



Comparison of the Comprehensive Complication Index and Clavien-Dindo systems in predicting perioperative outcomes following radical nephroureterectomy

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Background: Complications can occur following radical nephroureterectomy (RNU) in 20–40% of patients. The Comprehensive Complication Index (CCI) is an alternative grading system to the Clavien-Dindo (CD) grading system that aggregates all complications experienced by a patient on a continuous (as opposed to categorical) scale. We investigate whether the cumulative nature of CCI renders it superior to CD in predicting perioperative course after RNU.

Methods: The records of 596 patients who underwent RNU at 7 academic medical centers from 2005 to 2015 were reviewed. Complications occurring within 30 days of RNU were annotated using both the CD and CCI classification systems. Logistic regression was used to determine associations between CD and CCI with perioperative covariates as well as measures of convalescence [hospital length of stay (LOS) and readmission].

Results: A total of 377 men and 219 women with a median age of 71, BMI of 27, and Charlson comorbidity score of 4 were included. Over half underwent a minimally invasive RNU. Median LOS following RNU was 6.0 days (range, 1–37 days) and readmission within 30-days occurred in 45 (8%) patients. Overall, 136 patients (23%) experienced a post-operative complication with 91 having a single complication and 45 with multiple (range, 2–6); 44 (7%) patients had Clavien III or greater complications, and the median CCI for those patients experiencing a complication was 20.9 (range, 8.7–100). Both the upper quartile of CCI (≥ 75 th %) and major CD complications were associated with higher baseline Charlson score, ECOG ≥ 2 , and CKD stage \geq III (all $P < 0.05$). However, only the upper quartile of CCI was associated with LOS (8.9 vs. 5.4 days, $P < 0.01$) and hospital readmission (OR 3.2, 95% CI: 1.9–5.6, $P = 0.02$) after RNU.

Conclusions: The CD and CCI classification systems both are associated with similar baseline and perioperative characteristics for RNU patients. However, the cumulative nature of the CCI allows for superior prediction of postoperative course after RNU including LOS and readmission.

Keywords: Complications; Clavien-Dindo (CD); Comprehensive Complication Index (CCI); nephroureterectomy

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Introduction

Upper-tract urothelial carcinoma (UTUC) is an uncommon genitourinary malignancy that accounts for 5% of urothelial tumors (1). Although presenting infrequently, population-based studies implicate a steady rise in UTUC incidence over the past three decades (2). The current gold standard for management of bulky, high-grade or muscle-invasive UTUC is a radical nephroureterectomy (RNU) with excision of bladder cuff via a minimally invasive or open approach (1,3). Patients that develop UTUC tend to be elderly and harbor medical comorbidities thereby placing such patients at risk of complications following surgery (4). In fact, rates as high as 30–40% have been reported from high volume centers that rigorously annotate adverse events.

Historically, complications have been difficult to classify as terminology has been largely inconsistent and poorly standardized. The Clavien-Dindo (CD) scale was first proposed in 2004 and consisted of a five-point scale based on the severity of complication and type of treatment required to remedy the event (5,6). Indeed, the CD scale has demonstrated correlation with complexity of surgery as well as hospital duration in a large cohort of patients (6). However, this scale lacks a continuous element in its measurement and tends to categorize complications based on the highest severity event.

The Comprehensive Complication Index (CCI) is a newer classification scheme initially proposed in 2013 and provides a continuous (not categorical) scale from 0 to 100 in order to systematically score the severity of any combination of complications (7). This scale proved to be highly sensitive with regards to treatment effect and higher scores correlated with adverse postoperative health status of impacted patients (7).

Patients with urothelial carcinoma are at risk for experiencing treatment related complications. Use of CCI to predict perioperative course in this patient cohort is limited. Specifically, in 2015, Park and colleagues compared the CD and CCI grading systems in a single institution study of 100 RNU patients (8). The authors noted that although both classification schemes were similarly associated with baseline and perioperative characteristics, the CCI more accurately predicted short term recovery after RNU. A criticism of this study, however, was its relatively small sample size which originated from a single institution thereby questioning the generalizability of findings.

Here, we further investigate whether the cumulative

nature of the CCI renders it superior to CD in predicting perioperative course after RNU in a large, international multi-center cohort.

Methods

Following institutional review board (IRB) approval, the records of 596 consecutive patients who underwent RNU at 7 academic medical centers from 2005 to 2015 were reviewed. Preoperative clinical, demographic, and comorbidity variables included patient age, gender, race, BMI, Charlson comorbidity index (CCI), American Society of Anesthesiologists (ASA) score, Eastern Cooperative Oncology Group (ECOG) performance status, and history of chronic kidney disease. Perioperative variables included surgical approach, length of hospital stay (LOS), and complications and readmissions occurring within 30 days of surgery. Final pathology was confirmed as urothelial carcinoma in all cases.

Perioperative complications were graded using the modified CD classification scale and converted to the CCI[®] via the publically available CCI[®]-calculator (http://www.assessurgery.com/calculator_single/) accessed 12/31/19.

The Wilcoxon Rank Sum and Chi Square tests were used for comparison of continuous and categorical values, respectively. Logistic regression was used to determine associations between CD and CCI with preoperative covariates as well as with hospital length of stay (LOS) and readmissions. Focus was analyzing covariates associated with major CD complications (Clavien III–V) or CCI >75% (upper quartile) as these were considered the most clinically significant. Spearman correlation was performed for association of CCI and LOS. SAS version 9.4 was used for analysis.

Results

Clinical characteristics for the 596 individuals are presented in *Table 1*. In summary, a total of 377 men and 219 women with a median age of 71, BMI of 27, and Charlson comorbidity score of 4 were included. Almost 90% of this cohort were white and over 50% had baseline chronic kidney disease (CKD) stage III or greater. Over half of cases were performed using a minimally invasive approach. On final pathology, over 60% of tumors were muscle-invasive, 70% were high grade, and 8% had associated positive LNs. Median length of stay (LOS) was 6 days and almost 8% were re-admitted within 30 days of surgery.

Table 1 Clinical and pathologic characteristics for 596 RNU patients

Variable	Values
Median age (years) [range]	71 [27–93]
Gender, n (%)	
Male	377 (63.3)
Female	219 (36.7)
Race, n (%)	
White	508 (85.2)
Black	38 (6.4)
Other	43 (7.2)
Not specified	7 (1.2)
Median BMI (kg/m ²) [range]	26.6 [15–58.9]
Median Charlson Index [range]	4 [0–12]
ASA score, n (%)	
<2	69 (11.6)
≥2	470 (78.9)
Not specified	57 (9.6)
ECOG, n (%)	
<2	385 (64.6)
≥2	89 (14.9)
Not specified	122 (20.5)
Pre-op CKD stage, n (%)	
<III	254 (42.6)
≥III	271 (45.5)
Not specified	71 (11.9)
Surgical approach, n (%)	
MIS	318 (53.4)
Open	220 (36.9)
Not specified	58 (9.7)
Pathologic stage, n (%)	
< pT2	329 (55.2)
≥ pT2	263 (44.1)
Not specified	4 (0.7)
Pathologic grade, n (%)	
Low	167 (28.0)
High	425 (71.3)
Not specified	4 (0.7)
Median LOS (days) [range]	6 [1–37]
Readmission within 30 days, n (%)	45 (7.6)

In total, 136 patients (23%) experienced a post-operative complication with 91 having a single complication and 45 with multiple (range, 2–6); 44 (7%) patients had Clavien III or greater complications of which 38 experienced one major complication and 6 experienced multiple major complications. The median CCI for those patients experiencing a complication was 20.9 (range, 8.7–100), and upper-quartile of CCI was 36. There were 3 deaths (0.5%) noted in our cohort within 30 days of RNU.

Table 2 summarizes the univariate model highlighting associations between pre-operative variables and major CD complications as well as upper quartile of CCI. Several similar pre-operative variables were associated with both complication indices including Charlson score, ECOG performance status, baseline renal function, and open surgical approach. Conversely, variables including gender, BMI, and ASA score were not associated with more significant complications.

Variables significant in the univariate model were incorporated into a multivariate model whereby only Charlson score, ECOG performance status, and baseline eGFR were independently associated with both major complications and CCI >75% (*Table 3*).

The association of CCI and CD with respect to perioperative recovery metrics including LOS and readmission following RNU were determined by logistic regression. Only the upper quartile of CCI was associated with LOS (8.9 vs. 5.4 days, P<0.01) and hospital readmission (OR 3.2, 95% CI: 1.9–5.6, P=0.02) after RNU whilst major CD complications were not (LOS 7.4 vs. 5.6 days, P=0.14; readmission OR 1.4, P=0.21).

Discussion

Recognizing the risks associated with radical surgery is an important component of patient counseling, resource utilization, and clinical decision making. To this point, Joudi and colleagues identified 18,575 patients who underwent radical nephrectomy or RNU from 2000 to 2003 and evaluated the impact of complications on length of stay and mortality (8). Not surprisingly, the presence of one or more complications negatively impacted all of these outcomes significantly (P<0.001) after adjusting for confounding effects.

Due to the significant impact of operative complications on the healthcare system, a standardized and accurate classification system is essential to objectify risk and ultimately guide perioperative management. The CD

Table 2 Univariate model for association of pre-operative variables with complication indices

Variable	Major CD complications (grade III–V)			CCI >75th %		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age (years)	1.78	1.05–2.99	0.03	1.64	1.03–3.11	0.04
Male gender	1.08	0.73–2.21	0.37	1.16	0.88–1.88	0.44
White race	0.88	0.64–1.78	0.51	0.79	0.62–1.69	0.59
BMI (per unit)	1.18	0.93–1.44	0.67	1.31	0.87–1.51	0.61
Charlson (per 1 unit increase)	2.97	1.98–3.37	0.01	2.44	1.51–3.67	0.03
ASA score (per 1 unit increase)	1.05	0.92–1.22	0.76	1.03	0.86–1.19	0.88
ECOG (per 1 unit increase)	4.22	2.37–8.48	0.001	4.87	2.09–6.99	0.001
eGFR (per 10 mL/min/1.73 m ² decrease)	1.24	1.02–1.82	0.05	1.42	1.19–2.36	0.04
Open surgical approach	1.33	1.12–1.92	0.04	1.46	1.21–2.01	0.01

Table 3 Multivariate model for association of pre-operative variables with complication indices

Variable	Major CD complications (grade III–V)			CCI >75th %		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Charlson (per 1 unit increase)	2.23	1.88–3.11	0.02	1.98	1.07–2.99	0.03
ECOG (per 1 unit increase)	3.67	2.45–6.37	0.008	4.22	1.78–7.64	0.003
eGFR (per 10 mL/min/1.73 m ² decrease)	1.17	1.08–1.82	0.04	1.45	1.15–2.47	0.01

scoring system has been a well-established and recognized tool to classify complications. The principal limitation of this system, however, is categorization based solely on the most serious event. It is hypothesized that the CCI may more accurately reflect the potential post-operative morbidity following procedures due to its ability to capture complications on a cumulative scale.

The primary objective of this study was to utilize multicenter data to compare the CD and CCI classification systems in predicting the perioperative outcomes of patients who underwent RNU. Here, we identified 136 patients (23%) who experienced a complication, which is consistent with the range found in other peer-reviewed literature (3). When comparing the upper-quartile of CCI and major CD complications, we found that both were associated with higher Charlson score, ECOG ≥ 2 , and CKD stage \geq III.

However, only the upper quartile of CCI was associated with LOS and hospital readmission while major CD complications were not.

The data from this multi-institutional study is consistent with that a prior single center study. Park and colleagues compared CCI and CD classification schemes in a cohort of patients undergoing RNU and showed that (similarly) the upper quartile CCI and major CD complications were both associated with higher Charlson scores ($P=0.03$), lower baseline eGFR ($P=0.005$), intraoperative transfusion ($P=0.004$), open surgical approach ($P=0.019$) and symptoms of presentation ($P=0.019$). However, only upper quartile CCI was associated with postoperative LOS (8.25 *vs.* 5.61 days, $P<0.0001$) while major CD complications were not (7.98 *vs.* 6.32, $P=0.211$) (9). A notable criticism of this prior work was smaller sample size and single institution nature

of the practice which may have impacted findings and observations. Indeed, our larger series underscores those preliminary findings and highlights the value for medical centers to use CCI when tracking convalescence after RNU.

Post-operative complications significantly impact quality and cost-containment metrics such as length of stay and readmission and are one of the most significant contributors to rising healthcare costs (9-11). In the above-mentioned study, Joudi and colleagues noted that the hospital costs associated with radical nephrectomies (including RNU) increased by 33.3% with one complication and by 84% with two complications (8). Therefore, to accurately evaluate the risk associated with surgical procedures, it is important to account for the cumulative effect of all complications, rather than just the impact of the most serious event.

Limitations of this study include its retrospective design and perhaps the inconsistency with categorizing complications. Although our study included patients from seven multinational institutions, it may be possible that there are variations in the reporting and treatment of complications. Additionally, we did not have a single author that reviewed all the complications and assigned them a CD grade. Indeed, a systematic review indicated that the CD system was not properly used in 72 (35.3%) urological papers (12). Therefore, having a single reviewer that adequately understands the classification schemes may be necessary to preserve the uniformity in using the CD system. In extension, the validity of the CCI also depends on the accuracy of assigning CD grades to complications, so a standardized protocol is essential. Furthermore, the multinational nature of the study precludes cost analysis of the data particularly given variability in the respective cost of healthcare across different countries.

Conclusions

The CD and CCI classification systems both have their utility in evaluating baseline and perioperative characteristics for RNU patients. However, the continuous and cumulative nature of the CCI that accounts for complications severity appears to allow for superior prediction of perioperative course following RNU including LOS and readmission.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board Informed consent was taken from all individual participants.

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