and smoking status were not associated with Clavien grade 4 or 5 complications.

1.4 Discussion

As the bladder cancer patient population continues to age, it is increasingly important to identify those patients at increased risk of severe complications and mortality in the perioperative period. Risk stratification is especially important for radical cystectomy, as the majority of patients experience at least one post-operative complication within 30 days of surgery [7, 8, 21]. Furthermore, the severity of complications varies greatly and is something that could potentially be predicted pre-operatively.

Physicians are required to use their subjective judgment and clinical experience to estimate the patient's probability of having a severe adverse event following RC. However, Revenig et al have demonstrated that surgeons place too much importance on age when trying to assess frailty [22]. Due to this potential bias of age in making decisions about surgical candidacy, there is a need for objective measures of frailty that can be used by urologists to risk stratify patients pre-operatively undergoing radical cystectomy.

In this large cohort study of urothelial carcinoma patients undergoing radical cystectomy, we report that the mFI can serve as an objective tool to identify patients at a greater risk of severe (Clavien grade 4 or 5) post-operative complications including mortality. Moreover, the mFI score is indeed a stronger predictor of high-grade adverse outcomes than age. Our findings also show that for patients younger than 80 years old, age should not be used as a predictor of severe post-operative complications. Instead, these patients of lower chronological age represent a group that would benefit greatly from the use of the mFI score, instead of age, for pre-operative risk stratification, patient counseling, and determination of surgical candidacy.

The need for more information than age alone to determine postoperative outcomes in bladder cancer patients, has been previously demonstrated by studies showing that the patient's Charlson comorbidity index, Elixhauser index, Eastern Cooperative Oncology Group (ECOG) performance status are independent predictors of 90 day mortality rates and 5 year all-cause mortality following radical cystectomy [3, 23]. While these other comorbidity indices have predictive utility, the advantage of the mFI is due to its combination of the following factors: objective measure, contains only 11 variables, takes into account functional status and medical comorbidities, and can be easily calculated during a single clinical encounter. The inclusion of the pre-operative functional status of the patient is important, as it has been shown to be an independent predictor of complication rates in urological surgery patients [7].

For this study, a mFI score of 2 represents a cut-off at which the high-grade post-operative complication and mortality rates significantly increased among patients. These types of cut-offs provide clinical utility when creating future guidelines for taking care of patients who are of questionable surgical candidacy. While a score above this cut-off would not be an absolute or relative contraindication to radical cystectomy, it would serve as an important

clinical indicator that this patient may want to strongly consider other potential treatment options outside of radical cystectomy if oncological principles for treatment of bladder cancer would not be compromised with these alternative treatment options. At our center, preserving oncologic efficacy is of primary importance in the treatment of muscle-invasive bladder cancer. However, the decision to proceed with cystectomy is an individualized decision for each patient, and it is vital that patients have a comprehensive understanding of the oncologic efficacy of each treatment option available to them and the risk of low and high-grade complication rates in similar patients to appropriately weigh the risks and benefits. In some instances, patients may decide to choose treatments with equivalent or lower oncologic efficacy for the benefit of a lower high-grade complication rate. It is important to note that while the mFI can serve as a useful tool in pre-operative counseling and decision-making, there are several other factors including age, BMI, ASA class, and patient expectations that should still be taken into account when making a decision to proceed with radical cystectomy.

The use of mFI to risk stratify patients pre-operatively could play an important role in the reimbursement scheme used in pay for performance (P4P) models. Advocates of the P4P model argue the model incentivizes healthcare providers to provide the best quality of care for patients in order to improve overall patient outcomes [24]. The P4P reimbursement schemes are constructed to financially penalize providers for patients that experience post-operative complications. However, the insurance companies are failing to acknowledge that each patient is not equivalent in their likelihood of having a post-operative complication. By doing so, the insurance companies are incentivizing providers to avoid performing procedures, such as radical cystectomies, that have high perioperative complication rates. The mFI could be utilized to identify patients with a higher likelihood of adverse events for whom the urologist would face lower penalties or even no penalties at all for complications. The addition of this risk stratification in the reimbursement scheme would be in the best interest of the patient, as it would create more appropriate incentives for urologists. The information in order to calculate the mFI is not readily available at non-NSQIP facilities, which decreases the feasibility of using this method at those centers.

In this study, we found that gender is not associated with the rate of Clavien grade 4 or 5 complications following RC. This is consistent with Siergrist et al., which found that gender was not a significant predictor of the rate of both major (Clavien grade 3-5) and minor (Clavien grade 1 or 2) complications in the perioperative period [25]. However, a recent meta-analysis of 17 studies showed female gender is associated with a higher rate of cancer specific death (CSD), which we are not able to investigate this finding due to the limitations of the NSQIP database [26]. Previously it has been suggested this gender difference is due to women presenting with more advanced disease along with sociodemographic differences and the association of gender with CSD disappears when controlling for these confounders [27]. Nevertheless, the importance of gender in post-operative outcomes and mortality requires further investigation to elucidate potential associations and confounding factors.

There are several limitations to our study including that it is a retrospective analysis of prospectively collected data in the NSQIP database. Additional limitations of the database include a follow-up period limited to 30 days post-operatively along with the lack of

recording gastrointestinal complications, which are common in the radical cystectomy population [5,8,10,12,21]. Moreover, the NSQIP database does not provide information about the volume of cystectomies performed at the institutions, the quality of training of the surgeons, the type of urinary diversion performed, the histopathological staging of the bladder cancer, and whether the patient underwent neoadjuvant chemotherapy, which could all greatly affect the complication rates associated with this radical cystectomy. Additionally, the use of the mFI does not take into account the factors associated with the physical phenotype of frailty described earlier. Moreover, in the NSQIP database, there is no measure taking into account the patient's quality of life post-operatively, which is often an important factor for patients determining whether to proceed with surgery. Future studies are warranted to investigate the ability of frailty to prospectively predict post-operative complications and mortality rates. In spite of these limitations, it is important to recognize the NSQIP data set provides a large, multi-center database with patient heterogeneity that removes the biases associated with single-center studies [15].

1.5 Conclusions

The modified frailty index is a strong predictor of high-grade post-operative complications and mortality following radical cystectomy, and it has the potential to be a very important objective tool for risk stratification and perioperative counseling of bladder cancer patients.

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Highlights

- Applying the modified frailty index to assess surgical candidacy of radical cystectomy patients
- Higher mFI score correlates with higher rate of Clavien grade 4 and 5 complications.
- MFI score of 2 or greater represents potential threshold for surgical candidacy.
- Can use the mFI pre-operatively to risk stratify patients.

Table 1

Risk factors used to calculate the modified frailty index and incidence in cohort.

Risk Factor	Score	No. in Cohort
Functional health status prior to surgery: partially or totally dependent	1	39 (1.5%)
Diabetes Mellitus Type II	1	529 (19.8%)
Chronic Obstructive Pulmonary Disease	1	230 (8.6%)
Congestive Heart Failure	1	18 (0.67%)
History of myocardial infarction within past 6 months	1	3 (0.11%)
Prior cardiac surgery, percutaneous coronary intervention, or angina within past month	1	92 (3.43%)
Hypertension	1	1660 (62.0%)
Impaired sensorium	1	0
History of transient ischemic attack	1	10 (0.37%)
History of cerebrovascular accident	1	5 (0.19%)
Peripheral vascular disease requiring surgery or active claudication present	1	12 (0.45%)

The risk factors above were chosen by mapping the Canadian Study of Health and Aging Frailty Index to NSQIP comorbidities and activities of daily living [19]. The number of comorbidities a patient exemplified was tallied, and this total value was used as the mFI score. The incidence of each comorbidity is listed.

Table 2

Baseline demographics stratified by modified frailty index

Characteristic	mFI = 0	mFI = 1	mFI = 2	mFI >= 3	p-value
N	843 (31.5%)	1176 (43.9%)	555 (20.7%)	105 (3.9%)	
Mean Age (SD)	65.0 (11.9)	70.1 (10.1)	70.7 (9.7)	72.8 (9.0)	p<0.001
Gender					
- Female	180	217 (18.5 %)	99 (17.8%)	17 (16.2%)	P=0.24
- Male	(21.4%) 663 (78.6%)	959(81.5%)	456 (82.2%)	88 (83.8%)	
Race					
- Caucasian	676	974 (82.8 %)	468 (84.3%)	85 (80.9%)	P=0.2151
- Non-Caucasian	(80.2%) 167 (19.8%)	202 (17.2%)	87 (15.7%)	20 (19.1%)	
BMI (SD)	26.9 (5.2)	29.0 (5.9)	30.0 (6.4)	29.8 (6.6)	p<0.001
Pre-op	1.07 (0.61)	1.20 (0.65)	1.23 (0.75)	1.31 (0.59)	p<0.001
Creatinine (SD)					
Smoking Status					
- Smoker	81 (9.6%)	92 (7.8%)	50 (9.0%)	35 (33.3%)	p<0.001
- Non-smoker	762 (90.4%)	1084 (92.2%)	505 (91.0%)	70 (66.7%)	
ASA Class					
- Class 1	14 (1.7%)	1 (0.09%)	0	0	p<0.001
- Class 2	339	258 (22.0%)	64 (11.6%)	4 (3.8%)	
- Class 3	(40.3%)	850 (72.4%)	451 (81.4%)	76 (72.4%)	
- Class 4	469 (55.7%) 20 (2.4%)	65 (5.5%)	39 (7.0%)	25 (23.8%)	

In higher mFI groups, there were older patients with higher BMIs pre-operative creatinines, and ASA classification that were more likely to be smokers. There was no difference in gender and race between the mFI groups.

Table 3

Peri-operative outcomes stratified with cutoff of modified frailty index ≥ 2 .

Characteristic	mFI < 2	mFI ≥ 2	p-value
OR Time (min, with 95% CI)	352.1 (347-358)	353.6 (344-363)	p<0.01
Hospital Length of Stay (LOS)	10.0 (9.7-10.4)	11.0 (10.2-11.8)	p<0.01
Surgical Site			
Infection	100	38 (5.8%)	p=0.4169
- Yes	(5.0%)	622	
- No	1919		
Respiratory			
Complication	105	64 (9.7%)	p<0.001
- Yes	(5.2%)	596	
- No	1914		
Renal Complication			
- Yes	35 (1.7%)	21 (3.2%)	p=0.0240
- No	1984	639	
CV Complication			
- Yes	44 (2.2%)	29 (4.4%)	p=0.0024
- No	1975	631	
30-day			
Readmissions	401	137	p=0.6548
- Yes	(20.3%)	(21.1%)	
- No	1572	511	
30-day			
Reoperations	119	47 (7.1%)	p=0.2563
- Yes	(5.9%)	613	
- No	1900		
Overall Mortality			
- Yes	37 (1.8%)	23 (3.5%)	p=0.0128
- No	1982	637	
Overall			
Complications (Any grade)	1178 (58.3%)	407 (61.7%)	p=0.1319
- Yes	841	253	
- No			
Clavien grade 4 or 5 complication			p<0.001
- Yes	168	96	
- No	(8.3%)	(14.6%)	
	1851	564	

The patients in the higher frailty group had a higher rate of Clavien grade 4 or 5 complications, higher overall mortality, longer OR times, longer hospital length of stays, more respiratory, renal, and cardiovascular complications. There was no difference in overall complication rates, 30-day readmission, and 30-day reoperation rates between the two groups.

Table 4

Logistic regression model.

Characteristic	Clavien 4 or 5 Complications		Death	
Age				
- <50	Ref		Ref	
- 50-59	0.99 [0.46-2.16]	0.997	0.60 [0.07-5.18]	0.64
- 60-69	0.89 [0.57-1.37]	0.58	0.55 [0.20-1.51]	0.24
- 70-79	0.86 [0.62-1.19]	0.36	0.92 [0.47-1.83]	0.82
- >80	1.58 [1.11-2.27]	0.0121	2.72 [1.40-5.31]	0.0033
Gender				
- Female	Ref		Ref	
- Male	1.23 [0.87-1.74]	0.24	0.69 [0.38-1.26]	0.23
mFI				
- mFI0	Ref		Ref	
- mFI1	1.16 [0.83-1.62]	0.39	0.66 [0.34-1.28]	0.22
- mFI2	1.84 [1.28-2.64]	0.0010	1.24 [0.62-2.45]	0.55
- mFI3	2.58 [1.47-4.55]	0.0010	2.07 [0.78-5.49]	0.14
Race				
- Non-Caucasian	Ref		Ref	
- Caucasian	1.01 [0.72-1.42]	0.96	0.79 [0.42-1.49]	0.47
Smoking Status				
- Non-Smoker	Ref		Ref	
- Smoker	1.15 [0.86-1.54]	0.36	1.70 [0.96-3.03]	0.07

The model showed age >80 years old, mFI2 status, and mFI3 status are independent predictors of the likelihood of Clavien grade 4 or 5 complications with mFI3 being the strongest predictor.