



Charlson Comorbidity Index as a Predictor of Cancer Mortality Beyond 10 Years after Radical Prostatectomy

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Abstract

Objectives: To validate the Charlson Comorbidity Index (CCI) in prostate cancer and to assess the impact of comorbidity on survival, both beyond 10 years following Radical Prostatectomy (RP).

Subjects and Methods: A retrospective cohort study of 2,385 consecutive patients undergoing RP for localized prostate cancer between 1987 to 2007 was conducted at the Centre Hospitalier Universitaire (CHU) de Québec. We used CCI to quantify comorbidity at time of surgery. Death cause was determined from hospital records. The interaction CCI* time was tested with Cox model. Competing risk models with left truncation were used to estimate Sub-Hazard Risk (SHR) of Prostate-Cancer-Specific Mortality (PCSM) and Other Causes of Mortality (OCM) according to CCI.

Results: Out of the 2,385 subjects, 647 (27.1%) were monitored over 10-years. There was no significant CCI* time interaction on the prediction of PCSM (P=0.122) or OCM (P=0.178). Beyond 10-years, comorbidity increased the risk of both OCM (CCI>1: adjusted SHR=2.2; CI 95% =1.2–4.1) and of PCSM (CCI=1: adjusted SHR=3.1; CI 95% =1.2–8.3).

Conclusion: Baseline CCI is a good predictor of patient survival after RP for localized prostate cancer even after 10-years. A moderate increase in comorbidity (CCI=1) increases risk of PCSM. This highlights the clinical importance of evaluating and quantifying comorbidity in prostate cancer patients and may provide guidance to tailor long-term clinical follow-up.

Keywords: Comorbidity; Charlson comorbidity index; Prostate cancer; Specific mortality; Competing Risks

Introduction

Radical Prostatectomy (RP) remains a standard and effective treatment option for localized prostate cancer [1]. The benefit of this treatment depends on the clinical and pathological characteristics of the cancer and on comorbidity. Several studies have concluded that comorbidity conditions are an important predictor of post-RP survival [2,3]. Tools for quantifying comorbidity include life tables, comorbidity indices and nomograms. These facilitate patient counseling and estimation of life expectancy prior to choosing RP [4,5]. Although there is no consensus on which comorbidity tool is the most useful, the Charlson Comorbidity Index (CCI) is one of the most extensively studied in the case of prostate cancer. Introduced in 1989 by Mary Charlson and colleagues, the CCI was built from 1-year analyses of mortality in association with comorbidity in patients hospitalized in an internal medicine ward. Further validation focused on cancer patients, first in breast cancer cohorts with 10 years of follow-up [3,4,6]. The CCI is now validated for a wide range of clinical conditions, such as amputation, arthritis and cancer [7]. In prostate cancer patients, comorbidity has been shown to predict mortality due to other causes but not prostate cancer-specific mortality [8,9]. However, these studies were focused on only the first 10 years after RP. To the best of our knowledge, no study has examined the long-term (>10 years) predictive ability of CCI in this context. Meanwhile, current prostate cancer guidelines continue to claim that life expectancy following curative treatment for localized tumors should be greater than 10 years to consider treatment with curative intent [10]. It therefore appears necessary to assess the time effect on the capacity of the CCI measurement at surgery to predict patient's survival and to evaluate the impact of baseline comorbidity

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Table 1: Characteristics of radical prostatectomy patients stratified by follow-up duration.

Variable	Class	Up to 10 years post-RP			Beyond 10 years post-RP		
		N	(%)	Total	N	(%)	Total
CCI	0	1533	64.3	2385	412	63.7	647
	1	527	22.1	2385	167	25.8	647
	>1	325	13.6	2385	68	10.5	647
Age	<59	1249	52.4	2385	372	57.5	647
	59–69	687	28.8	2385	183	28.3	647
	>69	449	18.8	2385	92	14.2	647
Stage T	T2	1540	64.6	2384	374	58.9	646
	T3	806	33.8	2384	261	40.4	646
	T4	38	1.6	2384	11	1.7	646
ASA	1	711	31	2294	209	34.2	611
	2	1340	58.4	2294	355	58.1	611
	>2	243	10.6	2294	47	7.7	611
Stage N	N0	2152	90.3	2383	555	85.8	647
	N1	231	9.7	2383	55	8.5	647
Gleason Score	<7	863	36.2	2384	383	59.1	639
	7	1167	49	2384	173	26.7	639
	>7	354	14.8	2384	91	14	639
PSA	<10	1647	70.2	2347	374	58.5	647
	10–20	512	21.8	2347	187	29.2	647
	≥ 20	188	8	2347	78	12.2	647
Positive Surgical Margin	No	1384	58	2385	311	48.1	647
	Yes	1001	42	2385	336	51.9	647

Abbreviation: ASA: American Society of Anaesthesiologists Physical Status Classification System

beyond 10 years. The aim of this study was to perform this validation by analyzing the interaction between time and CCI on Prostate-Cancer-Specific Mortality (PCSM) and Other Causes of Mortality (OCM). We also examined the relationship between the burden of comorbidity and long-term PCSM. Based on existing data, we hypothesized that the intermediate (CCI=1) burden of comorbidity increased the long-term risk of PCSM [11,12].

Materials and Methods

A retrospective cohort study of 2,385 consecutive patients treated by RP for localized prostate cancer between 1987 and 2007 was conducted at the CHU de Québec. This project was approved by our Institutional Review Board (project #2018-4079). Surgical data, preoperative serum PSA, biopsy and Gleason pathology scores and clinical and final pathological stages were obtained from medical charts. Clinical and pathological stages were evaluated and recorded according to the TNM Classification of Malignant tumors [11,13]. Cancer grade was assessed according to the Gleason scoring system [14,15]. Follow-up duration was calculated for each patient as the time elapsed between RP and either the date of death or the date of the last clinical visit. Vital stats and cause of death were obtained from patient medical records. Both vital status and cause of death were validated by using the unique patient healthcare identifier to link our institutional database to the one of the provincial Institute de la Statistique du Québec, which includes information from death certificates. The initial disease or condition that ultimately

led to death (the underlying cause) was considered to be the cause of death. For the <1% of death cases with divergent cause of death information, institutional chart was reviewed again by a urologist and cause of death ascertained, occasionally correcting the death certificate information. The comorbidity burden was evaluated at the time of surgery. The CCI features 19 associated conditions (Table 1) to which a score of 1 to 6 are assigned according to the severity of the disease. Patients were classified in 1 of 3 CCI categories (0, 1, >1). Prostate cancer was not considered in the CCI. The Gleason score, serum Prostate-Specific Antigen (PSA), clinical pathology were classified the following way: Gleason scores <7 (1), =7 (2) or >7 (3). PSA <10 ng/mL (1), between 10 and 20 ng/mL (2) or >20 ng/mL (3) at the time of RP, and in pathological stages T1–T2 (1) and ≥ T3 (2). Descriptive statistics of baseline data were calculated and stratified by length of follow-up after prostatectomy (cut-off 10 years). Our multipronged approach, described hereafter, of testing the time* CCI interaction, combined with the specific examination of the data restricted beyond 10 years, validates CCI as a predictor of survival beyond 10 years after RP. Distributions of survival events both PCSM and OCM observed for the first 10 years after RP and beyond 10 years were compared. A correlation matrix and Pearson test of significance were carried out to assess dependencies among variables including CCI [16]. The Cox model extended with time-varying regression coefficients was used to evaluate the impact of interaction between follow-up time and the effects of CCI at RP on patient survival in order to test the potential time* CCI interaction [17]. This approach is similar to testing the proportionality assumption over time. The median survival time was estimated using actuarial methods [18]. Competing risk modeling with right censoring on the whole cohort was initially performed. Then the same modeling with left truncation and right censoring was used to analyze the impact of comorbidity on PCSM or OCM beyond 10 years. Left truncation at 10 years of follow-up was used to assess of the conditional survival beyond that time point, in an effort to specifically examine the validity of the CCI after 10 years. Right censoring was defined as the last clinical visit (Figure 1). An extension of the Fine & Gray procedure was used to estimate the sub-hazards risk (SHR) of the CCI effect on PCSM and OCM, allowing taking into account left truncation and right censoring [19]. Multivariate analyses were carried out according to each transition of the competing risk model. Adjustment variables were selected from the usual potentially relevant clinico-pathological variables and according to their specific informative value for those models. We examined the correlation between variables and excluded the variable when a high correlation >0.20 was encountered to control for multicollinearity. Our final models included all significant variables, excluding those without statistical contribution, based on the C-index. Cumulative incidence plots were generated for all examined endpoints and stratified according to CCI group in order to assess the cumulative rate of the mortality according to time [20]. Scaled Schoenfeld residuals were used to verify the proportional hazard assumption for each potential risk factor. The models were validated using the C-index [21]. We considered good models having C-indices in the 72% to 86% range [22]. All statistical analyses were performed using R 2.5.0 (R Foundation for Statistical Computing) and SAS version 9.3 (SAS Institute, Cary, NC).

Results

We found in our database 2,385 patients diagnosed with localized prostate cancer who were consecutively treated by RP at our institution between 1987 and 2017. A total of 647 (27%) of patients whom

Table 2: Risk of prostate cancer specific mortality, accounting for competing causes of mortality. Fine & Gray models, transition from radical prostatectomy to prostate-cancer-specific mortality.

		Univariate(C-index 60%)			Multivariate(C-index 80%)		
Variable	Class	SHR	CI (95%)	p	SHR	CI (95%)	p
CCI	0	1	-	-	-	-	-
	1	2.8	(1.1–7.2)	0.028	3.1	(1.2–8.3)	0.017
	>1	1.9	(0.5–7.3)	0.332	2.5	(0.7–9.7)	0.192
Stage T	T2	1	-	-	1	-	-
	T3+	4.2	(1.6–10.8)	0.003	3.8	(1.4–10.4)	0,008
Age	0	1	-	-	1	-	-
	1	0.5	(0.2–1.8)	0.312	0.4	(0.1–1.3)	0,132
	2	0.5	(0.2–1.4)	0.219	0.4	(0.2–1.1)	0,088
Margin	No	1	-	-	1	-	-
	Yes	1.9	(0.8–4.6)	0.15	1.4	(0.6–3.7)	0.448

Abbreviation: SHR: Sub-Hazard Ratio

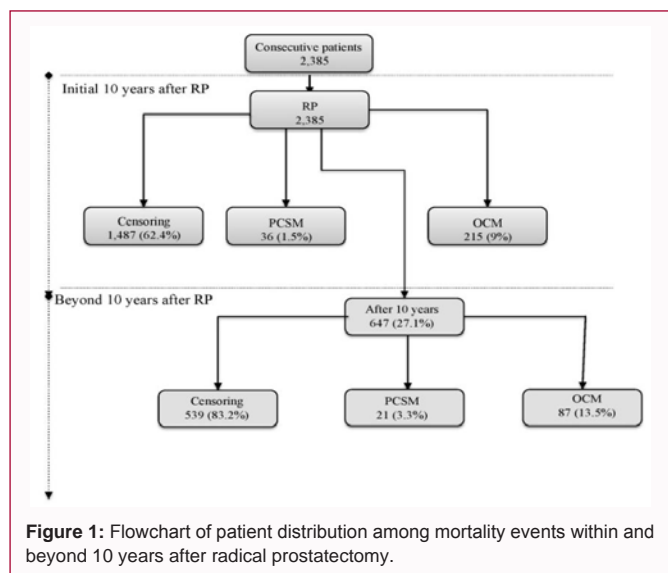


Figure 1: Flowchart of patient distribution among mortality events within and beyond 10 years after radical prostatectomy.

follow-up information was available survived 10 years after RP. The median survival time for that sub-cohort was of 18 years with an IQR of 16 years. The complete event distribution within 10 years of RP and beyond 10 years is shown in (Figure 1). The clinical characteristics of these 647 patients are shown in (Table 1) along with the details of the cohort followed for less than 10 years. The median age was 63 years (IQR=9.6) and the median time from RP until the last follow-up was 13 years (IQR=3). The baseline CCI was greater than 1 in 68 cases (10.5%) and equal to 1 in 167 cases (25.8%). Compared to the cohort followed for less than 10 years, the cohort followed for more than 10 years (thus operated in earlier calendar years) were similar for N stage (p=0.3) and ASA score (p=0.06), the differences being that they. Patients followed for more than 10 years were younger (58% vs. 52% were of age <59, p=0.01) and had slightly less comorbidities using the CCI (11% vs. 14% with CCI>1, p=0.03). They also had higher diagnostic PSA values (41% vs. 29% with PSA>10, p<0.001) lower tumour grade (59% vs. 36% with Gleason score <7, p<0.001), higher T3/T4 stage (42% vs. 35%, p=0.007) and higher positive surgical margins (52% vs. 42%). We observed a constant effect of CCI over time, up to 20 years of follow-up. There was no modification of the effect of CCI on survival-PCSM and OCM-over time (overall interaction PCSM transition P=0.122 and OCM transition P=0.178).

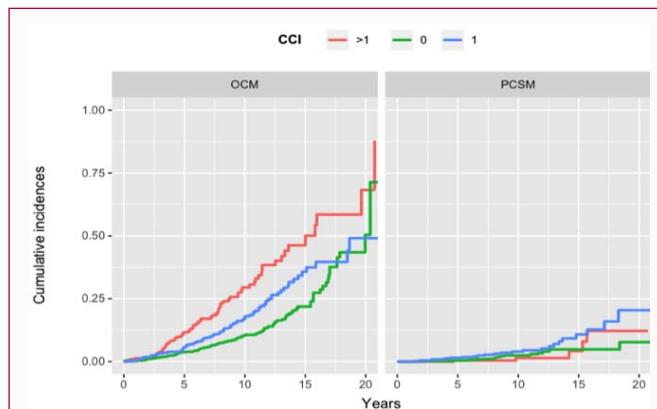


Figure 2: Cumulative incidence of Prostate-Cancer-Specific Mortality (PCSM) and Other Causes Mortality (OCM) stratified by the Charlson comorbidity index. Fine & Gray Models of the transition from radical prostatectomy to the events (OCM, PCSM and censoring) in the whole cohort (without left truncation).

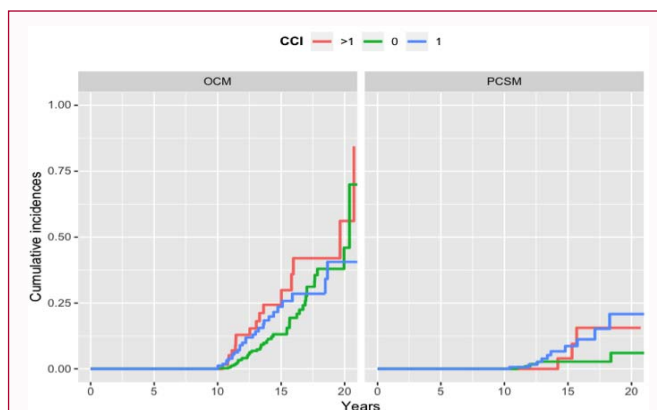


Figure 3: Cumulative incidence of Prostate-Cancer-Specific Mortality (PCSM) and Other Causes Mortality (OCM) stratified by the Charlson comorbidity index. Fine & Gray Models of the transition from radical prostatectomy to the events (OCM, PCSM and censoring) with left truncation at 10 years.

Supplementary Figure 2 shows a more detailed assessment testing this interaction between time and CCI on patient survival. We observe a constant distribution of the (beta) regression coefficient's residuals over time. The multivariate competing risk models show that CCI=1 is a predictor of PCSM after 10 years post-RP (SHR 3.1, CI 95% 1.2–8.3, Table 2). The C-index between 10 and 23 years represents 80% of the predictive capacity of the model. Similarly, CCI>1 is a predictor of OCM (multivariate SHR 2.2 CI 95% 1.2-4.1, Table 3). The cumulative incidences of PCSM and OCM in the total sample and the minimum 10-yr sub-sample are respectively depicted in (Figure 2 and 3).

Discussion

Our study shows that time does not alter the effect of the comorbidity burden at RP on patient survival; even beyond 10 years after the surgery. The CCI measurement thus appears to maintain its validity over time. To the best of our knowledge, our study is the first to validate the CCI measurement beyond 10 years after RP. This is relevant for prostate cancer patients, particularly those treated with curative intent such as with RP, as all must have a long expected survival to undergo treatment and thus have a low comorbidity burden [1]. Their risk of death before 10 years is thus expected to be low. The long-term examination of their survival is critical information for appropriate patient counseling and decision

Table 3: Risk of mortality due to other causes, accounting for competing prostate cancer specific mortality. Fine & Gray models, transition from radical prostatectomy to mortality due to other causes.

Variable	Class	Univariate(C-index 60%)			Multivariate(C-index 68%)		
		SHR	CI (95%)	p	SHR	CI (95%)	p
CCI	0	1	-	-	1	-	-
	1	1.4	(0.9–2.3)	0.163	1.3	(0.8–2.2)	0.313
	>1	1.9	(1.1–3.4)	0.028	2.2	(1.2–4.1)	0.01
PSA	0	1	-	-	1	-	-
	1	1.6	(1.0–2.5)	0.054	1.7	(1.0 – 2.8)	0.045
	2	1.2	(0.6–2.4)	0.564	1.4	(0.7 – 3.0)	0.377
Age	0	1	-	-	1	-	-
	1	2.1	(0.9–4.6)	0.074	2.6	(0.9–7.6)	0.071
	2	2.9	(1.4–5.8)	0.003	4	(1.6–10.1)	0.003
Margin	No	1	-	-	1	-	-
	Yes	0.7	(0.5–1.1)	0.103	0.8	(0.4–1.7)	0.543
Gleason	0	1	-	-	1	-	-
	1	1	(0.5–1.9)	0.957	0.6	(0.4–1.0)	0.067

Abbreviation: SHR: Sub-Hazard Ratio

making. We also show that patients with moderate comorbidity (CCI=1) present a significantly higher risk of PCSM compared to those without comorbidity. In contrast, patients with more severe comorbidity (CCI>1) are at greater risk of dying of other causes. To the best of our knowledge, we are the first group to specifically examine competing survival risks beyond 10 years in prostate cancer. This was possible in large part because each patient record in the database was reviewed and validated with a particular emphasis on cause of death. This current database has been rigorously maintained, validated and used in several previous studies of biomarkers [23-25]. Also, the overall follow-up time was longer than that studied in most institutional cohorts, with 27% of patients (n=647) surviving and followed for at least 10 years and a median survival time of 18 years for that group. Previously reported median survival times were shorter, particularly in institutional cohorts [26]. Even in one of the landmark studies evaluating CCI, based on SEER-Medicare data, the follow-up was limited to 10 years, which precluded an evaluation such as the current one. Much comorbidity in this cohort is established cardiovascular risk factors. One of the most important causes of death in general and also in this cohort is cardiovascular diseases, which actually share many risk factors with cancer. Although commonly considered as two separate entities, cardiovascular diseases and cancer possess various similarities suggesting a shared biology, possibly shared genes, for which evidence is emerging [11]. More research in other and ideally larger cohorts is needed to decipher which specific comorbidity drives the apparently increased PCSM risk. On the other hand, this increased PCSM risk from (moderate) comorbidities could be confounded by lifestyle. Many lifestyle habits such as diet and exercise are established cardiovascular risk factors. Surprisingly, intrinsic (including age and genetic) factors are thought to contribute only modestly to cancer development while extrinsic, often modifiable lifestyle factors, heavily affect cancer risk, particularly for prostate cancer [27]. Indeed, some lifestyle factors increase the risk of both cardiovascular diseases and cancer [11]. Diet and exercise, by affecting multiple physiological pathways and at least partly by their immuno-modulating effects driving chronic inflammation, both seem to affect the tumor microenvironment and risk of cancer progression [12,28]. Our analysis of the association

between CCI and both PCSM and OCM beyond 10 years gave results consistent with the initial 10 years after surgery. This is consistent with the CCI effect being constant over time. Other authors have found the association between CCI and OCM but not PCSM during these initial 10 years [9,29]. One reason for this divergence might be that in most published studies, CCI was used as a categorical variable with two levels: =0 and >0. This does not discriminate between patients with moderate comorbidity from those with more severe comorbidity. In fact, the burden of patients with moderate comorbidity (CCI=1) is sufficient to increase their risk of cancer recurrence but not enough to predispose them to dying of other causes. In patients with high comorbidity (CCI>1) the increased risk of death from other causes is greater than that from cancer, thus the significance of the cancer signal is lost in competing risks analysis although the cumulative incidence curves non-significantly trend in the same direction of increasing cancer risk in high comorbidity patients. By stratifying CCI in three categories (0, 1 and >1) our modeling reduces this heterogeneity. Some modeling aspects of this current study are worth mentioning. First, we observed time trends related to calendar year in (Table 1). These differences are not novel and are expected, given the evolution in prostate cancer diagnosis, pathology and patient selection over time. Important to note is that these differences were all considered for inclusion in our multivariable models. Second, the use of the competing risks modeling including left truncation and right censoring increases the relevance of our study, since this model takes into account the dependency between the PCSM and OCM, unlike the Cox model, which supposes the independence of these two events. This potential dependency is due to the fact that, given its long natural history, prostate cancer patients presents a high-risk of developing lethal comorbidities. Left truncation allows estimation of conditional survival for a patient who is followed beyond 10 years after RP if he has not succumbed to either event (PCSM or OCM) within the initial 10 years. The model does not estimate the SHR in the sub-sample (patients who lived for more than 10 years) but rather in the whole cohort while considering patients who had succumbed to the events of interest only 10 years after RP. This method thus reduces the bias due to left truncation [30]. It should be noted that in the (Figure 3), the cumulative risk curve is a constant equal to zero in the first 10 years after the RP. This period represents the truncation in the model where the events are not taken into account. However, in the global model where the truncation is not applied (Figure 2), the events are observed immediately after RP. The multivariable model for the association between CCI and PCSM presents a C-index of 80% between 10 years and 23 years after RP, emphasizing the robustness of the model estimation. Some limitations of our analysis are worth mentioning. First, as in most RP cohorts and despite long follow-up, the overall PCSM was low (1.9%), which can reduce the precision of our models. Second, model stability can also be affected by the problem of co-linearity between adjustment variables, which added some instability to the models. We have solved these issues by using established data-driven model building strategies and provided stable models. A surprising fact in this cohort was the tumour grade did not impact the PCSM and the OCM, likely because of multicollinearity with the other cancer variables. Thus, this tumor grade variable did not improve the model stability and was not included in our final models. Third, individual comorbidity burden typically increases with time, which helps physicians estimate the mortality risk in the clinic. Since we did not have access to that type of data, this change of comorbidities over time was not accounted for in this analysis. This is the case in most previously reported similar analyses. Fourth, as

previously discussed, many lifestyle factors affect longevity. However, we could not account for these factors, as we do not have lifestyle data for that cohort. Finally, our study also suffers of the insufficient number of events beyond 10 years after the RP. However, modeling greater number of events in the total cohort, we found similar results.

Conclusion

The baseline comorbidities, here measured by CCI, remain a very good predictor of survival after RP in prostate cancer patients even beyond 10 years after surgery. A moderate comorbidity burden (CCI=1) increases the risk of PCSM, even when accounting the increased risk of OCM. The effect of a heavier comorbidity burden is greater on OCM than on PCSM. This highlights the clinical importance of understanding and quantifying comorbidity in prostate cancer patients and may provide guidance to tailor long-term clinical follow-up. More research to decipher the potential links between comorbidity and cancer progression is needed and justified.

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