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Prediction of Mortality After Radical Prostatectomy by Charlson Comorbidity Index

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Abstract

Objectives—Prostate cancer treatment should depend on the characteristics of a patient's prostate cancer as well as overall health status. A possible adverse consequence of poor patient selection is a lack of benefit because of premature death from another cause. We evaluated the association between perioperative comorbidity and risk of death from causes other than prostate cancer in men who underwent radical prostatectomy (RP).

Methods—We conducted a retrospective cohort study of 14,052 men who underwent RP from 1983 to 2006. The Charlson Comorbidity Index (CCI) score was calculated using the discharge records for the prostatectomy hospitalization. Mortality status and cause of death were obtained via chart review and searches of national databases. Cox proportional hazards regression was used to estimate the hazard ratio (HR) of death from causes other than prostate cancer after RP by CCI score (0, 1, 2+).

Results—The median age at RP was 58.1 years. The median follow-up was 7.6 years (interquartile range 4.3–11.5). Of 849 deaths, 599 (70.6%) resulted from causes other than prostate cancer. On multivariable analysis, men with a CCI 2 had a statistically significantly higher risk of death from causes other than prostate cancer compared with those with lower CCI scores (HR 2.18, 95% CI 1.30–3.64, $P = .0003$).

Conclusions—Greater perioperative comorbidity was associated with a higher risk of death from causes other than prostate cancer in men who underwent RP. Physicians should consider using a standardized tool to assess perioperative comorbidities to enhance appropriate recommendation for surgical treatment.

The widespread use of prostate-specific antigen (PSA) testing in the United States has led to a dramatic increase in the detection of clinically localized prostate cancer and likely also an increased detection of clinically indolent disease.^{1,2} Although the majority of men diagnosed with prostate cancer today have low- to intermediate-risk disease, there is no definitive tool that perfectly predicts which tumors will progress and which will not. This inability to accurately stratify risk may lead to the treatment of men who are unlikely to die from their prostate cancer.

Surgical treatment for prostate cancer carries with it an inherent risk of post-treatment morbidity. Prostate cancer treatment can potentially alter sexual, urinary, and bowel function, which may adversely affect post-treatment quality of life. The recommendation of

surgical treatment of prostate cancer must be done to optimally balance the risks of treatment-related morbidity against the benefits of treatment. Ideally, definitive prostate cancer treatment would be offered to men with a life expectancy of at least 10 years.³⁻⁵ However, life expectancy is often assessed subjectively by clinicians without standardization, leading to significant inaccuracy.⁶

The presence of comorbid conditions is an important predictor of survival after the diagnosis of a variety of malignancies.⁷⁻¹⁰ Multiple studies have attempted to develop comorbidity tools, including life tables, comorbidity indexes, and nomograms for counseling patients about their life expectancy before undergoing radical prostatectomy (RP).¹¹⁻¹⁷ Although there is no consensus on which comorbidity tool is most useful, the Charlson Comorbidity Index (CCI) has been one of the most extensively studied in prostate cancer patients.¹⁸ The goal of this analysis was to evaluate the association between the CCI score and death from causes other than prostate cancer among men with clinically localized prostate cancer who underwent radical prostatectomy at a high-volume, tertiary referral center.

Material and Methods

We conducted a retrospective cohort study of 15,145 men who underwent RP via either an open, robotic, or laparoscopic approach for clinically localized prostate cancer (clinical stage T1-T3) at the Johns Hopkins Medical Institution between 1983 and 2006. This study was approved by the Institutional Review Board at Johns Hopkins. Age, height, and weight (from which body mass index [BMI] in kg/m² was calculated) at the time of surgery; date of surgery; race; preoperative serum PSA; biopsy and pathologic Gleason score; and clinical and final pathologic stage were abstracted. Mortality status and cause of death were obtained using patient medical records, the United States Social Security Administration's Death Master File, and the Centers for Disease Control and Prevention's National Death Index. Of the 15,145 men, complete follow-up data were available on 14,052 (93%). If prostate cancer was recorded as the underlying cause of death, or if a patient with known metastatic prostate cancer died, then mortality was considered to be a result of prostate cancer. Deaths in which prostate cancer was not the underlying cause were classified as causes other than prostate cancer.

The CCI score was calculated using hospital discharge records and assigned according to the guidelines based on the Dartmouth-Manitoba modification of the Charlson score, which may have more utility in studies of surgical patients.¹⁹ The CCI features 19 conditions for which weighted scores equal to 1, 2, 3, or 6 are assigned based on the severity of the condition. The CCI score was derived by adding the weighted scores for all comorbidities. Based on the distribution of CCI score in this cohort, the men were classified into 1 of 3 CCI score categories (0, 1, 2). Prostate cancer was not scored in the CCI calculation for this study.

The RP specimens were processed as previously published.^{20,21} Tumors were staged according to the 2002 American Joint Committee on Cancer staging guidelines. Patients were followed postoperatively with serum PSA (Hybritech tandem R and E, Beckman Coulter, San Diego, CA, and Tosoh, Tosoh Medics, San Francisco, CA) determinations every 3 months for the first year, semiannually for the second year, and then annually thereafter. Follow-up was calculated from time of surgery to the date of last known contact or death. The primary outcome for this analysis was death from causes other than prostate cancer.

The Kaplan-Meier method was used to estimate the actuarial probabilities of death from causes other than prostate cancer, as well as for all causes and prostate cancer by CCI category. Age-adjusted rates of death from causes other than prostate cancer or from

prostate cancer were calculated by CCI score. Cox proportional-hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of death from causes other than prostate cancer, all causes, or prostate cancer, adjusting for age, race, BMI, surgery date, preoperative PSA, pathologic stage, and pathologic Gleason score. Two-sided tests were performed and *P* values <.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.1 and Stata version 9.2.

Results

The median follow-up time was 7.6 years (interquartile range 4.3-11.5). The clinical and pathologic features of the 14,052 men with available mortality data are shown in Table 1. The mean age at the time of radical prostatectomy was 58.1 ± 6.5 years. Overall, 11,681 (83%) men had a preoperative serum PSA ≤ 10 ng/mL and 10,701 (76%) had a biopsy Gleason score ≤ 6 . On final pathologic review, 8583 (61%) men had a final Gleason score ≤ 6 , and 8968 (64%) had organ-confined disease (pT2).

CCI score was calculated to be 0 in 12,117 (86%), 1 in 1736 (12%), and ≥ 2 in 199 (2%) men, respectively. Overall, 849 (6%) men died during the follow-up period, of which 250 (29%) were due to prostate cancer and 599 (71%) were due to causes other than prostate cancer. Person-years of follow-up and age-adjusted mortality rates stratified by CCI score are shown in Table 2. The age-adjusted rate of death from causes other than prostate cancer significantly increased with increasing CCI score (5.2 deaths/1000 person years for CCI score = 0; 11.4 deaths/1000 person years for CCI score ≥ 2), whereas the rate of death from prostate cancer decreased with increasing CCI score (2.3 deaths/1000 person years for CCI score = 0; 0.7 deaths/1000 person years for CCI score ≥ 2).

The cumulative all-cause, nonprostate cancer-specific, and prostate cancer-specific survival probabilities in men 5, 10, and 15 years after RP are shown in Table 3. The 5-, 10-, and 15-year age-adjusted nonprostate cancer-specific survival estimates for men who underwent RP with a CCI score ≥ 2 was 96.6%, 88.2% and 74.9%, respectively. Men with a CCI score ≥ 2 had a higher risk for nonprostate cancer-specific mortality (Fig. 1; age-adjusted HR 2.18, 95% CI: 1.30, 3.64). Adjusting for known predictors of overall and prostate cancer-specific survival, including year of surgery, preoperative serum, pathologic stage, pathologic Gleason score, and age, race, and BMI, the association between CCI score and death from causes other than prostate cancer persisted (CCI score ≥ 2 vs 0: HR 2.09, 95% CI: 1.25-3.50). In whites, the adjusted hazard ratio for men with a CCI ≥ 2 compared with men with CCI = 0 was 1.90 (95% CI 1.04-3.45). The association appeared to be stronger in African Americans (CCI ≥ 2 vs 0: heart rate = 3.73, 95% CI: 1.25-11.13).

Comment

In our cohort of RP patients, CCI score was associated with a higher risk of death from causes other than prostate cancer. Most notably, men with a CCI score ≥ 2 had twice the risk of death from causes other than prostate cancer compared with those with a CCI score of 0; this association appeared to be stronger in African-American men than in white men. Our results highlight the importance of consideration of comorbid illnesses in proper patient selection for RP.

There were an estimated 192,280 cases of prostate cancer in the United States in 2009.²² Given the high number of newly diagnosed cases annually, a significant number of men with prostate cancer will present each year for surgical consultation. RP has proven to provide excellent long-term cancer control in several large series.^{23,24} Despite improved functional outcomes largely related to a better understanding of the anatomy of the neurovascular bundles and striated urethral sphincter, a significant percentage of men still have post-

treatment decrements in their quality of life. Of 1577 men who underwent RP at a large academic institution, 62% achieved optimal cancer control, continence, and potency outcomes, highlighting the potential for morbidity even in expert hands.²⁵ Studies have also observed that a significant number of men with prostate cancer will die of causes other than their cancer.^{26,27} Given the discrepancy in prostate cancer incidence relative to mortality, the potential for over-treatment is not insignificant. In light of the risk of post-treatment morbidity and the possibility of over-treatment, proper patient selection for RP is essential to minimize unnecessary patient morbidity and to manage health care costs.¹⁷

Definitive prostate cancer treatment is generally not offered to men unless their life expectancy is estimated to be >10 years.^{3,4,17,28} In doing so, the potential for over-treatment of men who are unlikely to succumb to their cancer may be minimized. However, the question of exactly which men will require treatment for clinically localized prostate cancer remains unanswered. Serum-based PSA screening has not only contributed to an increased diagnosis of clinically indolent prostate cancers, but also has resulted in a prostate cancer detection lead time of approximately 10 years compared with digital rectal examination alone.^{2,29} Although many men may have benefited from PSA screening, there is also potential for the diagnosis of prostate cancer that would have a low likelihood of causing mortality.

Discussing life expectancy with patients who are contemplating surgery is often difficult. Studies have shown that clinicians are not very accurate in predicting life expectancy.^{18,30} In an attempt to better identify patients who would benefit most from RP, several investigators have evaluated the utility of comorbidity in predicting the likelihood of nonprostate cancer-related death.¹¹⁻¹⁸ Multiple comorbidity indexes have been studied, but to date there is no consensus on which, if any, is ideal. In fact, the most contemporary guidelines for the treatment of clinically localized prostate cancer do not provide such detailed recommendations to clinicians.^{3,4} Albertsen et al evaluated 3 comorbidity indexes, including the CCI, in a cohort of 459 patients with prostate cancer and found all 3 indexes to be predictive of mortality.¹¹ This study was conducted in patients undergoing watchful waiting, many of whom were not candidates for RP; whether these results are generalizable to patients seeking active treatment for prostate cancer is unknown. Boulos et al compared 5 comorbidity indexes, including the CCI, Index of coexistent Disease (ICED), the Cumulative Illness Rating Scale (CIRS), the Kaplan-Feinstein Index and the Chronic Disease Score in a case-control study of 276 prostate cancer patients treated with curative intent and found all of them to be significantly associated with death from causes other than prostate cancer.¹⁵ More recent series have evaluated the ability of various comorbidity indexes to predict death from causes other than prostate cancer in contemporary cohorts of patients. Alibhai et al evaluated 4 comorbidity indexes, including the CCI, Diagnosis Count, ICED, and the number of medications in 345 men with prostate cancer; no single index was superior to another in predicting overall survival;¹³ the authors also found the CCI to be a significant predictor of the receiving of curative therapy. Froehner et al evaluated the CCI, the American Society of Anesthesiologists physical status classification (ASA), the New York Heart Association classification of heart insufficiency (NYHA) and the classification of angina pectoris of the Canadian Cardiovascular Society (CCS) in predicting death from causes other than prostate cancer in 1302 men who underwent RP. The clinical value of comorbidity classification was greatest in 63-69.9-year-old men, but comorbidity was a poor predictor of death from causes other than prostate cancer in both younger and older age categories.¹⁸ However, the relatively short follow-up (median 5.4 years) and low number of nonprostate cancer deaths (n = 81) in their study limit definitive conclusions.

Our study has a number of strengths. To our knowledge, it is the largest cohort of prostate cancer patients who underwent surgery for which comorbidity data are available. Furthermore, the 849 deaths in our cohort (of which 599 were nonprostate cancer-related) is

the largest series for which nonprostate cancer–specific mortality has been reported. Finally, CCI is easy to use and can be calculated in the office at the time the patient would be making decisions regarding definitive treatment. Our study has possible limitations that merit attention. This cohort study is retrospective in nature and analysis included only those patients with prostate cancer who underwent RP, thus making it a highly selected population that may not be generalizable to all men presenting with newly diagnosed prostate cancer. CCI scores were also assigned retrospectively and it is unclear whether preoperative knowledge of CCI score would change management in this patient population. In addition, CCI scores were assigned by a health care provider based on the medical record as opposed to prospectively via a patient-reported questionnaire, such as the Total Illness Burden Index (TIBI) which has been shown to be highly predictive of death from causes other than prostate cancer.²⁹ We therefore cannot compare a prospectively administered questionnaire to our cohort of patients. Finally, despite the large cohort of patients, only 1.4% had a CCI score of 2 because of already stringent selection of patients for surgery at our institution. Our results may not be generalizable to settings in which the patients have a greater prostate cancer burden and/or greater comorbidities. Despite these limitations, our data further support the use of assessment of comorbidity status as a valuable tool when selecting patients most appropriate for undergoing RP for prostate cancer.

Conclusions

Greater perioperative comorbidities were associated with an increased risk of death from causes other than prostate cancer in these men. Physicians should consider incorporating perioperative comorbidity information to improve appropriate patient selection for prostate cancer treatment. More research is needed to identify the optimal tool for determining risk of death related to existing comorbidities.

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Figure 1.

Kaplan-Meier curves for death from causes other than prostate cancer stratified by CCI score among men who underwent prostatectomy, Johns Hopkins Hospital.

Table 1
Clinical and pathologic features of 14,052 men undergoing RP at Johns Hopkins Hospital from 1983 to 2006 stratified by Charlson Comorbidity Index

	Entire Cohort n = 14,052	CCI = 0 n = 12,117	CCI = 1 n = 1,736	CCI 2 n = 199	P Value
Mean age $\pm$ (SD)	58.1 ($\pm$ 6.5)	58.0 ($\pm$ 6.5)	58.9 ($\pm$ 6.4)	59.9 ($\pm$ 5.7)	<.001
Median follow-up (IQR)	7.6 (4.3-11.5)	7.7 (4.4-11.6)	6.8 (3.6-10.7)	5.5 (3.1-9.7)	<.001
Biopsy Gleason score					.004
6	10,701 (76%)	9290 (77%)	1272 (73%)	1393 (70%)	
7 (3 + 4)	2002 (14%)	1704 (14%)	265 (15%)	33 (17%)	
7 (4 + 3)	798 (6%)	658 (5%)	126 (7%)	14 (7%)	
8	551 (4%)	465 (4%)	73 (4%)	13 (7%)	
PSA (ng/mL)					.004
<4	3068 (22%)	2646 (22%)	389 (22%)	33 (17%)	
4-9.99	8613 (61%)	7418 (61%)	1062 (61%)	133 (67%)	
10	2371 (17%)	2053 (17%)	285 (16%)	33 (17%)	
Pathologic Gleason score					.400
6	8583 (61%)	7471 (62%)	1012 (58%)	100 (50%)	
7 (3 + 4)	3383 (24%)	2882 (24%)	441 (25%)	60 (30%)	
7 (4 + 3)	1168 (8%)	986 (8%)	157 (9%)	25 (13%)	
8	918 (7%)	778 (6%)	126 (7%)	14 (7%)	
Pathologic stage					.592
Organ-confined	8968 (64%)	7735 (64%)	1116 (64%)	117 (59%)	
extracapsular extension	4142 (29%)	3569 (29%)	504 (29%)	69 (35%)	
Seminal vesicle/lymph node-positive	942 (7%)	813 (7%)	116 (7%)	1 (7%)	
Race					<.001
Caucasian	12,675 (90%)	11,005 (91%)	1510 (87%)	160 (80%)	
African American	870 (6%)	679 (6%)	161 (9%)	30 (15%)	
Asian	102 (1%)	82 (<1%)	18 (1%)	2 (1%)	
Other	405 (3%)	351 (3%)	47 (3%)	7 (4%)	
BMI (kg/m ²)					<.001
<24.9	3386 (24%)	2996 (25%)	364 (21%)	26 (13%)	

	Entire Cohort n = 14,052	CCI = 0 n = 12,117	CCI = 1 n = 1,736	CCI 2 n = 199	P Value
25 to <29.9	6517 (46%)	5694 (47%)	742 (43%)	81 (41%)	
30	1919 (14%)	1553 (13%)	319 (18%)	47 (24%)	
Not available	2230 (16%)	1874 (16%)	311 (18%)	45 (23%)	

Table 2
Overall and CCI stratified prostate cancer–specific and nonprostate cancer age-adjusted mortality rates

Variable	Total n = 14,052	CCI = 0 n = 12,117	CCI = 1 n = 1736	CCI = 2 n = 199
Person-years	110,852	96,966	12,590	1296
Mortality rate *	7.7	7.5	8.7	12.0
Prostate cancer specific mortality rate *	2.3	2.3	2.0	0.7
Nonprostate cancer specific mortality rate *	5.4	5.2	6.7	11.4

* Age-adjusted, per 1000 person-years.

Table 3
Overall causes other than prostate cancer, and prostate cancer survival probabilities
(95% confidence interval) in men 5, 10, and 15 years after undergoing RP, Johns Hopkins
Hospital, 1983-2006

Survival Probability (95% CI)			
Years	CCI = 0	CCI = 1	CCI = 2
Overall			
5	98.3 (98.0-98.5)	97.4 (96.4-98.1)	95.8 (90.9-98.1)
10	93.6 (93.0-94.1)	91.7 (89.6-93.4)	87.5 (78.9-92.8)
15	84.2 (82.9-85.5)	80.6 (76.3-84.2)	74.3 (54.1-86.6)
Nonprostate cancer-specific			
5	98.7 (98.5-98.9)	98.0 (97.0-98.6)	96.6 (91.9-98.6)
10	95.6 (95.1-96.1)	93.7 (91.8-95.1)	88.2 (79.5-93.3)
15	89.0 (87.8-90.1)	84.6 (80.5-87.9)	74.9 (54.4-87.2)
Prostate cancer-specific			
5	99.6 (9.4-99.7)	99.4 (98.8-99.7)	99.2 (94.5-99.9)
10	97.9 (97.5-98.2)	97.9 (96.6-98.7)	99.2 (94.5-99.9)
15	94.7 (93.8-95.4)	95.3 (92.6-97.0)	99.2 (94.5-99.9)