



## Development of a New Comorbidity Assessment Tool for Specific Prediction of Perioperative Mortality in Contemporary Patients Treated with Radical Cystectomy

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### ABSTRACT

**Purpose.** The Deyo adaptation of the Charlson comorbidity index (DaCCI), which relies on 17 comorbid condition groupings defined with 200 ICD-9-CM diagnostic codes, lacks specificity in the context of radical cystectomy (RC) for bladder cancer (BCa). We attempted to develop a new comorbidity assessment tool based on individual comorbid conditions and/or BCa manifestations for specific prediction of perioperative mortality after RC. **Methods.** We relied on 7076 T1–T4 nonmetastatic BCa patients treated with RC between 2000 and 2009 in the SEER-Medicare linked database. Within the development cohort ( $n = 6076$ ), simulated annealing (SA) was used to identify (1) individual comorbid conditions, (2) individual BCa manifestations, and (3) the combination of both, that

satisfy the criteria of maximal accuracy and parsimony for prediction of 90-day mortality after RC, after adjusting for several confounders. The accuracy of the newly identified groups of individual comorbid conditions and/or BCa manifestations and of the original DaCCI was tested in a 1000-patient external validation cohort.

**Results.** The combination of six individual comorbid conditions and two individual BCa disease manifestations (type II diabetes without complications, anemia, chronic obstructive pulmonary disease, congestive heart failure, aortocoronary bypass, cardiomegaly, urinary tract infection, and hydronephrosis), and seven individual comorbid conditions (type II diabetes without complications, anemia, chronic obstructive pulmonary disease, congestive heart failure, aortocoronary bypass, osteoarthritis, and cardiomegaly) respectively showed 71.1 and 70.2% accuracy versus 68.0% for the original DaCCI.

**Conclusions.** These new approaches are specific to contemporary RC patients and represent simpler methods compared with the original DaCCI, without any compromise in accuracy.

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Several comorbidity indices have been developed for quantification of comorbid conditions and have been assessed for their ability to predict survival in bladder cancer (BCa) patients who are candidates for radical cystectomy (RC).<sup>1</sup> These indices include the Charlson

comorbidity index (CCI),<sup>2,3</sup> Elixhauser Index,<sup>4</sup> American Society of Anesthesiologists (ASA) score,<sup>5</sup> Adult Comorbidity Evaluation 27 (ACE-27) score,<sup>6</sup> Eastern Cooperative Oncology Group performance score (ECOG PS),<sup>7</sup> and Karnofsky Performance Status (KPS).<sup>8</sup>

The Deyo et al. adaptation of the CCI (DaCCI)<sup>2,3</sup> is the most widely used tool for quantification of comorbid conditions in retrospective analyses relying on administrative databases, such as Surveillance, Epidemiology, and End Results (SEER)-Medicare, where International Classification of Disease-Ninth Revision-clinical modification (ICD-9-CM) codes are used. Despite its popularity, this index has limitations; For example, it was originally<sup>2</sup> devised for prediction of 1-year mortality based on a review of 599 hospital charts of medical patient admissions at a single hospital. Consequently, it is not devised or tailored for use in patients harboring conditions that differ from those encountered in medical patients, such as BCa patients or, even more specifically, BCa patients treated with RC. Moreover, the DaCCI<sup>3</sup> relies on 17 comorbid condition groupings defined with nearly 200 ICD-9-CM codes. It is of interest that, among those codes, several conditions are included that are not applicable to, or are of marginal importance to, contemporary RC patients. These include acquired immunodeficiency syndrome (AIDS), metastatic solid tumor, and hematologic malignancies, to name a few.<sup>9</sup>

Also, the other aforementioned comorbidity indices are not exclusive for BCa patients who underwent RC; For example, the Elixhauser Index<sup>4</sup> was devised for prediction of length of stay, hospital charges, and in-hospital mortality, relying on data drawn from 438 acute-care hospitals in California, and was developed by identifying comorbidities relevant to hospitalization rather than the primary reason for hospitalization and the severity of that condition. Therefore, it explicitly excludes the most common causes of hospitalization such as myocardial infarction and stroke, which are harbored by a nonnegligible proportion of RC patients. The ASA score<sup>5</sup> is a physical status classification of preoperative patients for anesthetic risk assessment that has been used as a method of estimating comorbidities in patients undergoing cancer surgery. The ACE-27 score<sup>6</sup> is a record-based comorbidity index specific to cancer patients, based on 26 comorbid conditions classified into three grades according to severity. Moreover, the ECOG performance score<sup>7</sup> and KPS<sup>8</sup> do not take into account comorbidities, but rather respectively physical and performance activity among cancer patients.

Based on consideration of such lack of specificity to RC populations, several authorities, including urological guidelines,<sup>1,9-11</sup> have recommended the development of a new comorbidity assessment tool for specific prediction of perioperative RC mortality. To address this

recommendation, we performed a systematic analysis of all ICD-9-CM diagnostic codes in order to identify and validate groups of individual comorbid conditions and/or BCa manifestations that could accurately predict perioperative mortality at 90 days after RC, based on the principles of maximal accuracy and parsimony.

## MATERIALS AND METHODS

### *Data Source and Study Population*

The current study relied on the SEER-Medicare insurance program-linked database.<sup>12</sup> A SEER-Medicare-specific approval was obtained through the US National Cancer Institute.

Between 2000 and 2009, we identified 10,522 patients with nonmetastatic (cM0) urothelial carcinoma of the urinary bladder (UCUB) treated with RC. Patients not enrolled in Medicare parts A or B for a minimum of 12 months prior to their first recorded diagnosis and for 3 months after RC were not considered. Patients who had health maintenance organization enrollment in the year prior to diagnosis or for any period following diagnosis were also excluded. To ensure that all subjects had at least 1 year of claims from which comorbidities are derived, only those aged  $\geq 66$  years were considered. This resulted in a final population of 7076 assessable UCUB patients treated with RC.

### *Variable Definition*

Patient characteristics included age at diagnosis, gender, race (White, Black, other), comorbid conditions, and BCa manifestations. We recorded all baseline comorbid conditions and BCa manifestations using unique ICD-9-CM diagnostic codes by classifying inpatient and outpatient claims, and physician billing claims for the 12-month interval preceding RC. Tumor characteristics included pathologic stage (T1, T2, T3, and T4) and lymph node stage (N0, N+, and Nx).

### *Outcomes and Statistical Analyses*

The endpoint of interest was to identify and validate groups of individual comorbid conditions and/or BCa manifestations that predict 90-day mortality after RC with the highest possible accuracy and maximal parsimony. Perioperative mortality at 90 days after RC was defined as overall mortality. The comparison benchmark consisted of the original DaCCI.<sup>3</sup>

Our analyses consisted of five steps. First, we randomly divided the population into development ( $n = 6076$ ) and validation cohorts ( $n = 1000$ ).

Within the development cohort, we calculated the frequency of all possible individual comorbid conditions and BCa manifestations, up to 12 months prior to RC. The inclusion of patients in our analyses that had BCa manifestations claims up to 12 months preceding their BCa claim ensured that disease manifestations were related to BCa and not to other causes (i.e., cystitis or kidney stone). We relied on simulated annealing (SA)<sup>13</sup> to identify (a) individual comorbid conditions, (b) individual disease manifestations, or (c) combinations of both, to best fulfill the requirements of maximal accuracy and parsimony for prediction of 90-day mortality after RC, after adjusting for age, gender, race, pathologic T stage, and pathologic N stage. In that process, unique ICD-9-CM diagnostic codes were used. Stepwise selection based on Akaike's information criterion (AIC)<sup>14,15</sup> was used in each iteration of SA to ensure parsimony.

Subsequently, within the validation cohort, we performed independent, external validation of the groups of individual comorbid conditions and/or disease manifestations that were identified in the development cohort. Thus-obtained accuracy estimates were fully adjusted for case mix (age, gender, race, pathologic T stage, and pathologic N stage).

Finally, for the purpose of comparison of the newly identified groups of comorbid conditions and/or disease manifestations for prediction of 90-day mortality after RC with the original DaCCI,<sup>3</sup> we also relied on the external validation cohort. Specifically, we validated the accuracy of the 17 comorbid condition groupings that form the original DaCCI.<sup>3</sup> The endpoint also represented 90-day mortality after RC, after adjusting for age, gender, race, pathologic T stage, and pathologic N stage. Receiver operating characteristics (ROC) curve analysis was used to assess the accuracy of the newly identified groups of comorbid conditions and/or disease manifestations for prediction of 90-day mortality after RC relative to the original DaCCI.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 (R Foundation, Vienna, Austria). All tests were two-sided with significance level set at  $p$  value  $< 0.05$ .

## RESULTS

### *Baseline Characteristics*

The median age was 74.9 and 75.2 years in the development and validation cohort, respectively. The majority of

patients were male (71.6% and 70.8%) and White (90.2% and 89.7%), and had pathologic T2 (35.9% and 34.6%) and pN0 stages (64.3% and 64.1%; Table 1). Overall, 90-day mortality rates after RC were 10.4 and 13.1% within the development and validation cohort, respectively.

Overall, we identified 5920 ICD-9-CM diagnostic codes. Of these diagnostic codes, 5572 (94.1%) denoted individual comorbid conditions, such as myocardial infarction, type I and II diabetes, essential hypertension, congestive heart failure, hypercholesterolemia, atrial fibrillation, osteoarthritis, and chronic obstructive pulmonary disease. The remaining 348 (5.9%) diagnostic codes defined individual disease manifestations, such as hematuria, pneumonia, urinary tract infection, dysuria, urinary frequency, and hydronephrosis.

### *The Most Accurate and Parsimonious Group of Individual Comorbid Conditions Predicting 90-Day Mortality*

Within the development cohort, SA identified seven individual comorbid conditions, based on unique ICD-9-CM diagnostic codes, that satisfied the criteria of maximal accuracy and parsimony for prediction of 90-day mortality after RC. These consisted of type II diabetes without complications (prevalence 25.2%), anemia (24.4%), chronic obstructive pulmonary disease (23.4%), congestive heart failure (11.9%), aortocoronary bypass (9.8%), osteoarthritis (9.8%), and cardiomegaly (9.5%).

On multivariable logistic regression analysis, all seven individual comorbid conditions, except for aortocoronary bypass, represented independent predictors of 90-day mortality (all  $p \leq 0.02$ ; Table 2).

Within the external validation cohort, the accuracy of the seven individual comorbid conditions identified by SA as most accurate and parsimonious was 70.2% (Table 3).

### *The Most Accurate and Parsimonious Group of Individual Disease Manifestations Predicting 90-Day Mortality*

Within the development cohort, SA identified two individual disease manifestations, based on unique ICD-9-CM diagnostic codes, that satisfied the criteria of maximal accuracy and parsimony for prediction of 90-day mortality after RC. These consisted of urinary tract infection (prevalence 60.0%) and hydronephrosis (22.9%).

On multivariable logistic regression analysis, both disease manifestations were independent predictors of 90-day mortality (both  $p < 0.001$ ; Table 2).

Within the external validation cohort, the accuracy of the two individual disease manifestations identified by SA as most accurate and parsimonious was 67.8% (Table 3).

**TABLE 1** Descriptive characteristics of 7076 patients with nonmetastatic urothelial carcinoma of the urinary bladder treated with radical cystectomy between 2000 and 2009 within the SEER-Medicare

Variable	Development cohort		Validation cohort	
	Overall <i>n</i> = 6076	90-Day mortality <i>n</i> = 630 (10.4%)	Overall <i>n</i> = 1000	90-Day mortality <i>n</i> = 131 (13.1%)
Age at diagnosis, years				
Median	74.9	77.5	75.2	78.8
IQR	70.2–79.7	72.6–81.8	70.3–80.8	74.5–83
Gender, <i>n</i> (%)				
Male	4352 (71.6)	424 (67.3)	708 (70.8)	87 (66.4)
Female	1724 (28.4)	206 (32.7)	292 (29.2)	44 (33.6)
Race, <i>n</i> (%)				
Other	308 (5.1)	31 (4.9)	51 (5.1)	*
White	5482 (90.2)	568 (90.2)	897 (89.7)	117 (89.3)
Black	286 (4.7)	31 (4.9)	52 (5.2)	*
Pathologic T stage, <i>n</i> (%)				
T1	1583 (26.1)	122 (19.4)	274 (27.4)	28 (21.4)
T2	2182 (35.9)	189 (30)	346 (34.6)	27 (20.6)
T3	1534 (25.2)	181 (28.7)	257 (25.7)	49 (37.4)
T4	777 (12.8)	138 (21.9)	123 (12.3)	27 (20.6)
N status, <i>n</i> (%)				
N0	3906 (64.3)	338 (53.7)	641 (64.1)	82 (62.6)
NX	1349 (22.2)	173 (27.5)	218 (21.8)	23 (17.6)
N+	821 (13.5)	119 (18.9)	141 (14.1)	26 (19.8)
Myocardial infarction	535 (8.8)	74 (11.7)	89 (8.9)	11 (8.4)
Congestive heart failure	786 (12.9)	144 (22.9)	131 (13.1)	24 (18.3)
Peripheral vascular disease	533 (8.8)	73 (11.6)	99 (9.9)	19 (14.5)
Cerebrovascular disease	1108 (18.2)	169 (26.8)	176 (17.6)	29 (22.1)
Dementia	*	*	*	*
Chronic pulmonary disease	1915 (31.5)	246 (39)	321 (32.1)	53 (40.5)
Rheumatologic disease	184 (3)	29 (4.6)	28 (2.8)	*
Peptic ulcer disease	159 (2.6)	22 (3.5)	22 (2.2)	*
Mild liver disease	37 (0.6)	*	*	*
Diabetes	1598 (26.3)	197 (31.3)	276 (27.6)	45 (34.4)
Diabetes with chronic complications	328 (5.4)	39 (6.2)	60 (6)	17 (13)
Hemiplegia or paraplegia	55 (0.9)	*	*	*
Renal disease	548 (9)	90 (14.3)	94 (9.4)	20 (15.3)
Leukemia/lymphoma	*	*	*	*
Moderate or severe liver disease	*	*	*	*
AIDS	*	*	*	*

The population was randomly divided into development (*n* = 6076) and validation cohorts (*n* = 1000). Comorbidities presented according to comorbid condition groupings of the Deyo adaptation of the Charlson Comorbidity Index

*IQR* interquartile range

\*Masked for protection of patient confidentiality reasons, as per National Cancer Institute regulations

### *The Most Accurate and Parsimonious Combination of Individual Comorbid Conditions and Disease Manifestations Predicting 90-Day Mortality*

Within the development cohort, SA identified eight ICD-9-CM diagnostic codes, denoting six individual

comorbid conditions and two individual BCa disease manifestations, that satisfied the criteria of maximal accuracy and parsimony for prediction of 90-day mortality after RC. These consisted of type II diabetes without complications, anemia, chronic obstructive pulmonary disease,

**TABLE 2** Logistic regression analyses to assess 90-day mortality in the development cohort ( $n = 6076$ ) using the most accurate and parsimonious group of (a) individual comorbid conditions, (b) individual disease manifestations, and (c) combination of individual comorbid conditions and disease manifestations

	Univariable		Multivariable	
	OR (95% CI)	<i>p</i> -Value	OR (95% CI)	<i>p</i> -Value
<b>(a) Individual comorbid conditions</b>				
Chronic obstructive pulmonary disease	1.61 (1.35–1.92)	< 0.001	1.50 (1.25–1.81)	< 0.001
Congestive heart failure	2.13 (1.73–2.62)	< 0.001	1.35 (1.07–1.71)	0.01
Anemia	1.94 (1.63–2.3)	< 0.001	1.49 (1.24–1.79)	< 0.001
Cardiomegaly	1.98 (1.58–2.5)	< 0.001	1.41 (1.1–1.8)	0.007
Type II diabetes mellitus without complications	1.36 (1.14–1.63)	0.001	1.25 (1.03–1.50)	0.02
Aortocoronary bypass	1.57 (1.23–1.99)	< 0.001	1.25 (0.96–1.62)	0.09
Osteoarthritis	1.67 (1.32–2.12)	< 0.001	1.37 (1.07–1.76)	0.01
<b>(b) Individual disease manifestations</b>				
Urinary tract infection	1.61 (1.35–1.92)	< 0.001	1.45 (1.2–1.74)	< 0.001
Hydronephrosis	1.68 (1.41–2)	< 0.001	1.43 (1.19–1.72)	< 0.001
<b>(c) Combination of individual comorbid conditions and disease manifestations</b>				
Chronic obstructive pulmonary disease	1.61 (1.35–1.92)	< 0.001	1.48 (1.23–1.78)	< 0.001
Congestive heart failure	2.13 (1.73–2.62)	< 0.001	1.35 (1.07–1.7)	0.01
Anemia	1.94 (1.63–2.30)	< 0.001	1.42 (1.18–1.71)	< 0.001
Cardiomegaly	1.98 (1.58–2.5)	< 0.001	1.39 (1.08–1.78)	0.01
Type II diabetes mellitus without complications	1.36 (1.14–1.63)	0.001	1.25 (1.04–1.51)	0.02
Aortocoronary bypass	1.57 (1.23–1.99)	< 0.001	1.26 (0.97–1.64)	0.07
Urinary tract infection	1.61 (1.35–1.92)	< 0.001	1.32 (1.09–1.58)	0.004
Hydronephrosis	1.68 (1.41–2.0)	< 0.001	1.32 (1.09–1.59)	0.004

All models adjusted for age, gender, race (White versus Black versus other), pathologic T stage (T1 versus T2 versus T3 versus T4), and pathologic N stage (N0 versus N+ versus Nx)

OR odds ratio; CI confidence interval

congestive heart failure, aortocoronary bypass, cardiomegaly, urinary tract infection, and hydronephrosis.

On multivariable logistic regression analysis, all eight individual conditions, except for aortocoronary bypass, represented independent predictors of 90-day mortality (all  $p \leq 0.02$ ; Table 2).

Within the external validation cohort, the accuracy of the eight individual conditions identified by SA as most accurate and parsimonious was 71.1% (Table 3).

#### *The Original Deyo et al. Adaptation of the Charlson Comorbidity Index*

Table 1 presents the prevalence of the 17 comorbid condition groupings according to the original DaCCI, within the development and validation cohorts. No instance of metastatic solid tumors of origin other than BCa was identified. Within the external validation cohort, the accuracy of the original DaCCI was 68.0% (Table 3).

#### *ROC Curves and Risk Calculators*

Figure 1 depicts the ROC curves of the newly identified groups of comorbid conditions and/or disease manifestations relative to the original DaCCI.

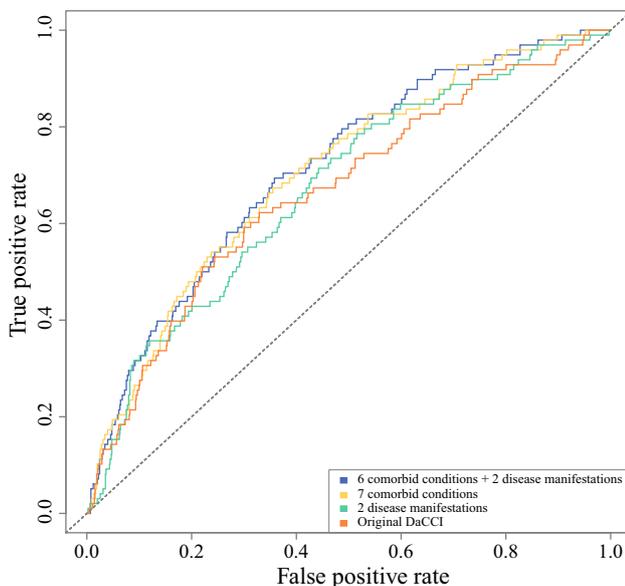
The multivariable-derived coefficients of the predictive model including six individual comorbid conditions + two individual BCa disease manifestations and of the predictive model including seven comorbid conditions (Table 2) were used to calculate the risk of 90-day mortality after surgery for each patient, and to develop corresponding risk calculators to simplify individual risk estimation (Supplementary Files 1 and 2).

## DISCUSSION

The objective of this study is to identify predictors of 90-day mortality after RC that satisfy the requirements of maximal accuracy and parsimony. The rationale stems from the lack of a contemporary tool to quantify the risk of

**TABLE 3** Externally validated accuracy estimates

	Accuracy (%)
(a) Seven individual comorbid conditions	70.2
Type II diabetes without complications	
Anemia	
Chronic obstructive pulmonary disease	
Congestive heart failure	
Aortocoronary bypass	
Osteoarthritis	
Cardiomegaly	
(b) Two individual disease manifestations	67.8
Urinary tract infection	
Hydronephrosis	
(c) Combination of six individual comorbid conditions and two individual disease manifestations	71.1
Type II diabetes without complications	
Anemia	
Chronic obstructive pulmonary disease	
Congestive heart failure	
Aortocoronary bypass	
Cardiomegaly	
Urinary tract infection	
Hydronephrosis	
Deyo adaptation of Charlson comorbidity index (17 comorbid condition groupings)	68.0



**FIG. 1** ROC curve

90-day mortality after RC according to comorbid conditions and/or disease manifestations. Such a tool could be used in retrospective analyses of administrative data, such as SEER-Medicare.

Our findings are noteworthy. First, using SA we identified seven individual comorbid conditions (type II diabetes without complications, anemia, chronic obstructive pulmonary disease, congestive heart failure, aortocoronary bypass, osteoarthritis, and cardiomegaly), two individual BCa manifestations (urinary tract infection and hydronephrosis), and a combination of both that included six individual comorbid conditions and two individual BCa manifestations (type II diabetes without complications, anemia, chronic obstructive pulmonary disease, congestive heart failure, aortocoronary bypass, cardiomegaly, urinary tract infection, and hydronephrosis) that predict 90-day mortality based on the principles of maximal accuracy and parsimony. Their respective ability to predict 90-day mortality after RC was 70.2, 67.8, and 71.1% versus 68.0% for the original DaCCI.<sup>3</sup> This implies that contemporary RC-specific comorbid conditions and/or combinations of comorbid conditions and disease manifestations can better predict 90-day mortality, using far fewer input variables than the original DaCCI. Specifically, only seven individual comorbid conditions (seven ICD-9-CM diagnostic codes) or a combination of six individual comorbid conditions + two individual BCa manifestations (eight ICD-9-CM diagnostic codes) may be used, instead of 17 comorbid condition groupings that relied on nearly 200 ICD-9-CM diagnostic codes.<sup>3</sup> These two considerations, viz. higher accuracy and reduction of required ICD-9-CM diagnostic codes, are of paramount importance in large-scale database analyses from the perspectives of workload and potential for error.

Second, with respect to content, the comorbid conditions used in the current analyses are entirely specific to contemporary RC patients, unlike the DaCCI that predicted 1-year mortality within a sample of 599 general medicine hospitalized patients. The same applies to disease manifestations used in the current analyses.

Third, our analyses relied on the principle of avoiding artificial weights of comorbidities, as was done in the original DaCCI,<sup>2,3</sup> For example, cerebrovascular disease, chronic pulmonary disease, and ulcer disease have the same weight, namely 1. Conversely, a weight of 2 was assigned, for example, to hemiplegia, leukemia, or lymphoma, and a maximal weight of 6 was associated with metastatic solid tumor and AIDS. Such a system may erroneously attribute excessive or insufficient importance to one or multiple conditions. To avoid such a methodology, we relied on the same approach used by previous authors,<sup>16,17</sup> where logistic regression-derived coefficients

define the strength of effect of each comorbid condition and/or disease manifestation on the risk of 90-day mortality.

Fourth, we demonstrated that several comorbid conditions included in the original DaCCI,<sup>3</sup> such as AIDS, metastatic solid tumor, and hematologic malignancies, are almost never seen in RC patients. Indeed, these conditions have not made their way into those identified within our analyses, confirming their outdated nature and lack of applicability in the context of 90-day mortality after RC.

Fifth, we demonstrated that several conditions that are not accounted for within the DaCCI satisfied the criteria of maximal accuracy and parsimony for prediction of 90-day mortality after RC. Some of these conditions are represented by BCa manifestations. Consequently, we introduce a new concept that validates the importance of disease manifestations in analyses focusing on 90-day mortality.

Sixth, to the best of the authors' knowledge, this is the first study aiming to identify predictors of 90-day mortality in contemporary RC patients that satisfy the criteria of maximal accuracy and parsimony, between all possible comorbid conditions and/or BCa manifestations identified by unique ICD-9-CM diagnostic codes. Note that our analyses focused on 90-day mortality. In consequence, the comorbid conditions and/or combinations of comorbid conditions and BCa manifestations identified by this analysis are strictly applicable to our context and should not be extrapolated for use in any other contexts, such as for example long-term mortality. Future studies should be developed to assess such findings for long-term outcomes.

Our findings validate the importance of several well-known comorbid conditions such as chronic obstructive pulmonary disease,<sup>18–21</sup> congestive heart failure,<sup>18,21–23</sup> anemia,<sup>18,24</sup> cardiomegaly,<sup>25</sup> and type II diabetes mellitus<sup>21,23,26–28</sup> to predict perioperative mortality. Our work also validates the previously established concept that hydronephrosis is an indicator of more aggressive disease.<sup>29,30</sup> Furthermore, it is of note that, to the best of the authors' knowledge, this work also illustrates a new concept that urinary tract infection recorded prior to RC represents a risk factor for 90-day mortality after surgery. A possible explanation of this finding could be related to the added difficulty in diagnosis of BCa that may be obscured by urinary tract infections.

In summary, the intent of this study is to provide a more accurate, less labor-intensive, and less error-prone approach for definition of comorbid conditions and disease manifestations that accurately predict 90-day mortality, in retrospective analyses, where ICD-9-CM diagnostic codes are used. Specifically, investigators can rely on the combination of six individual comorbid conditions and two individual BCa manifestations that provide optimal accuracy; alternatively, the second best option requires the use

of seven individual comorbid conditions without the added input of disease manifestations. In line with our findings, several investigators showed better accuracy of other tools, such as ASA score,<sup>5</sup> in predicting 90-day mortality after RC relative to the original DaCCI.<sup>31</sup> However, such tools are not widely accepted<sup>11</sup> and cannot be routinely applied in administrative databases, such as SEER-Medicare, where ICD-9-CM codes are used.

Despite its strengths, our study has several limitations. First, our findings are developed using administrative data, namely SEER-Medicare. Consequently, they are not applicable to databases that rely on codes different from ICD-9-CM. Second, the groups of individual comorbid conditions and/or BCa manifestations for prediction of 90-day mortality after RC are identified only in men aged 66 years and older. Consequently, they may not be applicable to younger patients. Future studies are urgently needed to validate our results using datasets from another sources, to confirm the applicability of these findings and allow physicians to better inform patients during pretreatment counseling, relying on a disease-specific comorbidity index.

## CONCLUSIONS

A new approach for prediction of 90-day mortality after RC using patient comorbid conditions and/or disease manifestations, instead of the classic approach that relies on the DaCCI, was devised. Specifically, a group of six individual comorbid conditions and two individual disease manifestations resulted in higher accuracy for prediction of 90-day mortality after RC than the entire DaCCI, which relies on 17 comorbid condition groupings (200 ICD-9-CM codes). We also tested an alternative that exclusively relies on seven individual comorbid conditions and yielded higher accuracy than the original DaCCI. In consequence, either proposed method offers a substantially simpler approach for prediction of 90-day mortality after RC relative to DaCCI, without compromising accuracy.

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## REFERENCES

1. Williams SB, Kamat AM, Chamie K, et al. Systematic review of comorbidity and competing-risks assessments for bladder cancer patients. *Eur Urol Oncol.* 2018;1(2):91–100.
2. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373–83.

3. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613–9.
4. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8–27.
5. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* 1941;2:281–4.
6. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA*. 2004;291(20):2441–7.
7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649–55.
8. Yates JW, Chalmer B, McKeegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer*. 1980;45(8):2220–4.
9. Dell'Oglio P, Tian Z, Leyh-Bannurah SR, et al. Short-form Charlson comorbidity index for assessment of perioperative mortality after radical cystectomy. *J Natl Compr Cancer Netw*. 2017;15(3):327–33.
10. Miller DC, Taub DA, Dunn RL, Montie JE, Wei JT. The impact of co-morbid disease on cancer control and survival following radical cystectomy. *J Urol*. 2003;169(1):105–9.
11. Witjes JA, Comperat E, Cowan NC, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. *Eur Urol*. 2014;65(4):778–92.
12. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(8 Suppl):IV-3-18.
13. Kirkpatrick S, Gelatt CD, Jr., Vecchi MP. Optimization by simulated annealing. *Science*. 1983;220(4598):671–80.
14. Burnham KP, Anderson DR. Multimodel inference understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33(2):261–304.
15. Burnham KP, Anderson DR. Model selection and multimodel inference: a practical information-theoretic approach. New York: Springer; 2002.
16. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–82.
17. Patel HD, Kates M, Pierorazio PM, et al. Comorbidities and causes of death in the management of localized T1a kidney cancer. *Int J Urol*. 2014;21(11):1086–92.
18. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. *JAMA*. 1992;267(17):2344–8.
19. Licker MJ, Widikker I, Robert J, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg*. 2006;81(5):1830–7.
20. Virani S, Michaelson JS, Hutter MM, et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. *J Am Coll Surg*. 2007;204(6):1284–92.
21. Davila JA, Rabeneck L, Berger DH, El-Serag HB. Postoperative 30-day mortality following surgical resection for colorectal cancer in veterans: changes in the right direction. *Dig Dis Sci*. 2005;50(9):1722–8.
22. Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology*. 2008;108(4):559–67.
23. Wilt TJ, Cowper DC, Gammack JK, Going DR, Nugent S, Borowsky SJ. An evaluation of radical prostatectomy at Veterans Affairs Medical Centers: time trends and geographic variation in utilization and outcomes. *Med Care*. 1999;37(10):1046–56.
24. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet*. 2011;378(9800):1396–407.
25. Weiner MM, Reich DL, Lin HM, Krol M, Fischer GW. Influence of increased left ventricular myocardial mass on early and late mortality after cardiac surgery. *Br J Anesth*. 2013;110(1):41–6.
26. Noordzij PG, Boersma E, Schreiner F, et al. Increased preoperative glucose levels are associated with perioperative mortality in patients undergoing noncardiac, nonvascular surgery. *Eur J Endocrinol*. 2007;156(1):137–42.
27. Krolikowska M, Kataja M, Poyhia R, Drzewoski J, Hynynen M. Mortality in diabetic patients undergoing non-cardiac surgery: a 7-year follow-up study. *Acta Anaesth Scand*. 2009;53(6):749–58.
28. Thourani VH, Weintraub WS, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. *Ann Thorac Surg*. 1999;67(4):1045–52.
29. Haleblan GE, Skinner EC, Dickinson MG, Lieskovsky G, Boyd SD, Skinner DG. Hydronephrosis as a prognostic indicator in bladder cancer patients. *J Urol*. 1998;160(6 Pt 1):2011–4.
30. Bartsch GC, Kuefer R, Gschwend JE, de Petriconi R, Hautmann RE, Volkmer BG. Hydronephrosis as a prognostic marker in bladder cancer in a cystectomy-only series. *Eur Urol*. 2007;51(3):690–7; (discussion 697–698).
31. Mayr R, May M, Martini T, et al. Predictive capacity of four comorbidity indices estimating perioperative mortality after radical cystectomy for urothelial carcinoma of the bladder. *BJU Int*. 2012;110(6 Pt B):222–7.