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Which better predicts mortality among older men, a prostate cancer (PCa) diagnosis or vulnerability on the Vulnerable Elders Survey (VES-13)?: A retrospective cohort study

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STRUCTURED ABSTRACT

OBJECTIVES—Older men with a prostate cancer (PCa) diagnosis face competing mortality risks. Little is known about the prevalence of vulnerability and predictors of mortality in this

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The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

DISCLOSURES AND CONFLICT OF INTEREST STATEMENTS

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Study Concept: S Mohile, W Dale, M Rodin

Study Design: J Hemmerich, W Dale

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Data Analysis and Interpretation: LM Lowenstein, S Mohile, W Dale, C Pandya, M Rodin, H Hopkins Gil

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population compared to men without a PCa diagnosis. We examined the predictive utility of the Vulnerable Elders Survey (VES-13) for mortality in older men with a PCa diagnosis as compared to controls.

MATERIALS AND METHODS—Men aged ≥65 years from an urban geriatrics clinic completed the VES-13 between 2003 and 2008. Each patient with a PCa diagnosis was matched by age to five controls, resulting in 59 patients with a PCa diagnosis and 318 controls. Cox proportional hazard models were used to determine the association of a PCa diagnosis and vulnerability on the VES-13 with mortality.

RESULTS AND CONCLUSIONS—The mean age for men with a PCa diagnosis and controls was 77.9 years and 76.1 years, respectively. Of those with a PCa diagnosis, 74.6% had no active disease or a rising PSA only. Regardless of PCa diagnosis, vulnerable individuals on the VES-13 were more likely to die during the study period (VES-13 ≤3: HR=4.46, $p<0.01$; VES13 ≥6: HR=3.77, $p<0.01$). Men with a PCa diagnosis were not more likely to die compared to age-matched controls (VES-13 ≤3: HR=1.14, $p=0.59$; VES13 ≥6: HR=1.06, $p=0.83$). Vulnerability for men with a PCa diagnosis was more predictive of mortality. Therefore, the assessment of vulnerability is important for establishing goals of care.

Keywords

prostate cancer; vulnerability; mortality

INTRODUCTION

Prostate cancer (PCa) is a disease associated with aging, with more than 70% of diagnoses in men over the age of 65 [1, 2] and 62% are aged 70 years or older. PCa is the second leading cause of cancer mortality among men, with 90% of deaths occurring in men over the age of 65 [3]. Additionally, the risk of developing PCa increases from 1 in 45 for those aged 40 to 59 years to 1 in 7 for those aged 60 or over [4]. PCa incidence is 1.7 times higher in African American men than in Caucasian men, and they have an increased risk of death [5, 6]. Additionally, more early stage cases are being diagnosed with the improved diagnostic techniques in the United States [7]. As a result, these older men are likely to live long-term with the effects of disease and treatment [6, 8]. In short, these men are more likely to die with the disease than from the disease [9].

Vulnerability, as assessed by the Vulnerable Elders Survey (VES-13), is predictive of disability and mortality among community dwelling older adults [10, 11]. The VES-13 is a short screening tool that assesses age and 12 other items including self-rated health, functional status and physical abilities. A score of ≤3 identifies someone as vulnerable, and increasing scores are associated with a higher risk of functional decline and/or death in community elders [12, 13] and older cancer patients [14]. The VES-13 is also sensitive and predictive of impaired functional status in older patients with cancer [15]. To date, researchers have not explored whether vulnerability as measured by the VES-13 in older PCa patients is predictive of mortality.

Initially, researchers have used the cut-point of 3 on the VES-13, but the original cut-point was developed with a population of community dwelling older patients. The original scoring assigned three points for age >85 years. Because of the heavy weighting of age in a community population, alternative cut-points have been suggested for some populations [11, 13, 16].

Our first objective was to compare the prevalence of vulnerability among older men with a PCa diagnosis compared with community-dwelling, age-matched controls among a predominantly urban African American population. Our second objective was to explore whether vulnerability on the VES-13 alone was a better predictor of mortality than having a PCa diagnosis. Our last objective was to determine whether an alternative cut-point may be more appropriate for an urban sample of older men with a PCa diagnosis.

MATERIALS AND METHODS

Research Design and Study Procedures

The study design was case-matched control to compare older men with a PCa diagnosis and community-dwelling controls. Researchers abstracted clinical record data from patients who were seen in the University of Chicago's South Shore Senior Center from July 2000 to December 2008. Clinical data was included if patients were ≥65 years of age and had a histologically confirmed PCa diagnosis. Researchers identified five controls matched on age, within 5-year groups, from the University of Chicago's South Shore Senior Center for every patient with a PCa diagnosis ("cases"). Age was chosen as the matching variable because vulnerability and the risk of developing PCa has been associated with age.

The VES-13 was administered via the phone as part of the intake process, a nurse administered the VES-13 over the phone, which was then reviewed at the clinic visit with the physician. The VES-13 was scored using points for age, self-rated health, self-assessed ability to perform daily functions, and influence of health on physical activities [10, 17, 18]. This study was approved by the University of Chicago Institutional Review Board.

Variables of Interest

The dependent variable of interest was survival time, defined as the time from the VES-13 administration to the end of the study. Date of death was abstracted from the National Death Index (NDI) database. Demographic variables included age, race, marital status, and education. Race was defined as Caucasian, African American or other. Marital status was dichotomized as married or other. Education status was divided into those with less than 9th grade level education, 9th grade to high school, some college, and associate degree or above.

The data collected from the VES-13 survey included age, self-reported health status, difficulties with physical activities, and functional status. Participants reported that their health was poor, fair, good, very good, or excellent compared to other people their age. Physical activities was assessed by asking participants how much difficulty they had with six different activities (no difficulty, a little difficulty, some difficulty, a lot of difficulty, and unable to do). Functional status was determined by assessing the patients' activities of daily living (ADL) and independent activities of daily living (IADL) with five activities.

All other independent variables were abstracted from the patient's medical records. PCa diagnosis at the time of VES-13 administration was categorized as no active disease, rising PSA, or metastatic. No active disease included patients who were stable, in remission, or had no evidence of disease. Rising PSA included patients who had evidence of early recurrence by an increasing PSA level. Metastatic included patients with clinical evidence of disease on imaging or symptoms from advanced cancer. Treatment at diagnosis and at VES-13 administration were collected. The number of comorbidities was collected from the medical record (categorized as 1, 2, and 3), and PCa diagnosis was not counted as a comorbidity. The most frequent comorbidities were coronary artery disease, hypertension, diabetes, COPD/emphysema, Parkinson's disease, congestive heart failure, hearing and vision loss, and arthritis. The number of medications was also collected and coded as counts.

Statistical Analyses

We conducted ANOVA and chi-squared tests to compare age, race, marital status, education, number of comorbidities, number of medications, and VES-13 scores between groups, including the subscores for health status, physical activity score, and functional status. Kaplan-Meier survival analyses were conducted for VES-13 and PCa diagnosis.

Cox-proportional hazard survival analyses were tested for each potential predictor of mortality, accounting for the length of follow-up, with PCa diagnosis, race, marital status, education, number of comorbidities, number of medications, total VES-13 scores, functional status, physical activities, and health status. Covariates were added to the multivariable model if they were significant at the $p < 0.10$ level. Multivariable Cox-proportional hazard survival analyses were conducted, accounting for the length of follow-up, to examine the association of survival time with the independent variables: PCa diagnosis versus VES-13 score. A model was tested to include the variable accounting for vulnerability and PCa diagnosis where 0=not vulnerable [control], 1=vulnerable [control], and 2=not vulnerable [PCa diagnosis], and 3=vulnerable [PCa diagnosis], and these indicator variables were dropped because these variables had a perfectly linear relationship with each other. A model was also run without the cases with metastatic disease, which did not change the effect estimates. The final adjusted models included VES-13 scores, PCa diagnosis, and number of comorbidities. Receiver operating curves (ROC) analysis was used to determine the optimal cut-off point for the VES-13. All analyses were conducted with STATA 13-MP.

RESULTS

Sample Characteristics

A total of 377 VES-13 surveys were collected from men who were 65 years, of which 59 had a PCa diagnosis and 318 were age-matched controls (Table 1). The median number of days that men with a PCa diagnosis and controls were followed was 1694 (range: 11, 3049) days and 1702 (range: 106, 3010) days, respectively. There were more African American men and fewer Caucasian men with a PCa diagnosis compared to the age-matched controls (94.74% vs 82.23%; 5.26% vs 14.63%, $p=0.05$); however, the difference was marginally significant due to rounding. There were no statistically significant differences in marital status, education, and number and types of comorbidities. Men with a PCa diagnosis took

more medications than the controls (5.93 vs 4.86 medications, p -value 0.03). Vulnerability as assessed by VES-13 scores did not differ between the two groups (PCa diagnosis=4.81 vs control=4.08, $p=0.13$). Additionally, within the VES-13 survey, self-rated health status, functional status, and physical activities between the two groups did not differ (Table 1). At the end of the study, 20 of the men with a PCa diagnosis (33.90%) died while 98 men in the control group (30.82%) died ($p=0.64$).

The majority of the men with a PCa diagnosis were previously treated with radiation (35.60%), prostatectomy (27.11%), hormone therapy (40.68%), and/or chemotherapy (1.69%). Of those with PCa diagnosis, 50 had no active disease or rising PSA, 7 had metastatic disease, and 2 with missing data. At the time of the VES-13 survey administration, 38.64% of the no active disease/rising PSA patients were receiving treatment, and 85.71% of the metastatic group were receiving treatment (p -value=0.04). Otherwise, the two groups (no active disease/rising PSA vs metastatic) did not differ significantly (results not shown).

Survival Analysis

The results of the Kaplan-Meier curve analysis (Figure 1) shows that the older men who were vulnerable (VES = 3) had higher mortality than other men. The Cox regression (Table 2) show that mortality did not differ between men with a PCa diagnosis and age-matched controls. Both cut-points on the VES-13 had similar predictive validity: a score of 3 had a hazard ratio (HR)=4.76 with a 95% confidence interval (95% CI)=2.99–7.59 and a score of 6 had HR=3.99 with a 95%CI=2.70–5.89. The individual components of the VES-13 were independently predictive of mortality: functional status (HR=1.39; 95%CI=1.25–1.54), physical activities (HR=1.82; 95%CI=1.49–2.23), and very poor health compared to excellent health (HR=2.77; 95%CI=1.26–6.07). The number of comorbidities was also independently associated with mortality (HR=1.14; 95%CI=1.05–1.24). Controlling for PCa diagnosis and number of comorbidities, individuals with a score of 3 on the VES-13 had an 80.9% increased probability of dying during the study period, and those with a score of 6 on the VES-13 had a 78.1% chance of dying by the end of the study (Table 2).

Sensitivity and Specificity Analysis

Table 3 presents the results of the ROC analysis. Cut-point scores of 6 and 3 had the same sensitivity (90.00%), but the cut-point score of 6 had slightly better specificity (61.54%) than cut-point score of 3 (51.28%). When we compared the predictive validity of the two cut-points, and they performed comparably in the logistic regressions. Less than a quarter of the total sample and the sample with a PCa diagnosis received 3-points due to age (16.7% and 22.0%, respectively).

DISCUSSION

This study was a retrospective, case-control study examining the overall mortality rate of older men with a PCa diagnosis compared to similar men without a PCa diagnosis in a predominantly urban, African American population. Our primary finding was that vulnerability based on VES-13 scores was associated with increased mortality. There was no

statistically significant difference in VES-13 scores and the likelihood of death between older patients with a PCa diagnosis and age-matched controls without PCa. Over 80% of the men with PCa were either disease-free or had biochemical recurrence only. We conclude that for men with minimal or treated PCa, the assessment of geriatric functional parameters is important for establishing overall goals of care.

Consistent with other studies, the number of comorbidities was associated with mortality [19–22]. Comorbidity, defined as the concurrent presence of ≥ 2 medical illnesses, combined with vulnerability, increases the risk of falls, hospitalizations, disability, and death [23]. Given the relatively long life-expectancy of most men with a PCa diagnosis, including older ones [24], our finding suggests that PCa should be treated like other chronic comorbidities, such as heart disease or diabetes, in the older adult population. Our findings support the general understanding that early stage PCa, with limited or only biochemical disease does not significantly affect performance status. So that for men with limited disease, the focus of care should be on the well-understood determinants of frailty functional impairment or other factors that predict survival and affect the quality of life [9].

Vulnerability on the VES-13, which acts as a short, simple, and validated screening tool to quickly identify patients at risk for geriatric disability, can be assessed using the traditional cut-point of ≥ 3, [10, 13, 18]. Our cohort averaged over 4 for the VES-13 for both the men with PCa diagnosis and their age-matched controls. Given the conventional cut-point of 3 indicating vulnerability [11, 13, 16], the higher average score suggests that our cohort might be a more vulnerable population than the groups in other studies. This highlights the importance of assessing vulnerability in these populations. The VES-13 is not the only available screening tool for vulnerability in older patients with cancer. There is on-going debate regarding which screening tool (e.g., G8 or VES-13) is best for identifying older patients with cancer at risk for geriatric disabilities, mortality, and poorer survival [25–28]. The G8 includes 7 items from the mini-nutrition assessment and 1 item on age, with scores ranging from 0 to 17, and a score ≤ 14 is considered abnormal [26, 29]. Both screening tools have their advantages, and either is fine depending on the context in which a full geriatric assessment (GA) is being considered. They are all composites of items drawn from other longer assessments. Differences in the accuracy of these screening tools could be the result of different methodologies – for example self-administered versus administered by a research assistant, nurse, or physician [13, 15, 17, 27, 30, 31]. What is more concerning is how infrequently any specific assessment is used to assess vulnerability in older cancer patients. Instead, there is a high reliance on physician-assessed performance status, which does not accurately characterize vulnerability in older cancer patients compared with a GA [32, 33]. There is a need for more regular use of effective screening tools, such as the VES-13 or the G8, to identify older adults with cancer who are at increased risk for adverse treatment effects, mortality, and survival.

African American men living in an urban setting made up the majority of the patients our study sample (84.3%). Compared to white men, a higher percentage of African American men are diagnosed with and die from PCa; African American race is one of the few known risk factors for PCa [34]. Furthermore, there are very few studies of the VES-13 that include significant numbers of African Americans. Therefore, looking at the VES-13 scores in this

population is important given that vulnerability plays a more important role than PCa in increasing their mortality rate. Given the long survival time among the majority of those diagnosed with PCa, including African Americans, combined with the shortened survival associated with high VES-13 scores, assessing the vulnerability of all older men is a vital clinical tool and can be used in treatment decision making with older PCa patients.

There are several limitations to this study. The median length of follow-up for the PCa patients was 4.64 years, and given that 99+% of PCa patients will live at least five years, longer term follow-up may be needed to detect differences between groups [34]. The sample was from a single institution and may not be generalizable to other settings. However, the high proportion of African American men, who are typically under-represented in PCa studies as well as studies of older adults, provide additional context for treating these men. Comorbidity was assessed using a count of the comorbidities documented in the medical chart instead of a validated scale (e.g., Charlson Comorbidity Index). If this was a prospective study, we would have obtained a more formal measurement of comorbidities, which was not feasible for this present study. The medical chart data did not contain information regarding whether the patients with PCa diagnosis had a tumor induced vulnerability.

CONCLUSIONS

Given the increasing incidence and long-term survival of men with PCa, the high prevalence of multiple comorbidities, and the likelihood of functional losses in older adults, clinics working with these individuals should routinely screen for vulnerability in patients with PCa. With appropriate screening, vulnerable older adults with modifiable risk factors identified by the VES-13 can be targeted for appropriate interventions to address vulnerability and improve both cancer-related outcomes and overall outcomes [28]. Future studies can examine the relationship between VES-13 scores and other common health conditions in older adults.

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Figure 1.

a. The Kaplan-Meier curve shows the survival distribution function when the VES-13 cut point is 3 (traditional cut-point) and PCa diagnosis.

b. The curve shows the survival distribution function when the VES-13 cut-point is 6 and PCa diagnosis.

Table 1

Participant characteristics

	PCa Diagnosis (n=59)	Controls (n=318)	p-value
	N (%)	N (%)	
Age (mean, sd)	77.93 (7.50)	76.05 (7.11)	0.06
Race			0.05
Caucasian	3 (5.26)	42 (14.63)	
African American	54 (94.74)	236 (82.23)	
Other	0 (0.00)	9 (3.14)	
Marital status			0.60
Married	37 (62.71)	188 (59.12)	
Other	22 (37.29)	130 (40.88)	
Education			0.29
Less than 9 th grade	7 (20.00)	38 (27.34)	
9 th grade-high school	16 (45.71)	50 (35.97)	
Some college	8 (22.86)	21 (15.11)	
Associate degree and above	4 (11.43)	30 (21.58)	
No. comorbidities ^a (mean, sd)	4.51 (2.05)	4.54 (2.19)	0.92
1	4 (6.78)	22 (6.92)	
2	5 (8.47)	33 (10.38)	
3 or more	50 (84.75)	263 (82.70)	
No. medications (mean, sd)	5.93 (2.98)	4.86 (3.44)	0.03
VES-13 (mean, sd)	4.81 (3.63)	4.08 (3.39)	0.13
Health status ^b			0.36
Excellent	7 (11.86)	24 (7.59)	
Very good	10 (16.95)	41 (12.97)	
Good	13 (22.03)	110 (34.81)	
Fair	19 (32.20)	93 (29.43)	
Poor	10 (16.95)	48 (15.19)	

	PCa Diagnosis (n=59)	Controls (n=318)	p-value
	N (%)	N (%)	
Physical activities ^b (mean, sd)	1.03 (0.96)	0.99 (0.94)	0.74
Functional status ^b (mean, sd)	2.24 (2.00)	1.83 (1.99)	0.15
Death	20 (33.90)	98 (30.82)	0.64
PCa status at VES-13 ^c			
No active disease	40 (67.80)	---	
Rising PSA	10 (16.94)	---	
Metastatic	7 (11.86)	---	
Treatment at VES-13			
No treatment ^d	35 (59.32)	---	
Hormone therapy	21 (35.59)	---	
Other	2 (3.39)	---	

^aPCa was not counted to derive the number of comorbidities.

^bThese items are part of the VES-13 screening tool.

^cPCa status at the time of VES-13 administration was categorized as no active disease, rising PSA, or metastatic. No active disease included patients who were stable, in remission, or had no evidence of disease. Rising PSA included patients who were newly diagnosed, currently undergoing treatment, or had rising PSA levels. PCa status was missing for 2 patients.

^dIncluded patients undergoing active surveillance. Statistically significant differences bolded.

Table 2

Survival analysis

	Unadjusted Model Hazard Ratio (95% CI)	Adjusted Model 1 Hazard Ratio (95% CI)	Adjusted Model 2 Hazard Ratio (95% CI)
VES-13 (3 cut-point)	4.76 (2.99, 7.59)	4.46 (2.77, 7.17)	---
VES-13 (6 cut-point)	3.99 (2.70, 5.89)	---	3.77 (2.51, 5.66)
PCa diagnosis	1.19 (0.74, 1.93)	1.14 (0.70, 1.85)	1.06 (0.65, 1.71)
No. comorbidities	1.14 (1.05, 1.24)	1.06 (0.98, 1.16)	1.04 (0.96, 1.14)
No. medications	1.03 (0.98, 1.09)	---	---
Age	1.06 (1.04, 1.09)	---	---
Functional status	1.39 (1.26, 1.54)	---	---
Physical activities	1.82 (1.49, 2.23)	---	---
Health status			
Very Good (ref)	---	---	---
Excellent	0.70 (0.27, 1.76)	---	---
Good	0.79 (0.36, 1.74)	---	---
Fair	1.62 (0.76, 3.45)	---	---
Poor	2.77 (1.27, 6.07)	---	---
Marriage	0.86 (0.60, 1.24)	---	---
Education			
Less than 9th grade (ref)	---	---	---
9th grade - high school	0.74 (0.39, 1.41)	---	---
Some college	0.48 (0.19, 1.20)	---	---
Associates degree or above	0.89 (0.42, 1.86)	---	---
Race			
White (ref)	---	---	---
Black	1.72 (0.87, 3.40)	---	---
Other	1.02 (0.22, 4.71)	---	---

Unadjusted models examined the association of each independent variable with mortality. Adjusted model 1 and model 2 examined the association of vulnerability controlling for cancer status and number of comorbidities with mortality using the two cut-points on the VES-13. Age, functional status, physical activity score, and health status were not included in the adjusted models because they are sub-components of the VES-13. Statistically significant at $p < 0.05$ associations are bolded.

Table 3

Vulnerable Elders Survey – 13 sensitivity and specificity analysis

Cut point	Sensitivity	Specificity	Correctly Classified	LR+	LR–
(0)	100.00%	0.00%	---	33.90	1.00
(1)	95.00%	25.64%	49.15%	1.28	0.19
(2)	90.00%	48.72%	62.71%	1.75	0.20
(3)	90.00%	51.28%	64.41%	1.85	0.19
(5)	90.00%	58.97%	69.49%	2.19	0.17
(6)	90.00%	61.54%	71.19%	2.34	0.16
(7)	80.00%	64.10%	69.49%	2.23	0.31
(8)	55.00%	84.62%	74.58%	3.57	0.53
(9)	30.00%	94.87%	72.88%	5.85	0.74
(10)	25.00%	100.00%	74.58%	0.75	---
(>10)	0.00%	100.00%	66.10%	1.00	---