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Validation of a Questionnaire-Suitable Comorbidity Index in Patients Undergoing Radical Cystectomy

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Keywords
Bladder · Comorbidity · International Consortium for Health Outcomes Measurement · Standard set · Cystectomy · Logit model · Proportional hazards model

Abstract
Objective: To investigate the capability of a modified self-administrable comorbidity index recommended in the standard sets for neoplastic diseases published by the International Consortium for Health Outcomes Measurement (ICHOM) to predict 90-day and long-term mortality after radical cystectomy. ***Methods:*** A single-center series of 1,337 consecutive patients who underwent radical cystectomy for muscle-invasive or high-risk non-muscle-invasive urothelial or undifferentiated bladder cancer were stratified by the modified self-administrable comorbidity index and Charlson score, respectively. Multivariate logit models (for 90-day mortality) and proportional-hazards models (for overall and non-bladder cancer mortality) were used for statistical work-up. ***Results:*** Considering 90-day mortality, both comorbidity indexes contributed independent information when analyzed together with age ($p < 0.0001$). The Charlson score performed slightly better (area under the curve [AUC] 0.74 vs. 0.72 for the ICHOM-recommended comorbidity index). Considering 5-year overall mortality in 727 patients with complete observation, the performance of both measures was similar (AUC 0.63 vs. 0.62, including age AUC 0.66 for both indexes). With 6-sided stratifications, the modified self-administrable comorbidity index separated the risk groups slightly better (p values for directly neighboring curves: 0.0068–0.1043 vs. 0.0001–0.8100). ***Conclusion:*** The ICHOM-recommended modified self-administrable comorbidity index is capable of predicting 90-day mortality and long-term non-bladder cancer mortality after radical cystectomy similarly to the commonly used Charlson score.

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Introduction

Of the major urologic procedures, radical cystectomy is associated with the highest perioperative mortality risk [1, 2]. Comorbidity is an important risk factor for periop-

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erative and long-term mortality after radical cystectomy. There is, however, no consensus on the best way to measure it in this setting [3, 4].

The International Consortium for Health Outcomes Measurement (ICHOM) is a nonprofit organization developing standard sets of outcomes and risk factors for various medical conditions [5–9]. Among urological cancers, until now, standard sets for localized and locally advanced prostate cancer have been published [5, 6]. Bedside standard sets for lung, breast and colorectal cancer are currently available [7–9]. In these standard sets, a modified self-administered comorbidity questionnaire is recommended for measuring the burden of concomitant diseases [5–9]. This comorbidity measure relies on 13 unweighted items and is relatively easily applicable. To our knowledge, this comorbidity measure has not yet been validated in patients with urologic cancer. The aim of this study was to test this simple and questionnaire-suitable comorbidity index in patients selected for radical cystectomy and to compare it with the currently most-commonly used comorbidity measure, the Charlson score [10], to provide data that could support the future development of a standard set for muscle-invasive bladder cancer.

Patients and Methods

A total of 1,337 consecutive patients who underwent radical cystectomy for muscle-invasive or high-risk non-muscle-invasive urothelial or undifferentiated bladder cancer at the University Hospital Dresden between 1993 and 2017 were studied. Demographic data are given in Table 1. Comorbid conditions were largely recorded by following the recommendations of the ICHOM standard sets for neoplastic diseases [5–9]. Only insignificant modifications were made in order to ease data collection by using data already recorded in the existing database (online suppl. Table 1; see www.karger.com/doi/10.1159/000507100 for all online suppl. material,). Data were abstracted in a structured manner by senior urologists (M.F., V.N., and U.H.) from preoperative cardiopulmonary risk assessment records and discharge letters. The Charlson score was assigned by using the same data sources following the original description [10] as far as the available data allowed. Differences between the ICHOM-recommended comorbidity index [5–9] and the original version of the Charlson score [10] are described in online supplementary Table 3.

Follow-up data were obtained from private doctors, patients and their relatives, the hospital information system, local authorities, the tumor register, and health insurance companies. Follow-up data for at least 90 days after surgery were available for all patients. Causes of death were classified by senior urologists (M.F. and U.H.). Multivariate logit models were used for the analysis of predictors of 90-day mortality. For comparison, beside the 2 comorbidity indexes in question, age and the American Society of Anesthesiologists (ASA) physical status classification [11] were included in the analyses evaluating the predictors of 90-day mortality. Kaplan-Meier curves, Mantel-Haenszel hazard ratios (HRs) and log-rank tests were used for univariate comparisons of overall mortality. Cumulative mortality curves for competing risks and Pepe-Mori tests were used for univariate comparisons with end points with competing risks. Cox proportional-hazards models and proportional-hazards models for competing risks were used in the multivariate analyses. Statistical analyses were performed with Statistical Analysis Systems v9.4(SAS Institute, Cary, NC, USA) by a senior biostatistician (R.K.).

Table 1. Demographic data of the study sample

Parameter	*n* (%)
Positive lymph nodes[1]	352 (26)
Bladder-confined primary tumor	776 (58)
Adjuvant cisplatin-based chemotherapy[2]	289 (22)
Any neoadjuvant chemotherapy	66 (5)
Female gender	286 (21)
Continent urinary diversion	429 (32)
Current smoker	374 (28)
ASA class 3–4	580 (43)
Charlson score ≥2 or higher	510 (38)
Death from	
Non-cancer causes	229 (17)
Bladder cancer	425 (32)
Second cancers	73 (5)
Unknown causes	6 (1)
Death within 90 days after surgery	56 (4.2)

ASA, American Society of Anesthesiologists physical status classification.
[1] Unknown in 32 cases; [2] unknown in 5 cases.

Results

The mean age was 68.7 years (median 70 years). The mean follow-up of the surviving (censored) patients was 6.9 years (median 5.3 years). A total of 733 patients died during follow-up (Table 1). Both the ICHOM-recommended comorbidity index and the Charlson score were independent predictors of 90-day mortality when included together with age as variables in the multivariate logit models (online suppl. Table 3). When the ASA classification as a powerful predictor of 90-day mortality was added, the ICHOM-recommended comorbidity index narrowly missed the significance level whereas the Charlson score still was an independent variable (online suppl. Table 3). Focusing on the area under the curve (AUC) for each parameter, both comorbidity measures almost showed agreement, slightly in favor of the Charlson score

Table 2. Optimal proportional hazard models predicting overall and non-bladder cancer mortality analyzing all individual conditions contributing to the modified self-administrable comorbidity index recommended in the ICHOM standard sets [5–9] separately

Parameter	End point overall mortality			End point competing mortality		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (continuous variable, per year)	1.03	1.02–1.04	<0.0001	1.02	1.02–1.05	<0.0001
Heart disease	1.39	1.18–1.64	<0.0001	1.62	1.26–2.10	0.0002
Hypertension						
Peripheral vascular disease	1.35	1.08–1.68	0.0087	1.41	1.03–2.02	0.0350
Lung disease	1.46	1.22–1.74	<0.0001	1.43	1.09–1.89	0.0108
Diabetes mellitus				1.46	1.14–1.87	0.0030
Kidney disease	1.58	1.20–2.09	0.0011			
Liver disease	1.64	1.13–2.38	0.0096			
Cerebrovascular/Parkinson disease/MS						
Tumor	1.42	1.12–1.80	0.0038			
Depression						
Connective-tissue disease						

Values for all comorbid conditions are given in comparison to not having that condition. Patients without the comorbid condition in question were taken as the reference. Since no patient had HIV/AIDS, this variable was not included in these analyses. HR, hazard ratio; CI, confidence interval, MS, multiple sclerosis.

(online suppl. Table 3). The 90-day mortality rates with stepwise-increasing risks stratified by the ICHOM-recommended mortality index and the Charlson score, respectively, are shown in online supplementary Table 4.

Considering long-term non-bladder cancer (competing) mortality, 9/12 single conditions contributing to the ICHOM-recommended mortality index were associated with significantly increased competing mortality in the univariate analyses (online suppl. Table 5). Patients with continent urinary diversion had higher 10-year overall survival rates than those with incontinent or no urinary diversion in almost all subgroups after stratification according to the ICHOM-recommended mortality index as well as the Charlson score (online suppl. Table 6). In a multivariate analysis including age and the ICHOM-recommended comorbidity index as continuous variables, age (HR/year 1.04; 95% confidence interval [CI] 1.02–1.05; $p < 0.0001$) and the ICHOM-recommended comorbidity index (HR/point 1.30; 95% CI 1.20–1.41; $p < 0.0001$) were independent predictors of long-term mortality risk. Analyzing all contributing conditions separately, 6/11 diseases were independent predictors of overall mortality and 4/11 diseases were independent predictors of non-bladder cancer mortality (Table 2). The cumulative overall and non-bladder cancer mortality rates with 6-sided stratification by the ICHOM-recommended comorbidity index and the Charlson score, respectively, are shown in Figures 1 and 2. The corresponding Mantel-Haenszel HR, 10-year overall survival rate, CI, and *p* value are shown in Table 3.

The first 727 patients of our sample were all observed for at least 5 years after surgery or until they died. When they were analyzed with 5-year overall mortality as the end point, the AUCs of the ICHOM-recommended comorbidity index (0.62) and the Charlson score (0.63) were almost identical. When age as a continuous variable was included, the AUCs were 0.66 (age and ICHOM-recommended comorbidity index) and 0.66 (age and Charlson score) in these 727 patients (for comparison, age alone: AUC 0.62).

Discussion

The self-administrable comorbidity index recommended in the ICHOM standard sets [5–9] is relatively easy to apply. It may, due to its suitability for use in a questionnaire, be administered in settings where medical records are not available [12]. This study has illustrated that the vast majority of the conditions assessed in the ICHOM-recommended comorbidity index [5–9] are relevant in the radical cystectomy setting, and that this index may be used as an equivalent substitute of the commonly used Charlson score. With the assessment of comorbidi-

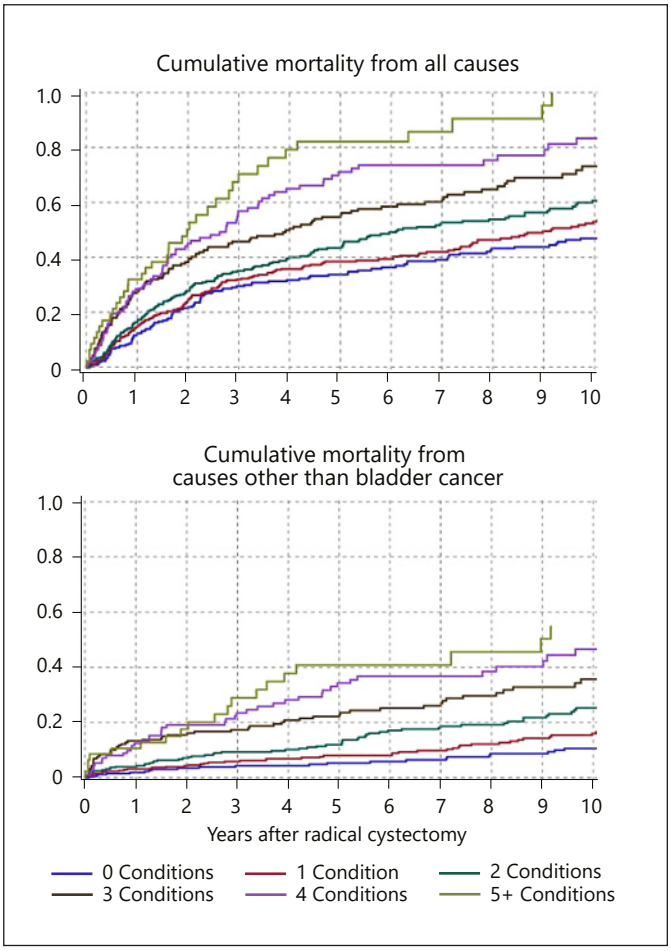

Fig. 1. Cumulative overall and non-bladder cancer (competing) mortality rates stratified by the modified self-administrable comorbidity index recommended in the ICHOM standard sets for neoplastic diseases [5–9].

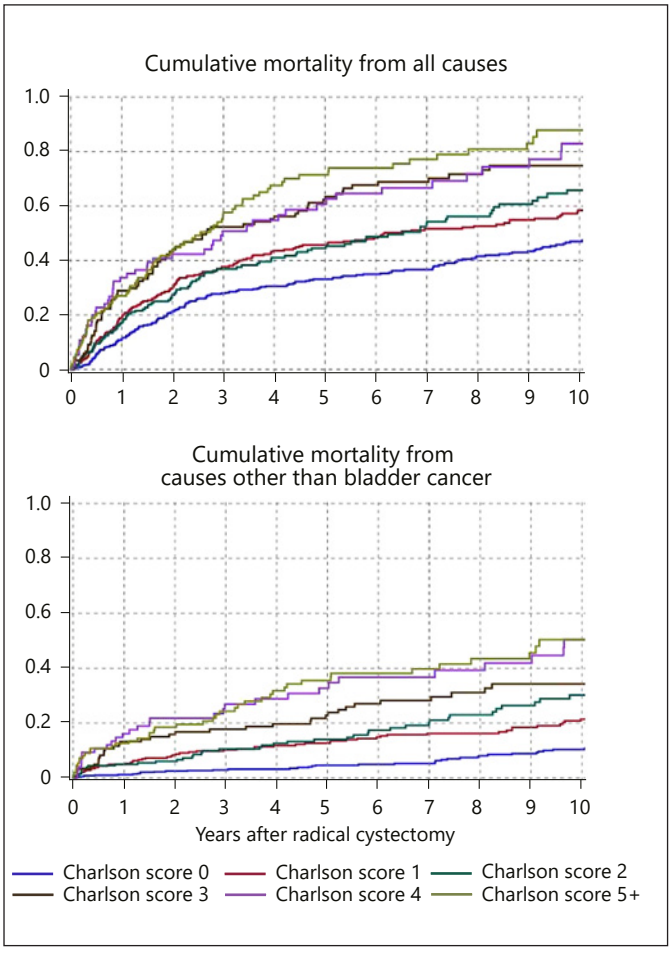

Fig. 2. Cumulative overall and non-bladder cancer (competing) mortality rates stratified by the Charlson score [10].

ty, more complex instruments may be expected to provide better predictive performance [13]. However, particularly when no detailed documentation of concomitant diseases is available, or when data are obtained via questionnaire from the patients themselves, complexity may hinder data collection. Complexity may also obstruct the application of comorbidity indexes in daily practice [14]. The relative simplicity of the ICHOM-recommended comorbidity index and its questionnaire-suitability may compensate for the slightly better performance of the Charlson score in predicting 90-day mortality, as seen in this study (online suppl. Table 3). Considering the prediction of long-term competing (non-bladder cancer) mortality, the performance of both indexes was virtually identical (indicated by narrowly identical AUCs). From a clinical point of view, the somewhat better separation of the cumulative mortality curves (Fig. 1, 2; Table 3) might even constitute a slight advantage of the ICHOM-recommended comorbidity index.

The results of the univariate analyses in this series are comparable to our previous study of 5,050 patients selected for radical prostatectomy, in which we recorded 745 deaths from causes other than prostate cancer. Here, 3 conditions (depression, connective-tissue disease, and liver disease) did not reach a level of significance [15]. However, in the multivariate analyses including age and all single contributing diseases in the radical cystectomy setting, only 4 conditions were independent predictors of non-bladder cancer mortality (Table 2). In contrast, in patients selected for radical prostatectomy, of the conditions contributing to the ICHOM-recommended comorbidity index, only liver disease and depression were not

Table 3. Mantel-Haenszel hazard ratio (HR), 10-year overall survival (OS) rate, confidence interval (CI), and *p* value for 6-sided stratifications of the modified self-administrable comorbidity index recommended in the ICHOM standard sets for neoplastic diseases [5–9] and the Charlson score [10], respectively

	n	10-year OS	95% CI	HR	95% CI	*p* (raw values)
ICHOM comorbidity index						
0	272	53.1%	46.1–59.6%	1 (ref.)		
1	389	47.1%	40.8–53.1%	1.20	0.96–1.51	1 vs. 0: $p = 0.1043$
2	327	39.4%	32.8–45.9%	1.54	1.23–1.94	2 vs.1: $p = 0.0228$
3	189	26.8%	19.1–35.2%	2.17	1.66–2.84	3 vs. 2: $p = 0.0068$
4	113	16.6%	8.9–26.5%	3.56	2.51–5.03	4 vs. 3: $p = 0.0381$
≥5	47	0%	not available	8.43	4.75–14.96	5 vs. 4: $p = 0.0580$
Charlson score						
0	506	53.0%	47.6–58.1%	1 (ref.)		
1	321	41.6%	35.2–47.8%	1.55	1.27–1.90	1 vs. 0: $p < 0.0001$
2	203	34.1%	25.6–42.9%	1.70	1.31–2.19	2 vs.1: p = 0.7538
3	121	25.1%	16.7–34.4%	3.35	2.42–4.65	3 vs. 2: $p = 0.0016$
4	75	17.1%	7.7–29.6%	3.72	2.43–5.69	4 vs. 3: $p = 0.8100$
≥5	111	12.2%	5.3–22.1%	4.85	3.39–6.96	5 vs. 4: $p = 0.3297$

independent predictors of competing mortality [15]. There are several possible explanations for these discrepancies. Compared with the prostatectomy sample [15], fewer competing deaths (i.e., causes of death other than the index disease) were recorded in our study due to the smaller sample size. Furthermore, compared with the radical prostatectomy setting, the mortality of bladder cancer as the index disease was clearly higher, superseding that of all other causes together (Table 1). Finally, it is likely that there was a higher prevalence of more severe comorbidity in patients undergoing radical cystectomy (a higher prevalence of combinations of serious conditions) than in a stricter selected radical prostatectomy population that could have covered the impact of less serious conditions, e.g., hypertension (Table 2).

Several comorbidity indexes have been investigated as predictors of perioperative and long-term mortality after radical cystectomy [3, 4, 16]. The ASA classification is frequently preferred for the assessment of perioperative mortality risk whereas the Charlson score is widely used for the estimation of long-term mortality [3, 4]. With the prediction of 90-day mortality, relying only on countable diseases and disregarding the general physical status assessed by the ASA classification leads to a loss of predictive information (indicated by lower AUCs; online suppl. Table 4). Considering the wide variety of already studied tools, simplification and standardization are possibly as important as the difficult development of novel instruments with higher accuracy. Therefore, using a simple, universal, and self-administrable comorbidity assessment tool as, is the case with the currently available ICHOM standard sets for neoplastic diseases [5–9], is an approach worth supporting. Until now, detailed information on comorbidity is frequently lacking in outcome studies evaluating elderly patients who have undergone radical cystectomy [17].

This study has some limitations. It was a retrospective study. Comorbidity data were obtained by chart review, so it was not possible to analyze patient-reported data. Questionnaire-derived patient-reported comorbidity data may be expected to correlate only moderately with a Charlson score assigned by chart abstraction by trained personnel [12]. Due to a limited number of events, the multivariate analyses of combined effects of the individual conditions contributing to the ICHOM-recommended comorbidity index are possibly preliminary.

Conclusion

The modified self-administrable comorbidity index recommended in the ICHOM standard sets for neoplastic diseases is able to predict 90-day mortality and long-term non-bladder cancer mortality after radical cystectomy, similarly to the commonly used Charlson score.

Acknowledgement

All individuals who have made substantive contributions to the research or the manuscript are included as co-authors.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Involved patients have given their written informed consent for data collection. Institutional review board approval was obtained (reference number EK84032009).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.F: Study design, data collection, statistical analysis, manuscript writing; R.K: statistical analysis, manuscript editing; U.H: data collection, manuscript editing; A.B: data collection, manuscript editing; M.H: data collection, manuscript editing; V.N: data collection, manuscript editing; M.P.W: supervision, manuscript editing; C.T: supervision, manuscript editing.

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