Frailty in Long-Term Prostate Cancer Survivors and Its Association With Quality of Life and Emotional Health

Valentin H. Meissner, MD[1]; Kolja Imhof, MD[1]; Matthias Jahnen, MD[1]; Lukas Lunger, MD, PhD[1]; Andreas Dinkel, DSc[2]; Stefan Schiele, PhD[1]; Donna P. Ankerst, PhD[3]; Jürgen E. Gschwend, MD[1]; and Kathleen Herkommer, MD, MBA[1]

Abstract

Background: Frailty is emerging as an important determinant for quality of life (QoL) and emotional health in older patients with cancer, and specifically in long-term prostate cancer survivors, but quantitative studies are lacking. The current study assesses the prevalence of frailty and its association with QoL and emotional health in long-term prostate cancer survivors after radical prostatectomy. **Patients and Methods:** A total of 2,979 prostate cancer survivors from the multicenter German Familial Prostate Cancer cohort completed questionnaires on frailty (Groningen Frailty Indicator [GFI]), QoL (EORTC QoL Questionnaire-Core 30), and emotional health (anxiety/depression symptoms via the Patient Health Questionnaire-4). Modified Poisson regression analysis was used to assess factors associated with frailty. **Results:** Average patient age was 79.4 years [SD, 6.4 years] and average time since radical prostatectomy was 17.4 years [SD, 3.8 years]. Among the cohort, 33.1% (n=985) of patients were classified as frail (GFI ≥4). Frail patients reported worse emotional health than nonfrail patients (depression symptoms: 24.0% vs 4.0%; anxiety symptoms: 20.6% vs 2.0%; both $P<.001$) and lower QoL (mean [SD], 53.4 [19.2] vs 72.7 [16.0]); $P<.001$). Higher age (relative risk [RR], 1.02; 95% CI, 1.01–1.03) and worse depressive (RR, 1.18; 95% CI, 1.12–1.24) and anxiety symptoms (RR, 1.17; 95% CI, 1.11–1.23) were associated with frailty. Living in a partnership (RR, 0.76; 95% CI, 0.67–0.86) and a higher QoL (RR, 0.86 for a 10-point increase; 95% CI, 0.84–0.89) were associated with nonfrailty. **Conclusions:** In a large German cohort, every third long-term prostate cancer survivor after radical prostatectomy was frail. The association of frailty with lower QoL and poorer mental health indicates the need for an integrated care approach including further geriatric assessment and possible interventions to improve health outcomes targeted to frail patients.

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Background

Frailty is an aging-related syndrome, which refers to a state of increased vulnerability to stressors due to a decline in physical and cognitive functioning.[1] Consequently, older individuals of the same chronologic age may exhibit considerably different biologic ages.[2] A cancer diagnosis significantly elevates the prevalence of frailty among older adults.[3] A systematic review including data from 20 studies evaluating 2,916 older patients with cancer reported a median prevalence of frailty of 42% (range, 6%–86%).[3] Individuals with both cancer and frailty are at increased risk of various worse outcomes, such as postoperative complications, chemotherapy-related adverse events, and reduced survival.[3–5]

Quality of life (QoL) and emotional health, which can be assessed by screening for depressive and anxiety symptoms, are further important outcome factors in older patients with cancer. A systematic review and meta-analysis demonstrated evidence of an inverse association between frailty and QoL among community-dwelling older people,[6] which was also demonstrated in patients with breast and colon cancer.[7,8] In patients with prostate cancer (PCa), QoL studies have been limited to metastatic disease[9,10] or the preoperative context, prior to radical prostatectomy (RP),[11] with results lacking in long-term PCa survivors. Prevalence of both depression and anxiety is almost doubled in patients with cancer compared with the general population[12] and, among patients with cancer, has been associated with a higher risk of reduced therapy adherence, longer hospital stays, suicide, and overall mortality.[13,14] A previous study reported that patients hospitalized for mental health illness in the 5 years preceding a PCa diagnosis had hazard rates for mortality twice as high as other patients.[15]

Recent interest in the impact of frailty on PCa outcomes is evident in the recommendations of the International Society of Geriatric Oncology,[16] which recommend that older patients with PCa receive adapted oncologic treatment. In addition, frailty might be a clearer indicator of risk stratification for geriatric oncology patients compared with multimorbidity.[17] The prevalence of frailty as well as its association with QoL and emotional health in long-term PCa survivors have not been investigated to date. Thus, the objective of this study was to assess the prevalence of frailty in a large nationwide registry-based sample of long-term PCa survivors after RP and to assess the association between frailty, QoL, and emotional health.

Patients and Methods

Database and Study Procedure

The study was approved by the ethical review committee of the Technical University of Munich, with informed consent obtained from each patient. The multicenter German Familial Prostate Cancer database, which comprises >36,000 index patients and their relatives, has consecutively recruited and surveyed newly diagnosed patients with PCa throughout Germany independent of their family history since 1993.[18]

Patients were eligible if they had RP as first-line treatment and submitted the completed frailty questionnaire, which was

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[1]Department of Urology, Klinikum rechts der Isar, School of Medicine and Health, Technical University of Munich, Munich, Germany; [2]Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, School of Medicine and Health, Technical University of Munich, Munich, Germany; and [3]Departments of Mathematics and Life Science Systems, Munich Data Science Institute, Technical University of Munich, Garching, Germany.

sent by mail between October and December 2021. The survey response rate was 55.9% (Figure 1). To further characterize any differences between patients excluded from this analysis, we performed a nonresponder analysis including those who did not respond at all (loss to follow-up, n=2,117) and those who did not respond to the frailty assessment (n=231) versus those who responded (n=2,979) (see Table S1 in the supplementary materials, available online with this article). The nonresponder analysis showed that patients who were excluded due to loss to follow-up or missing frailty data did not differ in partnership status (P=.927) and having children (P=.707). However, nonresponders were older (P<.001), had a lower level of education (P<.001), less often had organ-confined cancer (P=.004), and had a longer time since RP (P<.001).

A total of 382 patients had missing data other than frailty status and were therefore excluded from the final regression analysis. Finally, 2,597 of the 2,979 patients included were available for the final regression analysis. A dropout analysis showed that the 382 patients who were excluded from the regression analyses and the 2,597 patients who were included did not differ in frailty (P=.370), QoL (P=.212), depression and anxiety symptoms (P=.473 and P=.645, respectively), biochemical recurrence (BCR) status (P=.130), organ-confined disease (P=.225), partnership (P=.091), and secondary cancers (P=.430). However, there was a low, though statistically significant difference in age. Included patients were slightly younger at the time of survey (mean [SD], 79.3 [6.4] years) than patients who were excluded for missing data (mean [SD], 80.4 [6.5]; P=.001). Furthermore, those who were included in the regression analysis had a higher level of education (P<.001), had a better self-reported financial status (P<.001), and were less often receiving PCa therapy (P=.024) (Supplementary Table S1).

Measures

The primary outcome of frailty was assessed with the 15-item self-report version of the Groningen Frailty Indicator (GFI), which is a validated and reliable instrument to measure frailty in older patients with cancer.[19] A German language version has been established and indicated sufficient diagnostic test accuracy.[20] The GFI contains items on physical, cognitive, social, and psychological domains. Each item has a score of either 0 or 1, with 1 indicating a dependent problem, resulting in a total score ranging from 0 to 15. Frailty is defined as a score of ≥4.[19,21,22] Cronbach's alpha in the current sample was α=.75. Following a previous study suggesting a lower threshold for defining frailty as GFI ≥3 for screening geriatric patients,[23] a sensitivity analysis repeating all methods with this definition was performed (Supplementary Table S2).

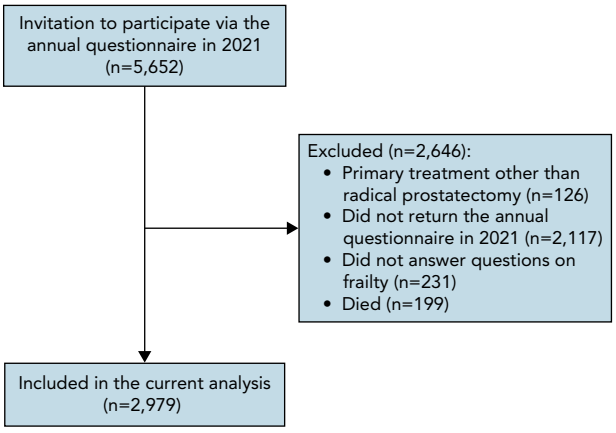

Figure 1. Patient flow through the study.

Sociodemographic characteristics included age at survey, level of education (low: ≤9 years of school; intermediate: 10–11 years of school; high: ≥12 years of school), self-reported financial status (very good/good, satisfied, poor), living in a partnership (yes, no), and having children (yes, no).

Clinicopathologic characteristics included years since RP, positive family history of PCa (defined as a patient with at least one affected relative with PCa), secondary cancer, organ-confined cancer (defined as ≤pT2c tumor at RP and pN0), BCR since RP (defined as a PSA level ≥0.2 ng/mL), current BCR, and current therapy (ie, radiation, androgen deprivation therapy [ADT], chemotherapy).

QoL was assessed using items 29 and 30 of the EORTC QoL Questionnaire-Core 30 (EORTC-QoL-C30).[24] Calculated mean scores were transformed to a range between 0 and 100, with higher scores indicating better QoL. Cronbach's alpha was α=.92. Emotional health (depression and anxiety symptoms) was assessed using the Patient Health Questionnaire-4 (PHQ-4), which is an ultra-brief screening including a 2-item depression scale (PHQ-2) and a 2-item anxiety scale (GAD-2). The German version has been proven reliable and valid, with a cutoff score ≥3 indicating clinical levels of depression and anxiety, respectively.[25] Cronbach's alpha coefficients in the current sample were α=.76 for the depression scale and α=.78 for the anxiety scale.

Statistical Analysis

Chi-square and Wilcoxon-Mann-Whitney tests were used to assess differences of categorical and continuous characteristics, respectively, between frail and nonfrail patients. Independent associations of risk factors were assessed using modified Poisson regression analysis. Based on the analysis comparing frail and nonfrail patients showing no differences in having children (P=.096) and positive family history of PCa (P=.910) (see Table 1), these parameters were not included for further analysis in the modified Poisson regression analysis. The factor "time since RP" was also not included due to its close similarity to the factor "age at survey." Results were reported in terms of relative risks (RRs), defined as the ratio of probability of frailty for the risk factor compared with not having the risk factor, or for a unit-increase for continuous risk factors, along with 95% confidence intervals and P values. All statistical tests were 2-sided, at the 0.05 level of significance, and performed using SAS 9.4 (SAS Institute Inc).

Results

Among the 2,979 patients who had received prior RP, 985 (33.1%) were classified as frail (GFI ≥4). Mean [SD] age at survey was 79.4 [6.4] years with mean time since RP of 17.4 [3.8] years. Frail patients were older than nonfrail patients (80.6 vs 78.8 years, respectively; P<.001), had lower education levels (42.0% vs 36.9%; P=.031), and were less likely to live in partnerships (80.2% vs 89.6%; P<.001) or have good financial status (60.5% vs 78.8%; P<.001). Frail patients had higher rates of secondary cancer (16.5% vs 12.2%; P=.002), BCR since RP (41.4% vs 34.1%; P<.001), current BCR (20.9% vs 16.0%; P<.001), and current PCa therapy use (14.5% vs 8.3%; P<.001), and lower rates of organ-confined

Table 1. Baseline Characteristics

	Overall n (%)	Frail[a] n (%)	Nonfrail n (%)	*P* Value
Total	2,979 (100)	985 (33.1)	1,994 (66.9)	
Sociodemographic characteristics				
Age at survey, mean [SD], y	79.4 [6.4]	80.6 [6.4]	78.8 [6.4]	<.001
Level of education[b]				.031
Low	1,102 (38.6)	396 (42.0)	706 (36.9)	
Intermediate	487 (17.1)	155 (16.4)	332 (17.4)	
High	1,266 (44.3)	392 (41.6)	874 (45.7)	
Good self-reported financial status	2,142 (72.8)	589 (60.5)	1,553 (78.8)	<.001
Living in a partnership	2,527 (86.5)	778 (80.2)	1,749 (89.6)	<.001
Having children	2,587 (88.2)	834 (86.8)	1,753 (88.9)	.096
Clinicopathologic characteristics				
Years since RP, mean [SD]	17.4 [3.8]	17.6 [3.7]	17.2 [3.8]	.009
Positive prostate cancer family history	1,190 (40.0)	392 (39.8)	798 (40.0)	.910
Secondary cancer	406 (13.6)	162 (16.5)	244 (12.2)	.002
Organ-confined cancer	2,125 (71.9)	663 (67.7)	1,462 (73.9)	<.001
Biochemical recurrence since RP	524 (36.5)	405 (41.4)	677 (34.1)	<.001
Current biochemical recurrence	524 (17.6)	206 (20.9)	318 (16.0)	<.001
Under current therapy	308 (10.3)	143 (14.5)	165 (8.3)	<.001
Quality of life and emotional health				
Quality of life, mean [SD]	66.4 [19.4]	53.4 [19.2]	72.7 [16.0]	<.001
Depression symptoms (PHQ-2 ≥3)	305 (10.5)	227 (24.0)	78 (4.0)	<.001
Anxiety symptoms (GAD-2 ≥3)	231 (8.0)	193 (20.6)	38 (2.0)	<.001

Percentages refer to the observed data and do not include missing data.
Abbreviations: GAD-2, Generalized Anxiety Disorder-2; PHQ-2, Patient Health Questionnaire-2; RP, radical prostatectomy.
[a]Frailty was defined as a Groningen Frailty Indicator score ≥4.
[b]Low: ≤9 years of school; intermediate: 10–11 years of school; high: ≥12 years of school.

disease (67.7% vs 73.9%; $P<.001$). They reported, on average, worse QoL (mean [SD], 53.4 [19.2] vs 72.7 [16.0]; $P<.001$) and worse emotional health (depressive symptoms: 24.0% vs 4.0%; $P<.001$; anxiety symptoms: 20.6% vs 2.0%; $P<.001$) compared with nonfrail patients (Table 1).

In the modified Poisson regression analysis, older age (RR, 1.02 [95% CI, 1.01–1.03]; $P<.001$) and worse emotional health (depressive and anxiety symptoms: RR, 1.18 [95% CI, 1.12–1.24], and 1.17 [95% CI, 1.11–1.23], respectively; both $P<.001$) were associated with a higher frailty risk, whereas living in a partnership (RR, 0.76 [95% CI, 0.67–0.86]; $P<.001$) and higher QoL (RR, 0.86 [95% CI, 0.84–0.89]; $P<.001$) were associated with a lower frailty risk (Table 2).

Sensitivity analyses repeating all methods with frailty defined as GFI ≥3 yielded similar results, with significant associations remaining significant at the 0.05 level, and additionally, with secondary cancer (RR, 1.11 [95% CI, 1.01–1.23]; $P=.032$) and worse self-reported financial status (RR, 1.12 [95% CI, 1.03–1.22]; $P=.006$) associated with higher frailty risk (Supplementary Table S2).

Discussion

Frailty entails increased susceptibility to stressors, resulting in lower homeostatic reserves and resilience, which subsequently contributes to adverse health outcomes. Consequently, frailty has become an important factor in the treatment-decision process in older patients with cancer. The gold standard, which is the integration of comprehensive geriatric assessment (CGA), in the decision-making process in oncology practice is time-consuming and requires the expertise of a geriatrician. To avoid unnecessary CGA of healthy and fit patients, a 2-step approach including screening tools such as the GFI, Geriatric-8 (G8),[26] or Vulnerable Elders Survey (VES)–13[27] is recommended. Research has shown that in the general population, 10% to 20% of individuals aged ≥65 years are classified as frail, increasing to 40% in those aged ≥85 years.[28,29] Additional cancer diagnoses further

Table 2. Modified Poisson Regression Analysis of Frailty (GFI ≥4)

	RR (95% CI)	*P* Value
Sociodemographic characteristics		
Age at survey, y	1.02 (1.01–1.03)	<.001
Level of education[a] (ref: low)		
Intermediate	1.02 (0.88–1.18)	.774
High	1.03 (0.92–1.16)	.577
Self-reported financial status (ref: good)	1.08 (0.97–1.21)	.160
Living in a partnership (ref: no)	0.76 (0.67–0.86)	<.001
Clinicopathologic characteristics		
Secondary cancer (ref: no)	1.08 (0.94–1.24)	.296
Organ-confined cancer (ref: yes)	1.06 (0.95–1.19)	.286
Biochemical recurrence since RP (ref: none)		
Previous recurrence	1.06 (0.93–1.22)	.384
Current recurrence	1.02 (0.88–1.17)	.811
Under current therapy (ref: no)	1.05 (0.89–1.23)	.596
Quality of life and emotional health		
Quality of life, mean (for a 10-point increase)	0.86 (0.84–0.89)	<.001
Depression symptoms (PHQ-2)	1.18 (1.12–1.24)	<.001
Anxiety symptoms (GAD-2)	1.17 (1.11–1.23)	<.001

Abbreviations: GAD-2, Generalized Anxiety Disorder-2; GFI, Groningen Frailty Indicator score; PHQ-2, Patient Health Questionnaire-2; RP, radical prostatectomy; RR, relative risk.
[a]Low: ≤9 years of school; intermediate: 10–11 years of school; high: ≥12 years of school.

increase frailty.[3] In the current study, the prevalence of frailty was 33.1% and thus largely comparable with other studies. In a Canadian multicenter prospective cohort study of 175 patients with metastatic castration-resistant PCa with a mean age of 75 years, the prevalence of frailty was 24% (assessed with the VES-13) and 39% (assessed with the G8),[9] showing dependence on the assessment method used. Further prevalence rates of frailty in patients with PCa are sparse and limited to small sample sizes.[30]

Although the validated and most often used cutoff score of the GFI is ≥4,[19,21,22] a further study demonstrated a higher sensitivity and negative predictive value when using a lower threshold of GFI ≥3.[23] Because evaluation of the optimal cutoff score was beyond the scope of this study, a further sensitivity analysis with a cutoff score of ≥3 was performed (Supplementary Table 2). However, results of that analysis largely confirmed previous results, and variables with significant associations remained significant. Additionally, having a secondary cancer was associated with a higher risk of frailty. The reason for this inconsistent result might be that we did not assess the entity and stage of the secondary cancer as well as a potential physical or psychological burden of this cancer. This might lead to the inclusion of cancers that were cured or did not affect the daily life of the survivors. Furthermore, a worse self-reported financial status was also associated with risk of frailty in the sensitivity analysis. A systematic review showed that a low socioeconomic status is associated with frailty.[31] However, although most of these studies are investigating socioeconomic status via absolute income numbers,[32,33] the current study did assess financial status subjectively by the patients, which might be one reason for this inconsistent result.

Despite the growing body of literature on the association between frailty and decreased QoL in patients with cancer,[34,35] there is little knowledge on this issue in patients with PCa. Moreover, results are limited to either metastatic PCa or the periinterventional context following surgery or radiotherapy, whereas studies on patients with long-term PCa after definitive treatment are lacking.[9,11,36] Results of the current study showed lower QoL in frail patients compared with their nonfrail counterparts. Similarly, lower QoL was independently associated with frailty in the modified Poisson regression analysis.

Older patients with cancer who screen positive for depression and anxiety have poorer treatment outcomes, reduced treatment adherence, and higher perception of physical symptoms.[14,37,38] The relationship between frailty and emotional well-being in older adults with and without cancer has been previously reported.[39–41] For instance, a nationwide cluster randomized trial from the United States described an association between frailty (assessed using a deficit accumulation index) and poorer emotional health in older patients with advanced cancer (mostly stage IV gastrointestinal and lung cancer). In this study, emotional health was assessed using screening tools for depression, anxiety, and distress.[41] Results of the current analysis investigating long-term PCa survivors confirmed these previous results. Although the causal direction of the relationship between frailty and emotional health is unknown, a recent study among older adults in China reported a bidirectional relationship between frailty and depressive symptoms.[42] Whether this bidirectional relationship also exists in older patients with cancer has not been examined.

Results of the current analysis suggest that by screening for emotional health, frail PCa survivors who might benefit from CGA could be more easily identified, which emphasizes the role of screening for emotional health in these patients. On the other hand, screening for frailty may also be able to identify patients with long-term PCa who would benefit from an integrated care approach, including further geriatric assessment and possible interventions to prevent the progression of frailty.

Unsurprisingly and confirming previous research,[43] older age was associated with a higher risk of being frail in the current analysis. Concerning the other sociodemographic characteristics, PCa survivors in a partnership were less likely to be classified as frail. A recent study reported that partner loss led to a higher risk of frailty. Interestingly, although women were more likely to recover from this stressful event over time, men's frailty persisted.[44] Furthermore, there is evidence that partnered individuals have better health and lower mortality rates, with a slightly higher protection effect among men.[45,46] Conversely, recent research has found that less social support is associated with frailty and falls.[47,48]

The current study has been the largest registry-based study assessing the prevalence of frailty in long-term PCa survivors after RP. Furthermore, it provides novel and unique data on the association between frailty, QoL, and emotional health in this patient population. Including only survivors after RP is a rigorous selection, but it allows good comparability and precise factor evaluation. However, a few limitations must be mentioned. First, data on the outcomes of interest (ie, frailty, QoL, and emotional health) were self-reported and are therefore at risk for bias, given that people with low self-assessment might tend to rate factors low, and vice versa for those with high self-assessment. This would lead to a bias in the direction of overestimating the associations among factors. Second, some PCa survivors were lost to follow-up or did not answer questions on frailty (Figure 1). This could contribute to nonrandom missing data, because these PCa survivors may be more frail compared with included PCa survivors, which is supported by results of the current nonresponder analysis showing older age among nonresponders compared with responders. Third, this study was conducted in Germany, and other health care systems might differ considerably, including hampered access to specialists, higher rates of uninsured, and economic/racial disparities leading to unequal access to health and cancer care.[49] Therefore, results of the current study must be interpreted with caution and might not be generalizable to other health care systems. Finally, causal results of the relationship between frailty and emotional health are limited by the retrospective design. Therefore, further longitudinal studies are highly warranted.

Conclusions

Results of this study demonstrate that frailty is prevalent in every third post-RP long-term PCa survivor and is associated with lower QoL and poorer mental health, indicating the need for targeted, multidisciplinary integrated care approaches. Assessment of QoL and emotional health might help identify patients who would benefit from CGA and possible interventions to prevent the progression of frailty. Conversely, screening for frailty might identify patients with poorer QoL and emotional health. Treating physicians should therefore consider the inclusion of geriatricians and psychologists for targeted interventions to improve QoL, emotional health, and frailty in PCa survivors.

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Correspondence: Valentin H. Meissner, MD, Department of Urology, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Strasse 22, 81675 Munich, Germany. Email: valentin.meissner@tum.de

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