Hypogonadism, frailty, and postoperative outcomes among men undergoing partial nephrectomy

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Introduction: *To determine the prevalence of hypogonadism in men undergoing partial nephrectomy (PN) and whether hypogonadism and frailty are associated with adverse postoperative outcomes.*

Materials and methods: *We identified men undergoing PN between 2012-2021 using the Merative Marketscan database. Patients were considered to have hypogonadism if diagnosed within 5 years prior to PN. Frailty was determined using the Hospital Frailty Risk Score (HFRS). Length of stay (LOS), complications, ED visits, and inpatient readmissions were compared. Sub-group analysis of men with hypogonadism was performed to determine if testosterone replacement therapy (TRT) improved clinical outcomes.*

Results: *Among 9,105 men who underwent PN, 809 (8.9%) were hypogonadal prior to PN. Hypogonadal men were significantly more frail compared to eugonadal men (HFRS score: median 6.7, IQR 4.1-10.1 vs. median 5.6, IQR 3.3-8.8, $p < 0.001$). However, there was no significant difference in LOS following PN nor in 90-day postoperative complications, ED visits, or inpatient readmission between men with and without hypogonadism. However, intermediate- and high-risk frailty were associated with increased risk of 90-day ED visits and 90-day inpatient readmission compared to low-risk patients. Among high-risk men with hypogonadism, TRT was associated with decreased risk of 90-day ED visits ($p = 0.04$).*

Conclusions: *Frailty was associated with postoperative outcomes following PN. Hypogonadism was associated with frailty, and treatment of hypogonadal men with TRT was associated with reduction in post-operative risk. These findings suggest a role for frailty assessment, and possibly testosterone screening, in men undergoing PN.*

Key Words: hypogonadism, frailty, partial nephrectomy, testosterone

Introduction

Renal cell carcinoma (RCC) is the seventh most prevalent malignancy in the United States with an anticipated 81,800 novel cases and 14,890 deaths in 2023.[1] While radical nephrectomy is considered the definitive treatment for large renal neoplasms,[2] small renal masses (SRMs) and lower stage tumors can be managed with either active surveillance or nephron-sparing treatments.[3,4] Partial nephrectomy (PN) has emerged as the preferred nephron-sparing approach, but the decision to pursue PN versus active surveillance relies on a number of clinical and

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radiographic factors, combined with clinical judgment in the context of a patient's overall health status.[5,6]

Frailty, a multifaceted syndrome stemming from age-related physiological decline, is typically characterized by a combination of clinical features including reduced muscle mass and strength, diminished bone density, and declining health-related quality of life. Frailty serves as a predictor of postoperative complications and mortality, affecting nearly 90% of elderly inpatients.[7-9] Among management options for localized renal masses, PN is associated with the highest rate of urologic complications,[10] and recent studies have shown an increased risk of postoperative complications and hospital readmission among frail patients undergoing PN.[11] These patients have a higher risk of acute kidney injury, sustained decline in renal function after surgery, and an increased risk of mortality from various causes.[12] Moreover, frail patients were more likely to pursue active surveillance or renal tumor ablation rather than surgical intervention.[13] In aggregate, these studies indicate a role for frailty measurement in patients considering treatment for RCC, especially those with SRMs.

One potentially important contributor to frailty in the male population with RCC is hypogonadism. There is a significant body of evidence linking low serum testosterone (T) levels and frailty.[14,15] Frailty and hypogonadism are characterized by an overlapping symptom profile including impaired muscle mass and health-related quality of life associated with aging. Importantly, many of these symptoms can be addressed and ameliorated in a timely fashion with testosterone replacement therapy (TRT), which offers a potential therapeutic intervention to improve frailty in the perioperative setting.[16] Despite the robust association between low T and frailty, the specific impact of low T on frailty and postoperative outcomes in PN patients remains unexplored. We sought to assess the prevalence of low T and its role as a predictor of frailty and perioperative morbidity among PN patients.

Materials and methods

Database and patient population

We used the Merative MarketScan database to identify inpatient admission encounters for male patients who underwent PN between 2012 to 2021.

This study was reviewed and exempted from requiring approval by the Institutional Review Board (IRB) at our institution, as MarketScan database collects deidentified patient information.

We used International Classification of Diseases (ICD)-9 and ICD-10, as well as Current Procedural Terminology (CPT) codes to identify men with a diagnosis of renal cancer who underwent PN. ICD-9/10 codes were also used to obtain preoperative comorbidities and clinical outcomes. Patients were considered to have hypogonadism if they received a diagnosis in the 5 years prior to PN. Within this subset, individuals were further classified as undergoing TRT if there existed a prescription for exogenous testosterone within 5 years prior to PN. Patients were excluded from analysis if they were < 18 years old, female, did not have a diagnosis of renal cancer in the year prior to PN, or had a medication prescription prior to PN associated with iatrogenic androgen deprivation therapy (ADT). Patients were also excluded if they had no available information on enrollment or no information on prescription drugs.

Study variables

Clinical and demographic data was analyzed. The Hospital Frailty Risk Score (HFRS) was calculated using ICD codes from the year prior to PN and used to determine frailty, and previously published score ranges were used to characterize patients as low-, intermediate-, or high-risk frailty.[17] Comorbidities were identified using ICD codes from the year prior to surgery and were coded using the comorbidity package for R.[18] Information on enrollment in commercial medical insurance or Medicare was used to define the end of follow up (i.e., censoring time) for our time-to-event analyses.

Outcome measures and covariates

The primary outcomes were postoperative length of stay, and 90-day emergency department (ED) visits and 90-day inpatient readmissions. Secondary outcomes were postoperative complications. We used multivariable Cox proportional hazards models for time-to-event analysis. Covariates in our model were chosen a priori as previously identified factors shown to influence testosterone or adverse clinical outcomes for PN which included patient age at PN, obesity, diabetes, cerebrovascular disease (CVD), and frailty. Figure 1 shows the effect mediators and confounding factors in a directed acyclic graph.

Statistical analysis

Data were analyzed using R (version 4.2.3) and the R package survival.[19] Descriptive characteristics are presented as median (interquartile range) or % (n), and difference between the hypogonadal

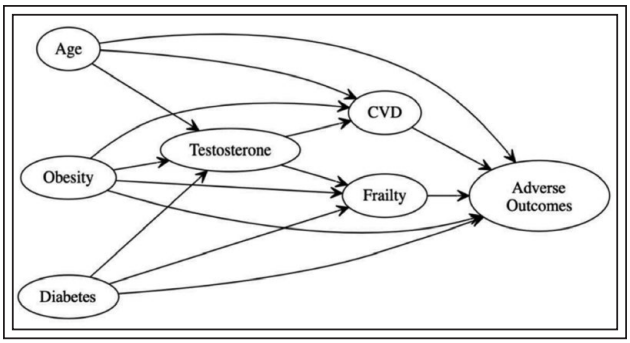

Figure 1. Directed acyclic graph depicting the confounders and effect mediators among testosterone, frailty, and adverse postoperative outcomes.

and non-hypogonadal cohorts were assessed via Kruskal-Wallis and Chi-squared tests, as appropriate. Multivariable Cox proportional hazards models were used to evaluate the association between frailty and risk of ED visits and inpatient readmissions, as well as hypogonadism and risk of ED visits and inpatient readmissions. Multivariable Cox proportional hazards models were also used for sub-group analysis of hypogonadal men to determine the effect of TRT and frailty on risk of postoperative outcomes. Patients who were still enrolled in commercial insurance or Medicare and had not experienced the event of interest were censored at 90 days. All tests of significance were two-sided, and p value < 0.05 was deemed statistically significant.

TABLE 1. **Demographic and clinical characteristics of men with hypogonadism and men without hypogonadism who underwent partial nephrectomy**

	No hypogonadism (n = 8,296)	**Hypogonadism (n = 809)**	**p value (< 0.05)**
Demographic characteristics			
Age (years)	58 (50-63)	58 (51-62)	**0.0025**
Insurance type			**< 0.001**
Commercial	79.0 (6,543)	86.0 (692)	
Medicare	21.0 (1,753)	14 (117)	
Region			**< 0.001**
Northeast	26.0 (2,165)	20.0 (159)	
North central	24.0 (1,955)	15.0 (119)	
South	35.0 (2,937)	53.0 (426)	
West	14.0 (1,139)	12.0 (99)	
Unknown	1.2 (100)	0.74 (6)	
Clinical data			
Medical comorbidities			
CAD/CVD	21.0 (1,718)	22.0 (181)	0.29
Diabetes	26.0 (2,161)	34.0 (274)	**< 0.001**
Obesity	30.0 (2,460)	40.0 (322)	**< 0.001**
CCI	3 (2-4)	3 (2-4)	0.35
HFRS score	5.6 (3.3-8.8)	6.7 (4.1-10.1)	**< 0.001**
HFRS range			**< 0.001**
Low-risk	43.0 (3,607)	34.0 (272)	
Intermediate-risk	50.0 (4,141)	59.0 (476)	
High-risk	6.6 (548)	7.5 (61)	
Surgical approach			0.42
Laparoscopic/robotic	68.0 (5,673)	70.0 (567)	
Open	28.0 (2,324)	27.0 (219)	
Unknown	3.6 (299)	2.8 (23)	

Categorical variables are shown as % (n). Continuous variables are shown as median (interquartile range). BMI = body mass index; CAD = coronary artery disease; CCI = Charlson Comorbidity Index; CVD = cerebrovascular disease; DM = diabetes mellitus; HFRS = Hospital Frailty Risk Score

Results

Overall, 9,105 patients underwent PN between 2012-2022 and met inclusion criteria, among whom 809 (8.9%) had a diagnosis of hypogonadism within 5 years prior to PN. Men with hypogonadism were significantly older than men without hypogonadism (median 58 years, interquartile range [IQR] 51-62 years vs. 58 years, IQR 50-63, p = 0.003). They were also more likely to have diabetes (34.0% vs. 26.0%, p < 0.001) and obesity (40.0% vs. 30.0%, p < 0.001). Moreover, men with hypogonadism were significantly more frail prior to surgery (HFRS score: median 6.7, IQR 4.1-10.1 vs. median 5.6, IQR 3.3-8.8, p < 0.001) and had higher rates of intermediate- (59% vs. 50%) and high-risk frailty (7.5% vs. 6.6%) (p < 0.001). Demographic and clinical information is detailed in Table 1.

There was no significant difference in perioperative outcomes (length of stay, 90-day postoperative complications, ED visits, and inpatient readmission) among men with and without hypogonadism, Table 2.

Among men with hypogonadism, 335 (41.4%) had a prescription for TRT. Men with a prescription for TRT were significantly younger (median 57 years, IQR 50-61 vs. median 58 years, IQR 51-62.8, p = 0.041) and more likely to have obesity (45.0% vs. 36.0%, p = 0.018) compared to men without a prescription for TRT, Table 3. However, there was no difference in length of stay nor 90-day postoperative complications, ED visits, and inpatient readmissions between groups,Table 4.

Multivariable cox proportional hazards model analyses showed men with hypogonadism did not have an increased risk of 90-day ED visits (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.85-1.22, p = 0.8) or 90-day inpatient readmission (HR 0.85, 95% CI 0.65-1.11, p = 0.2). However, both intermediate- and high-risk frailty were independently associated with both increased risk of 90-day ED visits and 90-day inpatient readmission compared to low-risk frailty patients, Table 5.

Subgroup analysis of all men with hypogonadism showed that TRT was not associated with reduced risk for either 90-day ED visits or 90-day inpatient readmission, Table 5. However, among high-risk frailty men with hypogonadism, TRT was associated with decreased risk of 90-day ED visits (p = 0.04), Figure 2. High-risk frailty was associated with increased risk of 90-day ED visits when compared to low-risk frailty patients (HR 2.76, 95% CI 1.60-4.79, p < 0.001).

Discussion

We utilized the Merative Marketscan database to evaluate the association between preoperative hypogonadism, frailty, and postoperative outcomes following PN. Using the HFRS, we found that hypogonadal men were

TABLE 2. **90-day clinical outcomes and complications of men with hypogonadism and men without hypogonadism who underwent partial nephrectomy**

	No hypogonadism (n = 8,296)	**Hypogonadism (n = 809)**	**p value (< 0.05)**
ED visit	16.0 (1,358)	17.0 (136)	0.78
Inpatient readmission	8.1 (674)	7.4 (60)	0.52
Acute kidney injury	11 (929)	11 (90)	1
Arrhythmia	6.7 (557)	5.8 (47)	0.36
Bowel obstruction	2.3 (188)	2.1 (17)	0.86
Cardiac arrest	0.34 (28)	0.49 (4)	0.68
Ileus	6.8 (568)	7.2 (58)	0.78
Myocardial infarction	1.2 (98)	0.99 (8)	0.75
Pulmonary embolism	1.6 (136)	1.5 (12)	0.85
Sepsis	2.4 (202)	2.6 (21)	0.87
Stroke/CVA	0.8 (66)	1.2 (10)	0.27
Length of stay (days)	2 (1-4)	2 (1-4)	1

Categorical variables are shown as % (n). Continuous variables are shown as mean ± standard deviation.
CVA = cerebrovascular accident; ED = emergency department

TABLE 3. **Demographic and clinical characteristics comparing men on testosterone replacement therapy (TRT) for hypogonadism undergoing partial nephrectomy**

	No TRT (n = 474)	TRT (n = 335)	p value (< 0.05)
Demographic characteristics			
Age (years)	58 (51-62.8)	57 (50-61)	**0.041**
Insurance type			**0.015**
Commercial	83.0 (393)	89.0 (299)	
Medicare	17.0 (81)	11.0 (36)	
Region			0.23
Northeast	21.0 (99)	18 (60)	
North central	15.0 (69)	15.0 (50)	
South	50.0 (239)	56.0 (187)	
West	14.0 (65)	10.0 (34)	
Unknown	0.42 (2)	1.2 (4)	
Clinical data			
Medical comorbidities			
CAD/CVD	23.0 (108)	22.0 (73)	0.8
Diabetes	36.0 (170)	31.0 (104)	0.18
Obesity	36.0 (172)	45.0 (150)	**0.018**
CCI	3 (2-4)	3 (2-4)	1
HFRS score	6.4 (3.8-10.1)	6.9 (4.3-10.0)	0.27
HFRS range			0.44
Low-risk	34.0 (162)	33.0 (110)	
Intermediate-risk	59.0 (281)	58.0 (195)	
High-risk	6.5 (31)	9.0 (30)	

Categorical variables are shown as % (n). Continuous variables are shown as median (interquartile range). BMI = body mass index; CAD = coronary artery disease; CCI = Charlson Comorbidity Index; CVD = cerebrovascular disease; DM = diabetes mellitus; HFRS = Hospital Frailty Risk Score

significantly more frail compared to eugonadal men, yet there were no significant differences in perioperative outcomes between the two groups. Moreover, hypogonadism did not emerge as an independent risk factor for adverse perioperative outcomes, whereas frailty was significantly associated with elevated risks of 90-day ED visits and readmissions.

Our results are notable for multiple significant findings. First, hypogonadal men undergoing PN exhibited significantly greater frailty than their eugonadal counterparts. This is consistent with a recent study by our group demonstrating an association between frailty and hypogonadism in men undergoing radical cystectomy.[20]

Second, we found that both intermediate- and high-risk frailty were significantly associated with perioperative complications following PN, consistent with multiple recent studies. Rosiello et al performed a retrospective analysis of 1282 patients at a single center who underwent PN for clinical T1 RCC. Using the modified frailty index, the authors found that frailty status predicted increased risk of overall complications and higher risk of non-cancer mortality.[12] The same group utilized the National Inpatient Sample database to assess the effect of frailty on surgical outcomes among patients undergoing PN for localized RCC and found that PN has become more prevalent among frail patients, and frailty status independently predicted length of hospital stay and overall and major complications.[21]

A prospective study analyzed frailty and comorbidity status of 150 patients undergoing PN in a single center in Germany. Wunderle et al used different frailty indexes (e.g. John Hopkins frailty score, Groningen frailty index, low handgrip strength, Full Tandem Stand score and prospective geriatric assessment) to demonstrate that increased frailty was associated with major postoperative complications and failure to achieve the Trifecta outcome (negative surgical margin, ischemia time < 25 minutes, no major complications).[22] Our

TABLE 4. **90-day clinical outcomes and complications of men on testosterone replacement therapy (TRT) for hypogonadism undergoing partial nephrectomy**

	No TRT (n = 474)	**TRT (n = 335)**	**p value (< 0.05)**
ED visit	16.0 (76)	18.0 (60)	0.54
Readmission	6.5 (31)	8.7 (29)	0.32
Acute kidney injury	11.0 (51)	12.0 (39)	0.78
Arrhythmia	5.1 (24)	6.9 (23)	0.35
Bowel obstruction	2.5 (12)	1.5 (5)	0.44
Cardiac arrest	0.42 (2)	0.6 (2)	1
Ileus	7.6 (36)	6.6 (22)	0.67
Myocardial infarction	0.63 (3)	1.5 (5)	0.39
Pulmonary embolism	1.9 (9)	0.9 (3)	0.39
Sepsis	2.1 (10)	3.3 (11)	0.42
Stroke/CVA	1.5 (7)	0.9 (3)	0.68
Length of stay (days)	2 (1-4)	2 (1-3)	0.94

Categorical variables are shown as % (n). Continuous variables are shown as mean ± standard deviation. CVA = cerebrovascular accident; ED = emergency department

results, combined with these studies, indicate that frailty is an important preoperative risk-factor, suggesting a role for formal frailty assessment in patients undergoing PN.

Third, despite the association between frailty and perioperative outcomes, we did not find a difference in perioperative outcomes between hypogonadal and

TABLE 5. **Hazard ratio for 90-day ED visit and 90-day readmission adjusted for mediators (frailty, cardiovascular disease) and confounders (age, diabetes, obesity)**

	90-day ED visit HR (95% CI)	**p value (< 0.05)**	**90-day readmission HR (95% CI)**	**p value (< 0.05)**
	All men undergoing partial nephrectomy (n = 9,105)			
Hypogonadism status				
Eugonadal	Ref.	–	Ref.	–
Hypogonadal	1.02 (0.85-1.22)	0.8	0.85 (0.65-1.11)	0.2
HFRS range				
Low-risk	Ref.	–	Ref.	–
Intermediate-risk	1.15 (1.03-1.28)	**0.016**	1.20 (1.02-1.41)	**0.029**
High-risk	1.78 (1.48-2.14)	**< 0.001**	2.58 (2.03-3.27)	**< 0.001**
	Men diagnosed with hypogonadism undergoing partial nephrectomy (n = 809)			
TRT status				
Not on TRT	Ref.	–	Ref.	–
TRT	1.10 (0.79-1.55)	0.6	1.34 (0.81-2.23)	0.3
HFRS Range				
Low-risk	Ref.	–	Ref.	–
Intermediate-risk	1.30 (0.87-1.92)	0.2	1.35 (0.75-2.43)	0.3
High-risk	2.76 (1.6-4.79)	**< 0.001**	1.93 (0.79-4.70)	0.15

HFRS = Hospital Frailty Risk Score

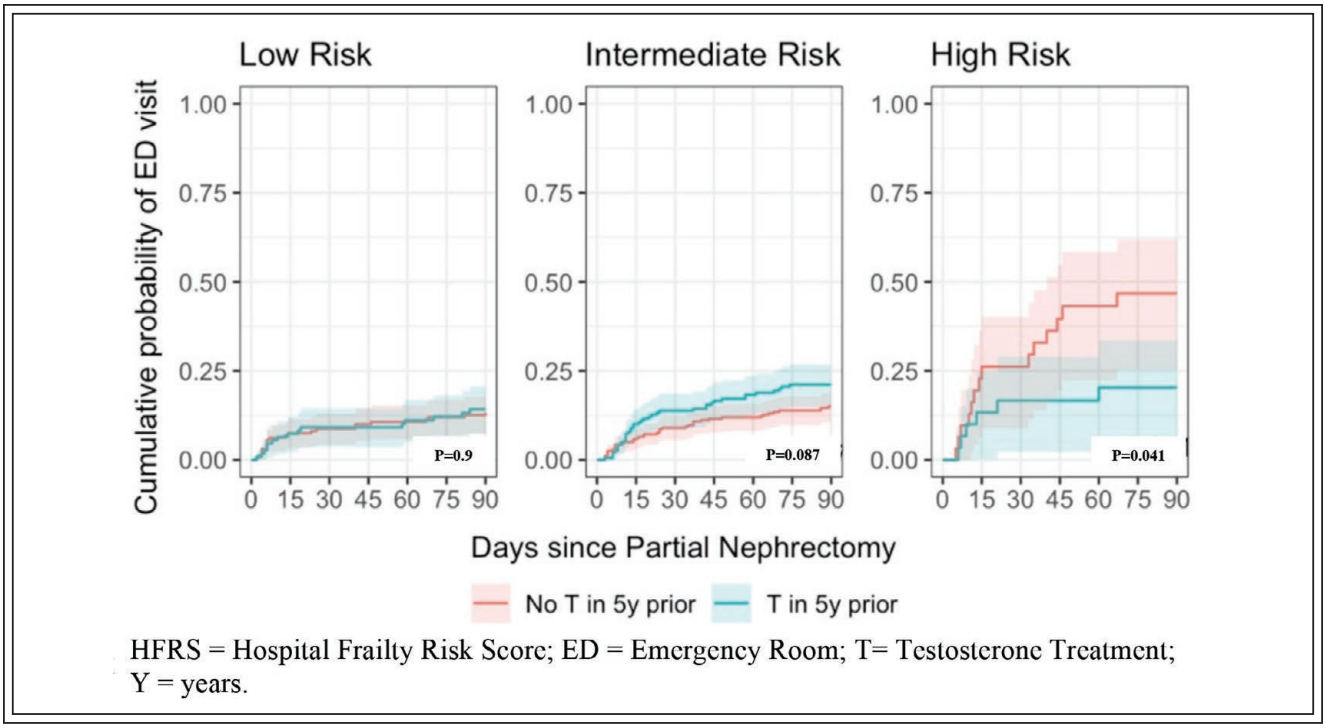

Figure 2. Cumulative probability of 90-day ED visit stratified by HFRS for Partial Nephrectomy patients.

eugonadal men undergoing PN. While this is the first study to assess the impact of hypogonadism on perioperative outcomes after PN, these findings are consistent with a previous study by our group showing no significant association between hypogonadism and perioperative outcomes following radical cystectomy.[20] However, the findings are limited by the low prevalence of hypogonadism (8.9%) in this cohort, which was likely underestimated due to the reliance upon diagnosis codes alone in the absence of universal serum T assessment. Another possible explanation could be a selection bias, wherein only individuals with hypogonadism deemed suitable surgical candidates were chosen to undergo PN. Given prior population-level data on age-related prevalence of hypogonadism,[23-25] we would have expected a higher prevalence of low T in this cohort.[23] Indeed, other studies that utilized serum T measurement to assess low T in the setting of oncologic surgery have found much higher prevalence of low T. For example, Ralla eta al found hypogonadism in 15.2% of men with metastatic RCC, and Smelser et al found low T in 52.5% of radical cystectomy patients.[26,27] Likewise, Hudnall et al found that among men who underwent serum T evaluation prior to major oncologic surgery (urologic and non-urologic), 54.8% had low T.[15] As such, additional prospective studies with serum T measurement (and symptom assessment) are needed to determine whether hypogonadism may be associated with perioperative surgical outcomes in PN.

Fourth, we found a signal that TRT may impact perioperative outcomes in the frailest men undergoing PN. Overall, we found no association between TRT exposure and differences in postoperative complications, 90-day ED visits or 90-day readmissions among hypogonadal men undergoing PN. However, on subgroup analysis of men with high-risk frailty and hypogonadism, TRT was associated with decreased risk of 90-day ED visits. This is the first study to demonstrate a potential therapeutic benefit for TRT in localized RCC, adding to the existing literature showing a benefit to TRT in the metastatic setting. Tsimafeyeu et al conducted a phase 2 randomized trial of TRT among patients with metastatic RCC treated with targeted therapy (sunitinib or pazopanib), which found significant reduction in fatigue and improved symptom control in men receiving TRT.[28] TRT can improve mood, physical function, and contribute to higher health-related quality of life. These outcomes were not assessed in the current study, but future prospective research is warranted to investigate the risks and benefits of TRT for hypogonadal patients undergoing PN.

Our findings should be interpreted within the framework of certain limitations. First, as noted above, our observed rate of preoperative hypogonadism

is lower than the previously reported rates in the general population, likely due to the reasons which were previously depicted. Second, the absence of tumor characteristics and histopathology limited our ability to make meaningful comparisons regarding stage, grade, and tumor size among cohorts, which may impact perioperative outcomes. Lastly, we restricted our analysis to male patients, given the absence of a distinct diagnosis code that would enable identification of female patients with low testosterone. However, prior studies have noted a relationship between testosterone and frailty in women, and further studies are needed to determine the significance of this relationship in the perioperative context.[29]

For summary, frailty was associated with postoperative ED visits and hospital readmission following PN. Hypogonadism, although not an independent risk factor for perioperative complications, was associated with frailty, and treatment of hypogonadal men with TRT was associated with reduction in postoperative risk. These findings suggest a role for frailty assessment, and possibly testosterone screening, in men undergoing PN. Future prospective studies should consider characterizing preoperative serum testosterone levels, symptoms of hypogonadism, and patient-reported outcomes to further understand the role of testosterone and hypogonadism on frailty and outcomes of PN. □

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