A Prospective Evaluation of Different Frailty Indices in Patients Undergoing Transurethral Resection of Bladder Tumor

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Abstract

Background Most studies investigating the relationship between preoperative frailty and postoperative outcomes among bladder cancer patients only assess frailty retrospectively in patients who have undergone radical cystectomy. Transurethral resection of bladder tumor (TURBT) is a commonly performed procedure in outpatient settings for a large number of bladder cancer patients. The prevalence of frailty among bladder cancer patients and its impact on postoperative complications and mortality are not well studied.

Methods To assess the prevalence of frailty among bladder cancer patients planned for TURBT at a tertiary cancer center using the modified frailty index (mFI) and Risk Analysis Index (RAI) and further assess the impact of these indices on 30-day postoperative complications and mortality rates.

Results Between May 2020 and March 2021, 343 consecutive patients were enrolled. The mean age of the cohort was 64.8 ± 13.1 years, 86.6% were male, and 82% had non–muscle-invasive bladder cancer (NMIBC). The majority of the cohort (92%) was found to have low American Society of Anesthesiologists (ASA) score class (I + II), while 35.3% were labeled as frail using mFI 2+, and 32.1% based on RAI (III, IV). The 30-day readmission, postoperative complications, and mortality rates in this cohort were 3.8%, 2.3%, and 6.6%, respectively. RAI was a better indicator of mortality compared to mFI. As such, patients with low RAI score (I, II) had 0.054 odds for 30-day mortality compared to the patients with high RAI score (III, IV) (OR 0.054; CI 95%, 0.004 to 0.784; $P = 0.033$).

Conclusion Frailty, as measured by Risk Analysis Index, is an independent predictor of early mortality in patients undergoing TURBT. Preoperative frailty assessment may improve risk stratification and patient counseling prior to surgery.

Introduction

Frailty, a state of decreased homeostatic reserve, is characterized by dysregulation across multiple physiologic and molecular pathways, and a limited ability to compensate for and recover from stressors. It is particularly relevant to the perioperative period, during which patients are subject to high levels of stress and inflammation. Surgery is a major stressor, and current preoperative evaluation methods fail to assess the physiological reserve of patients with the same chronological age. Frailty has been shown to be an independent predictor of prolonged length of stay in hospital and increased postoperative complications[1]. Frailty is an age-independent index, which is more prevalent in elderly due to an increase in comorbidities and functional decline. The routine implementation of a frailty assessment could provide a more comprehensive and individualized perioperative risk stratification[1–4].

Key Words

Frailty, bladder cancer, TURBT, postoperative complications, risk assessment

Competing Interests

None declared.

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Abbreviations

ASA American Society of Anesthesiologists
AUC area under the curve
CI confidence interval
mFI modified frailty index
MIBC muscle-invasive bladder cancer
NMIBC non–muscle-invasive bladder cancer
OS overall survival
RAI Risk Analysis Index
ROC receiver operating characteristic
TURBT transurethral resection of bladder tumor

Most studies investigating the relationship between preoperative frailty and postoperative outcome only assess frailty retrospectively, and the actual benefit from a routine frailty assessment followed by an individualized treatment plan is lacking[5–7]. In muscle-invasive bladder cancer (MIBC), Fried Frailty Criteria (FFC) including grip strength, gait speed, exhaustion, physical activity, and shrinking was predictive of high-grade complications in patients undergoing radical cystectomy. Performance status, tumor size, and extent of resection are perioperative factors associated with postoperative complications and mortality in patients undergoing transurethral resection of bladder tumor (TURBT)[8]. The prevalence of frailty varies widely between different cohorts, yet frailty is one of the most significant factors affecting outcomes. Modified frailty index (mFI) and Risk Analysis Index (RAI) are frailty assessment scores that involve 11 and 15 items, respectively, which include important factors such as functional status, chronic obstructive pulmonary disease (COPD), and recent pneumonia as well as activities of daily living. Both indices have been used previously to predict MM, but they have never been assessed prospectively in patients undergoing TURBT[8–10].

In this study we aim to assess the prevalence of frailty among bladder cancer patients planned for staging and restaging TURBT using mFI and RAI, and assess the impact of frailty indices on 30-day postoperative complications and mortality[8].

Methods

This is a prospective observational study of bladder cancer patients planned for staging and restaging TURBT at a tertiary cancer center that seeks to assess the prevalence of frailty preoperatively and its relationship to 30-day postoperative complications and mortality rates.

Between May 2020 and March 2021, 343 bladder cancer patients who were planned for staging TURBT or restaging TURBT were identified. We prospectively collected mFI and RAI for those patients with bladder cancer who were planned for staging and restaging TURBT and collected the 30-day postoperative complications and mortality rates after the planned procedure. All patients were mandated to have a negative COVID-19 PCR test result 24 hours before the surgery. Participants were enrolled before the surgical intervention. During the encounter, a member of the treatment team filled out the required information for the frailty scale. Patients received a unique identifier number that was maintained in our research database in a secure, encrypted, password-locked file and on an institutionally secured and managed device. 30-day postoperative complications and mortality were collected prospectively from the hospital administrative database. The database is linked to the national population census, and any death incident is captured without specific cause of death. As part of the routine follow-up for outpatient procedures in our institution, all patients receive calls on days 1, 7, and 28 post-discharge, any events such as admission in another facility, or intervention usually documented in the patients' chart.

The mFI was proposed and validated by Chimukangara et al., and the following variables were included: COPD or recent pneumonia, congestive heart failure, functional status (not independent), hypertension requiring medications, and diabetes mellitus. This was an abridged version of the 11-item mFI. The score is calculated by the number of listed comorbidities, and it's categorized as 0, 1, and 2+. The higher the score, the sicker the patient[9].

RAI assessment is based on 15-item survey relying on patients' reporting and includes 4 items to evaluate activities of daily living and other 11 variables, which overall predicts 6-month mortality based on analysis of Minimum Data Set Mortality Risk Index-Revised. The score is classified into 4 groups: Class I: ≤ 15; Class II: 16–25; Class III: 26–35; and Class IV: ≥ 36[10].

Univariate analyses were performed using the chi-square and unpaired Student t test for categorical and continuous variables, respectively. A receiver operating characteristic (ROC) curve was generated with a 95% confidence interval (CI) for the area under the curve (AUC). Multivariate logistic regression analysis adjusting for preoperative variables was performed to identify predictors of mortality. Univariate Cox regression analysis was performed to identify correlation between mFI, RAI, and stage of cancer with overall survival (OS). Kaplan-Meier survival was utilized to determine OS and stage-specific survival. A P-value < 0.05 was considered statistically significant. All analyses were performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0.

Armonk, New York: IBM Corp.). This study was approved by the institutional review board at King Hussein Cancer Center, Amman, Jordan (Protocol number: 20-KHCC-43).

Results

In total, 343 bladder cancer patients participated in the study. The mean age of the cohort was 64.8 ± 13.1 years, 86.6% were male, and 87.5% had non–muscle-invasive bladder cancer (NMIBC). Of the cohort, 92% were found to have low American Society of Anesthesiologists (ASA) class (I + II). Overall, 60.9% of the patients had stage 0 disease, 21.9% had stage 1, and only 5.8% had metastatic disease. Preoperatively, among the 343 patients, 129 (37.6%) received intravesical treatment with either Bacillus Calmette-Guérin (BCG) or chemotherapy such as mitomycin.

Patients with MIBC were more likely to have a higher ASA class, were more frail based on both RAI and mFI scores, and had lower preoperative hemoglobin and preoperative albumin levels. All these factors might explain why these patients had a higher mortality rate compared to NMIBC (Table 1).

Tables 2 and 3 display the prevalence of frailty, and operative and postoperative outcomes using the mFI and RAI, respectively. While 35.3% of the patients were labeled as frail using mFI 2+, 32.1% were labeled frail based on RAI (III, IV). The 30-day readmission, postoperative complications, and overall mortality rates in the entire cohort were 3.8%, 2.3%, and 6.6%, respectively. Table 4 summarizes the recorded complications in our cohort.

RAI was a better indicator of the mortality compared to mFI (AUC, 0.832; P = 0.049; and AUC, 0.672; P = 0.063, respectively), as shown in Figure 1. RAI at a cutoff of 26.5 has 81.0% sensitivity and 57.8% specificity in predicting post-TURBT mortality identified by ROC. As such, patients with a low RAI score (I, II) had 0.054 odds for mortality compared to patients with a high RAI score (III, IV) (95% CI, 0.004–0.784; P = 0.033), using logistic regression analysis.

As illustrated in Figure 2, Kaplan-Meier curve shows OS difference between different cancer stages and invasiveness. Similarly, Figures 3 and 4 show Kaplan-Meier curves for OS by mFI and RAI classifications. Cox regression analysis showed that MIBC status had a hazard ratio (HR) of 0.051 (95% CI 0.013 to 0.202; P < 0.001), and other factors such as mFI and RAI did not have a significant impact on OS.

Discussion

In this study, using both RAI and mFI to assess the relationship between preoperative frailty and

TABLE 1.

Patients' characteristics, and operative and postoperative outcomes based on muscular invasiveness

N (%)	Non–muscle-invasive bladder cancer 300 (87.5%)	Muscle-invasive bladder cancer 43 (12.5%)
Gender		
Male	260 (86.7%)	37 (86.0%)
Female	40 (13.3%)	6 (14.0%)
Age, mean ± SD (years)	64.8 ± 13.1	64.7 ± 14.1
BMI, mean ± SD (kg/m^2)	28.9 ± 5.3	27.2 ± 5.5
ASA class		
I + II	281 (93.7%)	35 (81.4%)
≥ III	19 (6.3%)	8 (18.6%)
Previous intravesical treatment	109 (36.3%)	20 (46.5%)
Re-TURBT	109 (36.3%)	20 (46.5%)
Previous radiotherapy	0 (0.0%)	2 (4.7%)
30-day complications	8 (2.7%)	0 (0.0%)
All-cause mortality	4 (1.4%)	17 (40.5%)
Readmission	10 (3.3%)	3 (7.0%)
RAI		
I (1–15)	1 (0.3%)	0 (0.0%)
II (16–25)	216 (72.0%)	16 (37.2%)
III (26–35)	55 (18.3%)	5 (11.6%)
IV (≥36)	28 (9.3%)	22 (51.2%)
mFI		
0	114 (38.0%)	9 (20.9%)
1	82 (27.3%)	17 (39.5%)
+2	104 (34.7%)	17 (39.5%)
Preoperative hemoglobin, mean ± SD (g/dL)	14.9 ± 8.1	12.8 ± 1.6
Hypoalbuminemia (<3.5 g/dL)	4 (1.3%)	6 (14.0%)
EBL, mean ± SD (mL)	9.4 ± 34.9	26.5 ± 46.3

ASA: American Society of Anesthesiologists; BMI: body mass index; EBL: estimated blood loss; mFI: modified frailty index; RAI: Risk Analysis Index; SD: standard deviation; TURBT: transurethral resection of bladder tumor.

TABLE 2.

Patients' characteristics, and operative and postoperative outcomes of the different 5-Item mFI

N (%)	All 343	mFI = 0 123 (35.9%)	mFI = 1 99 (28.9%)	mFI ≥ 2+ 121 (35.3%)	*P*-value
Gender					0.451
Male	297 (86.6%)	109 (31.8%)	87 (25.4%)	101 (29.4%)	
Female	46 (13.4%)	14 (4.1%)	12 (3.5%)	20 (5.8%)	
Age, mean ± SD (years)	64.8 ± 13.1	59.1 ± 10.1	64.9 ± 11.5	70.6 ± 9.1	0.034
BMI, mean ± SD (kg/m^2)	28.7 ± 5.3	28.0 ± 5.8	28.9 ± 5.1	29.3 ± 5.0	0.165
ASA class					<0.001
I + II	316 (92.1%)	123 (35.9%)	91 (26.5%)	102 (29.7%)	
≥ III	27 (7.9%)	0 (0.0%)	8 (2.3%)	19 (5.5%)	
Clinical cancer stage					0.089
0	209 (60.9%)	78 (22.7%)	63 (18.4%)	68 (19.8%)	
I	75 (21.9%)	30 (8.7%)	18 (5.2%)	27 (7.9%)	
II	21 (6.1%)	3 (0.9%)	11 (3.2%)	7 (2.0%)	
III	2 (0.6%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	
IV	20 (5.8%)	5 (1.5%)	5 (1.5%)	10 (2.9%)	
Previous intravesical treatment	129 (37.6%)	45 (13.1%)	37 (10.8%)	47 (13.7%)	0.934
Previous radiotherapy	2 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0.158
30-day complications	8 (2.3%)	6 (1.7%)	0 (0.0%)	2 (0.6%)	0.047
All-cause mortality	21 (6.6%)	4 (1.3%)	3 (0.9%)	14 (4.4%)	0.009
Readmission	13 (3.8%)	6 (1.7%)	4 (1.2%)	3 (0.9%)	0.611
RAI					<0.001
I (1–15)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	
II (16–25)	232 (67.6%)	116 (33.8%)	69 (20.1%)	47 (13.7%)	
III (26–35)	60 (17.5%)	5 (1.5%)	21 (6.1%)	34 (9.9%)	
IV (≥ 36)	50 (14.6%)	1 (0.3%)	9 (2.6%)	40 (11.7%)	
Preoperative hemoglobin, mean ± SD (g/dL)	14.6 ± 7.7	14.8 ± 1.8	15.6 ± 13.9	13.6 ± 1.8	0.147
Hypoalbuminemia (<3.5 g/dL)	10 (2.9%)	2 (0.6%)	3 (0.9%)	5 (1.5%)	0.507
EBL, mean ± SD (mL)	11.5 ± 36.2	9.7 ± 29.5	11.9 ± 21.8	12.8 ± 49.5	0.792

ASA: American Society of Anesthesiologists; BMI: body mass index; EBL: estimated blood loss; mFI: modified frailty index; RAI: Risk Analysis Index; SD: standard deviation.

TABLE 3.

Patients' characteristics, and operative and postoperative outcomes of the different RAI classes

N (%)	All	I (0–15) 1 (0.3%)	II (15–25) 232 (67.6%)	III (26–35) 60 (17.5%)	IV (> 35) 50 (14.6%)	*P*-value
Gender						0.085
Male	297 (86.6%)	0 (0.0%)	201 (58.6%)	53 (15.5%)	43 (12.5%)	
Female	46 (13.4%)	1 (0.3%)	31 (9.0%)	7 (2.0%)	7 (2.0%)	
Age, mean ± SD (years)	64.8 ± 13.1	33.0 ± 0.0	60.8 ± 41.2	74.6 ± 6.2	72.3 ± 14.4	0.012
BMI, mean ± SD (kg/m^2)	28.7 ± 5.3	28.1 ± 0.0	29.2 ± 5.4	26.8 ± 5.4	28.7 ± 5.3	0.034
ASA class						0.001
I + II		316 (92.1%)	1 (0.3%)	222 (64.7%)	53(15.5%)	40 (11.7%)
≥ III	27 (7.9%)	0 (0.0%)	10 (2.9%)	7 (2.0%)	10 (2.9%)	
Clinical cancer stage						<0.001
0	209 (60.9%)	1 (0.3%)	152 (44.3%)	36 (10.5%)	20 (5.8%)	
I	75 (21.9%)	0 (0.0%)	53 (15.5%)	15 (4.4%)	7 (2.0%)	
II	21 (6.1%)	0 (0.0%)	10 (2.9%)	3 (0.9%)	8 (2.3%)	
III	2 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	
IV	20 (5.8%)	0 (0.0%)	6 (1.7%)	1 (0.3%)	13 (3.8%)	
Previous intravesical treatment	129 (37.6%)	0 (0.0%)	92 (26.8%)	18 (5.2%)	19 (5.5%)	0.475
Previous radiotherapy	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0.008
30-day complications	8 (2.3%)	0 (0.0%)	6 (1.7%)	1 (0.3%)	1 (0.3%)	0.973
All-cause mortality	21 (6.6%)	0 (0.0%)	4 (1.3%)	3 (0.9%)	14 (4.4%)	<0.001
Readmission	13 (3.8%)	0 (0.0%)	9 (2.6%)	3 (0.9%)1	1 (0.3%)	0.611
Preoperative hemoglobin, mean ± SD (g/dL)	14.6 ± 7.7	11.0 ± 0.0	15.3 ± 9.1	13.6 ± 1.7	12.9 ± 2.0	0.115
Hypoalbuminemia (<3.5 g/dL)	10 (2.9%)	0 (0.0%)	0 (0.0%)	3 (0.9%)	7 (2.0%)	<0.001
EBL, mean ± SD (mL)	11.5 ± 36.2	5.0 ± 0.0	10.6 ± 38.5	9.4 ± 15.2	18.2 ± 42.7	0.550

ASA: American Society of Anesthesiologists; BMI: body mass index; EBL: estimated blood loss; mFI: modified frailty index; RAI: Risk Analysis Index; SD: standard deviation.

TABLE 4.

Postoperative complications

	n (%)
Overall rate	8 (2.3)
Urine retention	2 (0.6)
Pneumonia	1 (0.3)
Hematuria	2 (0.6)
Urinary tract infection	1 (0.3)

postoperative outcomes among bladder cancer patients who underwent staging and restaging TURBT, our results revealed that although mFI labeled a higher percentage of patients as frail in comparison to RAI, RAI was better in predicting mortality rates post-TURBT. However, frailty as assessed by RAI and mFI was not a predictor of overall survival.

Frailty index is used as a predictor of postoperative mortality. Previous studies have found an association between high mFI and postoperative complications and mortality in patients with MIBC, as patients with

FIGURE 1.

Receiver operating characteristic (ROC) curves for Risk Analysis Index (RAI) with an area under curve (AUC) = 0.832, $P = 0.049$, and modified frailty index (mFI) with AUC = 0.672, $P = 0.063$.

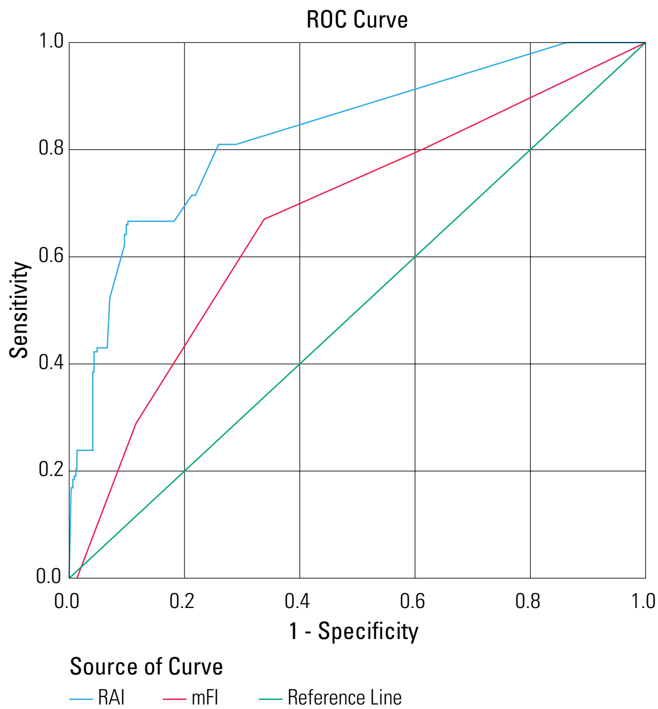


FIGURE 2.

Kaplan-Meier curve for overall survival for bladder cancer by invasiveness and stage; log-rank test for survival was significant ($P < 0.001$). Mean follow-up period (months): NMIBC, 31.1; MIBC, 21.3; stage IV, 25.6; unknown, 38.2. MIBC: muscle-invasive bladder cancer; NMIBC: non–muscle-invasive bladder cancer.

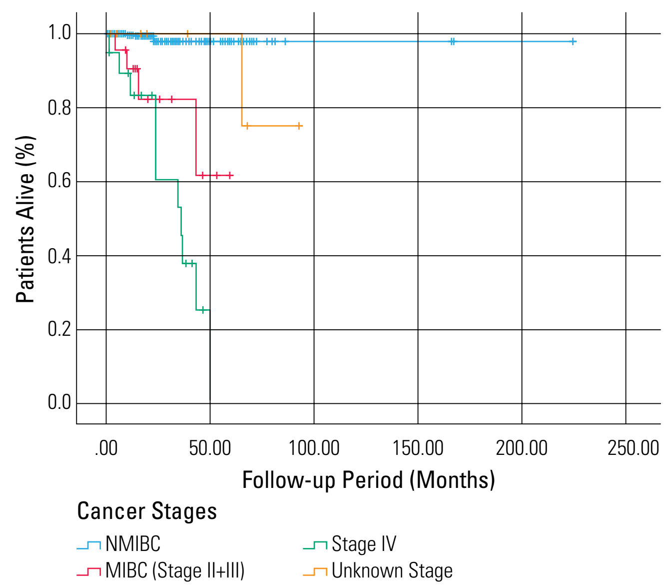


FIGURE 3.

Kaplan-Meier curve for overall survival for bladder cancer by modified frailty index (mFI) classification; log-rank test for survival was significant ($P = 0.001$). Mean follow-up period (months): mFI 0, 30.7; mFI 1, 26.9; mFI +2, 32.7.

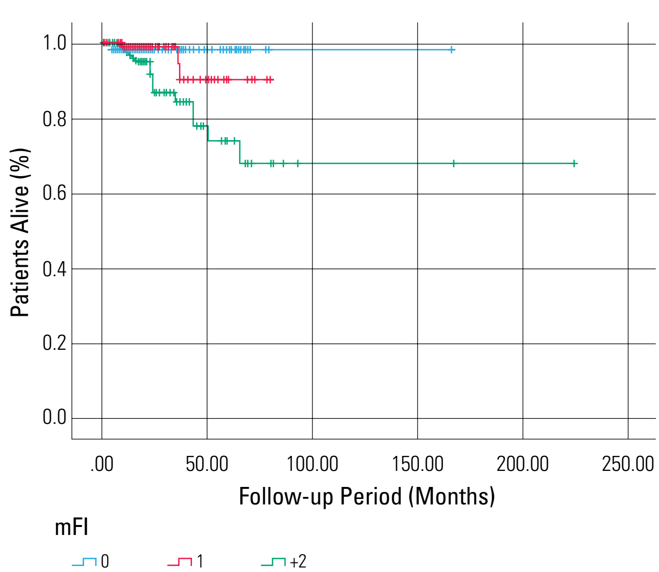
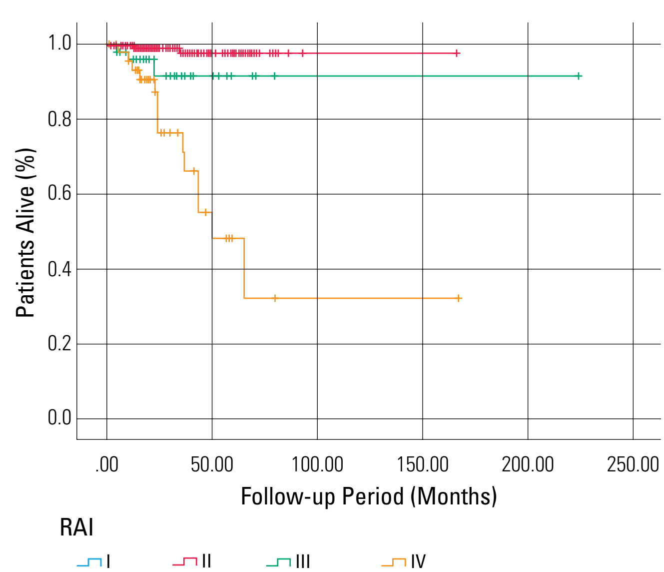


FIGURE 4.

Kaplan-Meier curve for overall survival for bladder cancer by Risk Analysis Index (RAI) classification (I-IV); log-rank test for survival was significant (P < 0.001). Mean follow-up period (months): RAI Class 1, 6.7; class 2, 30.5; class 3, 29.3; class 4, 30.7.



Clavien-Dindo grade ≥ 3 at 30 and 90 days postoperatively had significantly higher mFI compared to patients with Clavien-Dindo grade < 3—odds ratio of mFI for serious complications within 30 days was 1.5 (95% CI 1.1 to 2.1; $P = 0.010$) and for 90 days was 1.5 (95% CI 1.1 to 2.1; $P = 0.008$)[9]. Another study that assessed frailty among 2679 bladder cancer patients who underwent radical cystectomy concluded that mFI can identify those patients at greatest risk for severe complications and mortality. When stratified at a cutoff of mFI > 2, the overall complication rate was not different (61.7% vs. 58.3%; $P = 0.1$), but mFI ≥ 2 group had a significantly higher rate of Clavien-Dindo 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[11–13].

Our results in the context of TURBT are consistent with these prior studies in the context of radical cystectomy. However, because of the low number of complications in our TURBT cohort, there was no association between frailty and postoperative complications. Our study showed that the prevalence of frailty in patients with MIBC was higher than in patients with NMIBC, hence the higher mortality rate after TURBT. Therefore, a different workflow for TURBT in patients with suspicious MIBC might be needed, where a senior urologist might be involved early on in these cases intraoperatively and define the goal of the procedure, which may involve resection of minimum tissue to establish diagnosis, without resecting the whole intravesical tumor, or considering computed tomography (CT)-guided biopsy to establish diagnosis[14]. Recently, there has been heightened interest in incorporating magnetic resonance imaging (MRI) in the staging of bladder cancer, as such preliminary data from the BladderPath trial showed that it might be feasible to direct patients with possible MIBC to multiparametric MRI (mpMRI) for staging instead of TURBT[15].

It is noteworthy that the 30-day overall mortality rate in our cohort was higher than the observed rate in the National Surgical Quality Improvement Program database[16]. This might be explained by several factors such as our institutional database being able to capture death more accurately than complications and readmissions to other hospitals and the fact that large numbers of patients in this cohort were operated during the first wave of COVID-19.

There are few studies in the literature that use frailty indices prospectively in perioperative planning and management, and even fewer studies examining bladder cancer surgical therapies specifically[3–5]. This is the first prospective study that examined the prevalence of frailty in bladder cancer patients who underwent TURBT and used two different tools to assess frailty. In this study, RAI was better than mFI in predicting 30-day mortality rates post-TURBT.

Preoperative counseling of bladder cancer patients before TURBT usually entails the anticipated oncological outcomes, procedural comorbidities, as well as the need for second-look TURBT in high-grade tumors or in instances of inadequate pathology for complete staging[17]. However, surgeons might face challenges using tools such as different postoperative risk calculators, as these calculators use complex formulas requiring extensive clinical history documentation that might limit their applicability during clinical encounters. On the other hand, the RAI score is a simple tool that can be rapidly computed by urologists without delaying the patient encounter[18].

There are several limitations to our study including a small sample size and lack of data on tumor size and characteristics. Complications were collected prospectively using our institutional database; however, we cannot exclude the possibility that other complications were missed, as some patients may have sought urgent help in other centers. The low number of complications observed in this cohort affected to the ability to study the correlation between frailty and postoperative complications. Other frailty measures such as hand grip using manometry were not used in this study due logistical and funding issues. In addition, this data was collected during the first wave of the COVID-19 pandemic, and we cannot exclude the influence of COVID-19 on the mortality rate. Finally, we cannot exclude referral bias to our center. In order to better predict complication rates, larger, well-designed multicenter studies are needed to prospectively examine the efficacy of frailty indices preoperatively in diverse patient categories and for different therapies. Nevertheless, despite these limitations, our study represents a robust cross-sectional analysis that correlates preoperative frailty to important 30-day postoperative outcomes

Conclusion

Frailty, as measured by Risk Analysis Index, is an independent predictor of adverse early mortality in patients undergoing TURBT. Preoperative frailty assessment may improve risk stratification and patient counseling prior to surgery.

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