Frailty is an independent predictor of 90-day complications following robot-assisted radical prostatectomy

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ABSTRACT

Objective: The aim of this study is to analyze the association between the 11-item Modified Frailty Index (mFI) and 90-day post-operative complications in prostate cancer patients undergoing Robot-Assisted Radical Prostatectomy (RARP).

Methods: The Modified Frailty Index was calculated in 216 men who underwent RARP at a single institution. Mean ranks and proportions were compared with the Kruskal-Wallis test, Chi-square test of independence, and Fisher's exact test. Multivariate logistic regression was performed to determine predictors of 90-day post-operative complications after RARP.

Results: Patients with higher pre-operative mFI (≥ 2) were more likely to be older in age ($P = 0.047$), have worse ECOG performance status ($P = 0.019$), and worse ASA scores ($P < 0.01$). Intra-operative variables and pathological characteristics were similar between mFI groups. Multivariate logistic regression showed that mFI ≥ 2 was a predictor of overall 90-day complications after surgery (OR = 3.32, CI = 1.16–9.54, $P = 0.026$). Multivariate logistic regression also showed that mFI >2 was a predictor of high-grade 90-day complications after surgery (OR = 2.69, CI = 1.24-5.85, $P = 0.012$).

Conclusion: Prostate cancer patients with higher pre-operative mFI scores were more likely to have a 90-day complication after RARP. The Modified Frailty Index should be assessed pre-operatively in prostate cancer patients to determine the risk of post-operative morbidity and the best treatment plan.

Keywords: Frailty, robot-assisted radical prostatectomy, prostate cancer, Clavien-Dindo

INTRODUCTION

Urologists perform more than two-thirds of all urological procedures on patients aged 65 and older.[1] Currently, prostate cancer is the most diagnosed cancer in men, with an estimated 248,530 new cases in 2021.[2] Unlike other cancers, the incidence of prostate cancer increases with age more than any other risk factor, with the largest cohort being men aged between 75–79.[3] As the population of the United States shifts towards older individuals, the management of older patients with prostate cancer should receive more emphasis in the healthcare system.

Frailty is defined as reduced physiological reserve that leads to increased probability of adverse health outcomes and death and can serve to assess patient care.[4] Currently, two well-established conceptual frameworks of frailty provide the basis for most studies in the literature. The Fried Frailty Criteria uses physiological phenotypes to assess frailty.[5] The Canadian Study of Health & Aging Frailty Index (CSHA-FI) is a 70-item index that uses comorbidities, cognitive impairments, and disabilities to measure frailty.[6] An 11-item modified frailty index (mFI) uses 11 criteria from the original 70-item CSHA-FI: 1) functional health

status; 2) diabetes mellitus type II; 3) chronic obstructive pulmonary disease; 4) congestive heart failure; 5) myocardial infarction within 6 months; 6) prior cardiac surgery, percutaneous coronary intervention, or angina within 1 month; 7) hypertension; 8) impaired sensorium; 9) transient ischemic attack; 10) cerebrovascular accident; 11) peripheral vascular disease requiring surgery/active claudication present. The mFI has been validated in studies with patients undergoing urological surgeries.[7–10]

Prostate cancer has a wide variety of treatments, including radical prostatectomy or other conservative measures, like radiotherapy and hormone therapy.[11,12] Robot-Assisted Radical Prostatectomies (RARP) have become a popular treatment option for prostate cancer as RARP decrease blood loss and the rates of complications when compared to open prostatectomies.[13] Because the incidence of prostate cancer remains high, in tandem with the increase in number of RARP performed, analyzing frailty with RARP could prove worthwhile.

Urologic studies show that the 11-item mFI has been associated with increased complications following urologic surgeries.[7–10] However, studies on the association between mFI and RARP are still limited. In this study, we aim to analyze the association between frailty and 90-day post-operative outcomes following RARP.

METHODS

With Institutional Review Board approval, 216 patients with prostatic adenocarcinoma who underwent RARP were retrospectively identified at Texas Tech University Health Sciences Center from January 1, 2010, to January 31, 2020. Exclusion criteria included patients under the age of 18, any diagnosis other than primary adenocarcinoma of the prostate, including benign prostatic hyperplasia or metastatic prostate cancer, and patients who underwent open or laparoscopic prostatectomies. Patients with prior treatment with radiation or hormone ablation were also excluded from this study.

The 11 mFI variables were identified for each patient, along with measures of age, race, BMI,

American Society of Anesthesiology (ASA) scores, Eastern Cooperative Oncology Group (ECOG) scores, smoking status, and prostate specific antigen (PSA). The mFI was categorized into 0, 1, and ≥2 based on the distribution of the population. Post-operative outcomes were also collected, including estimated blood loss, length of stay, 90-day overall complications, 90-day high grade complications (classified as Clavien-Dindo score ≥3), and 90-day readmissions. The pathologic outcomes collected included radical prostatectomy Gleason grade, Pathologic T and N stages, surgical margins, and biochemical recurrence.

Continuous variables were analyzed with ANOVA; categorical variables were analyzed with Chi-Square analysis. A multivariate logistic regression was performed to determine if mFI was a predictor of any 90-day complications, 90-day high-grade complications, and 90-day readmission adjusting for age, ASA, and ECOG. Odds ratio and 95% confidence intervals were reported in this analysis. Statistical significance was determined by $P < 0.05$.

RESULTS

The clinical demographics of our study population are summarized in Table 1, post-operative outcomes in Table 2, and pathological characteristics in Table 3. Patients with higher mFI scores were more likely to be older with the mean age of patients with mFI scores of 0, 1, and ≥2 being 61, 63, and 64, respectively ($P = 0.047$). Patients with mFI scores of 0, 1, and ≥2 had 13.1%, 20.4%, and 33.9% of ECOG scores ≥1, respectively ($P = 0.019$). American Society of Anesthesiology (ASA) scores were also higher in more frail patients; ASA was ≥3 in 37.7% of patients with an mFI of 0, 46.2% with an mFI of 1, and 75.8% with an mFI of ≥2 ($P < 0.001$, Table 1).

There was an inverse relationship between frailty and estimated blood loss in which patients with mFI of 0, 1, and ≥2 had estimated blood losses of 229.1 mL, 228.9 mL, and 155.6 mL respectively ($P = 0.007$). More frail patients were also more likely to have 90-day overall complications with the percent of complications increasing from 67.2% with an mFI

Table 1. Clinical Demographic Characteristics of Study Population

	Modified Frailty Index				
	0 (n = 61)	**1 (n = 93)**	**≥2 (n = 62)**	**Total (n = 216)**	**P**
Mean age, years (SD)	61 (8.8)	63 (6.6)	64 (8.4)	63 (7.9)	**0.047**
Race, *n* (%)					0.523
White	40 (65.6)	62 (66.7)	34 (54.8)	136 (63.0)	
Black	6 (9.8)	10 (10.8)	11 (17.7)	27 (12.5)	
Hispanic	15 (24.6)	21 (22.6)	17 (27.4)	53 (24.5)	
Mean BMI, kg/m² (SD)	28.6 (4.9)	29.1 (4.3)	29.7 (5.6)	29.1 (4.9)	0.448
ASA, *n* (%)					**<0.001**
≤2	38 (62.3)	50 (53.8)	15 (24.2)	103 (47.6)	
≥3	23 (37.7)	43 (46.2)	47 (75.8)	113 (52.3)	
ECOG, *n* (%)					**0.019**
0	53 (86.9)	74 (79.6)	41 (66.1)	168 (77.8)	
≥1	8 (13.1)	19 (20.4)	21 (33.9)	48 (22.2)	
Tobacco abuse, *n* (%)					0.378
None	24 (39.3)	44 (47.3)	21 (33.9)	89 (41.2)	
Former	30 (49.2)	38 (40.9)	29 (46.8)	97 (44.9)	
Current	7 (11.5)	11 (11.8)	12 (19.4)	30 (13.9)	
Mean PSA, ng/ml (SD)	14.0 (25.9)	12.7 (16.8)	9.7 (5.9)	12.2 (17.9)	0.391

ASA: American Society of Anesthesiologists, SD: Standard deviation, BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, PSA: Prostate specific antigen.

of 0, 77.4% with an mFI of 1, and 90.3% with an mFI of ≥2 (P = 0.008). Percent of 90-day high-grade complications increased from 36.1% in patients with an mFI of 0 to 46.2% in patients with an mFI of 1 and 58.1% in patients with an mFI of ≥2 (P = 0.05). Ninety-day readmissions were higher in patients with an mFI of ≥2; however, it was not statistically significant. Modified Frailty Index scores of 0, 1, and ≥2 had 18.0%, 15.1%, and 30.6% readmissions, respectively (P = 0.053, Table 2). Pathologic characteristics were not different in the three frailty groups (Table 3).

Multivariate logistic regression analysis showed that higher mFI scores (categorized as a score ≥2) was associated with increased probability of 90-day overall complication (OR = 3.32; CI = 1.16-9.54, P = 0.026). Age was also associated with a higher 90-day overall complication rate (OR = 1.05; CI = 1.01–1.1, P = 0.022, Table 4). The analysis also shows that higher mFI scores were associated with increased probability of 90-day high grade complications (OR = 2.69; CI = 1.24–5.85; P = 0.012, Table 5).

DISCUSSION

Several other studies have used the mFI to analyze frailty in patients undergoing urological procedures; however, many have used the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. A major limitation to this database involves the lack of longitudinal follow-up after 30 days. A study by Burg et al. analyzed complications after radical cystectomies prospectively using the Fried Frailty Criteria and found that frailty is a significant factor for both 30 days post-operative and 90 days post-operative complications.[14] This shows that adverse outcomes can appear even after 30 days post-operative surgery. Analyzing the mFI up to 90 days post-operatively will better assess the

Table 2. Post-operative Outcomes after RARP

	Modified Frailty Index				
	0 (n = 61)	**1 (n = 93)**	**≥2 (n = 62)**	**Total (n = 216)**	**P**
Mean EBL, mL (SD)	229.1 (243.0)	228.9 (167.7)	155.6 (84.8)	208.1 (178.2)	**0.007**
Mean LOS, days (SD)	1.3 (0.8)	2.1 (8.5)	1.4 (0.9)	1.7 (5.6)	0.629
90-day overall complication, *n* (%)					**0.008**
No	20 (32.8)	21 (22.6)	6 (9.7)	47 (21.8)	
Yes	41 (67.2)	72 (77.4)	56 (90.3)	169 (78.2)	
90-day Clavien, *n* (%)					**0.008**
0	20 (32.8)	21 (22.6)	6 (9.7)	47 (21.8)	
I	19 (31.1)	29 (31.2)	20 (32.3)	68 (31.5)	
II	14 (23.0)	37 (39.8)	25 (40.3)	76 (35.2)	
III	8 (13.1)	3 (3.2)	9 (14.5)	20 (9.3)	
IV	0 (0.0)	2 (2.2)	1 (1.6)	3 (1.4)	
V	0 (0.0)	1 (1.1)	1 (1.6)	2 (0.9)	
90-day overall high-grade complications					**0.05**
No	39 (63.9)	50 (53.8)	26 (41.9)	115 (53.2)	
Yes	22 (36.1)	43 (46.2)	36 (58.1)	101 (46.8)	
90-day readmission, *n* (%)					0.053
No	50 (82.0)	79 (84.9)	43 (69.4)	172 (79.6)	
Yes	11 (18.0)	14 (15.1)	19 (30.6)	44 (20.4)	

EBL: Estimated Blood Loss, LOS: Length of stay.

use of frailty as a tool to predict adverse outcomes in RARP. This study shows that patients undergoing RAPP with higher mFI scores have an increased probability of developing 90-day overall complications and 90-day high grade complications.

Lascano et al. evaluated the mFI in predicting adverse outcomes in patients undergoing curative surgery for urologic oncology, including prostatectomy, partial and radical nephrectomy, nephroureterectomy, and cystectomy.[7] Multivariate analysis showed that mFI was associated with increased risk of Clavien-Dindo IV complication after 30 days for open prostatectomies. A similar study was conducted by Suskind et al.; however, 21 different urologic procedures were considered.[10] They concluded that mFI strongly correlated with increased risk of complications following any urologic surgery they studied; however, when analyzing prostatectomies individually, high mFI was

not associated with increased risk of complications.[10] Another study by Shahait et al. showed that frailty was associated increased risk of adverse events and mortality following radical prostatectomies using a 5-point modified frailty index that includes 1) COPD; 2) CHF; 3) dependent functional status; 4) hypertension; and 5) diabetes.[15]

The major limitation to these studies includes limited follow-up data of only 30 days. Furthermore, urologists are beginning to perform more minimally invasive prostatectomies rather than open prostatectomies.[16] Therefore, studying mFI as a predictor of adverse outcomes following robot assisted prostatectomies is necessary.

A study by Levy et al. showed that mFI had a higher risk of Clavien-Dindo IV complications in patients undergoing RARP. They further showed that

Table 3. Pathological Characteristics of Resected Prostates

	Modified Frailty Index				
	0 (n = 61)	**1 (n = 93)**	**≥2 (n = 62)**	**Total (n = 216)**	**P**
RP Gleason grade group, *n* (%)					0.77
1	10 (16.4)	14 (15.1)	10 (16.1)	34 (15.7)	
2	32 (52.5)	42 (45.2)	28 (45.2)	102 (47.2)	
3	12 (19.7)	28 (30.1)	19 (30.6)	59 (27.8)	
4 (scores 4–6)	4 (6.6)	8 (8.6)	4 (6.5)	16 (7.6)	
5 (scores 7–9)	3 (4.9)	1 (1.1)	1 (1.6)	5 (2.4)	
Pathological T Stage, *n* (%)					0.679
T2	41 (67.2)	58 (62.4)	37 (59.7)	136 (63)	
T3	20 (32.8)	35 (37.6)	25 (40.3)	80 (37.0)	
T4	0	0	0	0 (0.0)	
Pathological N Stage, *n* (%)					0.513
NX	29 (47.5)	43 (46.2)	36 (58.1)	108 (50.0)	
N0	27 (44.3)	42 (45.2)	24 (38.7)	93 (43.1)	
N1	5 (8.2)	8 (8.6)	2 (3.2)	15 (7.1)	
Surgical margins, *n* (%)					0.161
Negative	45 (73.8)	56 (60.2)	44 (71.0)	145 (67.1)	
Positive	16 (26.2)	37 (39.8)	18 (29.0)	71 (32.9)	
Biochemical recurrence, *n* (%)					0.169
No	55 (90.2)	73 (77.8)	51 (82.3)	179 (82.9)	
Yes	6 (9.8)	20 (22.2)	11 (17.7)	37 (17.4)	

RP: Radical Prostatectomy.

mFI combined with ASA had a high sensitivity and specificity for predicting mortality within in 30 days.[9] However, because this study used the ACS-NSQIP database, follow-up was limited to 30 days post-operation. Our study is the first to retrospectively analyze mFI as a predictor of adverse outcomes following RARP up to 90 days post operation.

Recently, new measures of frailty have been introduced in the literature. Rosiello et al. used The Johns Hopkins Adjusted Clinical Group (ACG) frailty defining indicator to assess post-operative outcomes following radical prostatectomies.[17] The Johns Hopkins ACG consists of 10 clusters of frailty-defining illnesses, including neurologic deficits, malnutrition, urinary and fecal incontinence, frequent falls, and motor impairments that categorize patients as frail, or non-frail.[17]

Using the National Inpatient Sample database, this study concluded that frail patients had higher rates of overall complications, major complications, longer length of stay, and total hospital costs following radical prostatectomy.[17]

Another frailty assessment called the Geriatric 8 (G8) has been used to assess frailty in patients with prostate cancer. The G8 consists of 8 factors that can be scored. The total score is on a scale of 0–17, and frail is defined as a score >14.[18] Multiple studies have evaluated post-operative outcomes following RARP using the G8 frailty assessment. Frail patients (G8 > 14) had more moderate and severe pain following RARP.[18] However, there was no significant association with frailty and worse health-related-quality-of-life or lower urinary symptoms following RARP.[19]

Table 4. Predictors of Overall 90-day Complications

	Odds Ratio	Lower 95% CI	Upper 95% CI	P
Age				
	1.05	1.01	1.1	**0.022**
ASA				
≥3 (reference: ≤2)	1.33	0.64	2.74	0.446
ECOG				
≥1 (reference 0)	1.55	0.58	4.11	0.378
Modified Frailty Index				
1 (reference: 0)	1.41	0.67	2.99	0.366
2 (reference: 0)	3.32	1.16	9.54	**0.026**

ASA: American Society of Anesthesiologists Physical Status Classification System, ECOG: Eastern Cooperative Oncology Group Performance Status.

A few limitations exist in this study. Due to the retrospective nature of the study, some confounding variables may exist. This study was performed using electronic health record data from one institution, leading to a smaller sample size, and results may not be applicable to other healthcare organizations. A measure of comorbidities was not included in our analysis as the Charlson Comorbidity Index scores were not collected. In addition, some patients were lost to follow-up. Therefore, the assumption was made that the patients lost to follow-up had no post-operative complications, leading to possible under-reported complication rates. It is possible that the patients lost to follow up could have been significantly different from patients analyzed with follow-up; however, this cannot be assessed. Mean follow-up data were not included due to inconsistencies with follow up information and a large population of incarcerated patients in our sample. This could skew the mean follow-up time, and therefore was not included in this study. In addition, it is possible that because there are similar variables within the ASA, ECOG and mFI, collinearities may exist in our analysis.

CONCLUSION

Patients undergoing RARP for prostate cancer with higher frailty scores using the mFI are more likely to have any 90-day complications and 90-day high grade complications post-operatively. Therefore, we recommend that urologists assess mFI pre-operatively in patients undergoing RARP. Pre-operative determination of mFI for these patients can serve to determine the risk for post-operative morbidity and complications and can offer options for determining the best treatment plan for more frail patients.

Table 5. Predictors of High-grade 90-day Complications

	Odds Ratio	Lower 95% CI	Upper 95% CI	P
Age				
	0.99	0.95	1.02	0.472
ASA				
≥3 (reference: ≤2)	0.92	0.51	1.65	0.769
ECOG				
≥1 (reference 0)	0.95	0.48	1.88	0.881
Modified Frailty Index				
1 (reference: 0)	1.59	0.81	3.12	0.175
2 (reference: 0)	2.69	1.24	5.85	**0.012**

ASA: American Society of Anesthesiologists Physical Status Classification System, ECOG: Eastern Cooperative Oncology Group Performance Status.

REFERENCES

1. Drach GW, Griebling TL. Geriatric urology. J Am Geriatr Soc 2003;51:S355–8.

2. Howlader N NA, Krapcho M, Miller D, et al. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

3. Grozescu T, Popa F. Prostate cancer between prognosis and adequate/proper therapy. J Med Life 2017;10:5–12.

4. Rockwood K, Stadnyk K, MacKnight C, et al. A brief clinical instrument to classify frailty in elderly people. Lancet 1999;353:205–6.

5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.

6. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173:489–95.

7. Lascano D, Pak JS, Kates M, et al. Validation of a frailty index in patients undergoing curative surgery for urologic malignancy and comparison with other risk stratification tools. Urol Oncol 2015;33:426.e1–12.

8. Chappidi MR, Kates M, Patel HD, et al. Frailty as a marker of adverse outcomes in patients with bladder cancer undergoing radical cystectomy. Urol Oncol 2016;34:256.e1–6.

9. Levy I, Finkelstein M, Bilal KH, et al. Modified frailty index associated with Clavien-Dindo IV complications in robot-assisted radical prostatectomies: A retrospective study. Urol Oncol 2017;35:425–31.

10. Suskind AM, Walter LC, Jin C, et al. Impact of frailty on complications in patients undergoing common urological procedures: a study from the American College of Surgeons National Surgical Quality Improvement database. BJU Int 2016; 117:836–42.

11. McKibben MJ, Smith AB. Evaluation and management of the geriatric urologic oncology patient. Curr Geriatr Rep 2015; 4:7–15.

12. Wallis CJD, Saskin R, Choo R, et al. Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:21–30.

13. Sirisopana K, Jenjitranant P, Sangkum P, et al. Perioperative outcomes of robotic-assisted laparoscopic radical prostatectomy, laparoscopic radical prostatectomy and open radical prostatectomy: 10 years of cases at Ramathibodi Hospital. Transl Androl Urol 2019;8:467–75.

14. Burg ML, Clifford TG, Bazargani ST, et al. Frailty as a predictor of complications after radical cystectomy: A prospective study of various preoperative assessments. Urol Oncol 2019;37:40–7.

15. Shahait M, Labban M, Dobbs RW, et al. A 5-item frailty index for predicting morbidity and mortality after radical prostatectomy: an analysis of the American College of Surgeons National Surgical Quality Improvement Program Database. J Endourol 2021;35:483–9.

16. Lowrance WT, Eastham JA, Savage C, et al. Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States. J Urol 2012;187: 2087–92.

17. Rosiello G, Palumbo C, Knipper S, et al. Preoperative frailty predicts adverse short-term postoperative outcomes in patients treated with radical prostatectomy. Prostate Cancer Prostatic Dis 2020;23:573–80.

18. Masaki Momota SH, Osamu Soma, Itsuto Hamano, et al. Frailty is a predictor of moderate to severe pain after robot-assisted laparoscopic prostatecomy: A case-control study (FRAP study). BJUI Compass 2020;1.

19. Togashi K, Hatakeyama S, Kojima Y, et al. The effect of frailty on the quality of life and lower urinary symptoms following robot-assisted radical prostatectomy: A longitudinal analysis (FRARP-QL Study). Urol Oncol 2021;39:192.e7–e14.