Original Research

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Defining the Morbidity of Robot-Assisted Radical Cystectomy with Intracorporeal Urinary Diversion: Adoption of the Comprehensive Complication Index

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Abstract

Background and Objective: The Clavien–Dindo Classification (CDC) only reports the postoperative complication of highest grade. It is thus of limited value for radical cystectomy, after which patients usually experience multiple complications. The Comprehensive Complication Index (CCI) is a novel scoring system, which incorporates all postoperative events in one single value. The study aimed to adopt the CCI for the evaluation of complications in patients undergoing robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) and explore its advantages in the analysis of the morbidity of RARC with ICUD.

Patients and Methods: A multicentric cohort of 959 patients undergoing RARC+ICUD between 2015 and 2020, whose complications are encoded in local prospective registries. Postoperative complications at 30 days

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were assessed using both the CDC and CCI. The CCI was calculated using an online tool (assessurgery.com). Risk factors for overall, major complications (CDC ≥III), and CCI were evaluated using uni- and multivariable logistic and linear regressions. To analyze the potential advantage of using the CCI in clinical trials, a sample size calculation of a hypothetic clinical trial was performed using as endpoint reduction of morbidity with either the CDC or CCI.

Results: Overall, 885 postoperative complications were reported in 507 patients (53%). The CCI improved the definition of postoperative morbidity in 22.6% of patients. Male sex and neobladder were associated with major complications and to a significant increase in CCI on adjusted regressions. In a hypothetical clinical trial, 80 patients would be needed to demonstrate a ten-point reduction in CCI, compared with 186 needed to demonstrate an absolute risk reduction of 20% in overall morbidity using the CDC.

Conclusion: CCI improves the evaluation of postoperative morbidity by considering the cumulative aspect of complications compared with the CDC. Implementing the CCI for radical cystectomy would help reducing sample sizes in clinical trials.

Clinical Trial Registration number: NCT03049410.

Keywords: complications, robotics, radical cystectomy

Introduction

ROBOT-ASSISTED RADICAL CYSTECTOMY (RARC) with intracorporeal urinary diversion (ICUD) is gaining increasing acceptance across Urology departments worldwide,[1,2] although EAU guidelines still consider open radical cystectomy (ORC) as gold standard.[3] Two randomized controlled trials[4,5] assessed the noninferiority of RARC in terms of oncological results; while associated with significantly lower intraoperative estimated blood loss and blood transfusion rate[6] compared with ORC, a significant decrease in postoperative complications has not yet been demonstrated.[7,8]

Presently, the most widely adopted classification for postoperative surgical complications is the Clavien–Dindo classification (CDC). Initially described for general surgery,[9] this classification has rapidly gained popularity across surgical specialties and has widely been implemented in Urology. The randomized controlled trials comparing ORC and RARC,[6,7,10] including the recent RAZOR trial,[4] have all compared complication rate across the two approaches using the CDC. However, the CDC does have some limitations: it only considers the complication with the highest grade and not every postoperative event that the patient may experience. For surgeries such as radical prostatectomy, in which complications are rare,[11] the CDC works perfectly. However, for radical cystectomy, patients often experience several complications[12] and the CDC might not capture the global morbidity of their postoperative course.

Therefore, the Comprehensive Complication Index (CCI) has been developed[13] to consider every single postoperative complication and incorporate them in one unique score ranking 0 (no complication) to 100 (perioperative death). Hence, the CCI could improve the description of surgical morbidity of radical cystectomy and shed more light on nuances across techniques that CDC may not capture. To this day, the CCI has never been applied for patients undergoing RARC with ICUD, whereas for ORC only data from single-center studies are available.[12,14]

The aim of this study is to compare the CCI and the CDC when implemented in a multicenter cohort of patients undergoing RARC with ICUD and explore its benefits in the assessment of complications.

Materials and Methods

The current project was launched by the European Association of Urology-Young Academic Urologists, Urothelial carcinoma working group in October 2020. A large multi-centric database (15 centers) of patients undergoing RARC with ICUD was constructed. Only centers that maintain a local prospective registry of patients undergoing RARC with ICUD were invited to participate and they provided Ethics Committee and Institutional Review Board approval. We included patients operated on between January 2015 and December 2020; at time of analysis, the database contained 974 patients.

RARC with ICUD was performed to treat muscle invasive bladder cancer or high-risk nonmuscle invasive bladder cancer. No formal contraindications for RARC with ICUD were imposed. Neoadjuvant therapy was administered following multidisciplinary tumor board decision according to the protocols of each center. Exclusion criteria included cystectomy for nononcological reason ($n = 10$) and urinary diversions other than ileal conduit, neobladder, or ureterocutaneostomy ($n = 5$).

All RARC procedures were performed using DaVinci Si® or Xi® robotic platforms. No bowel preparation was performed before surgery. All centers implemented an enhanced recovery after surgery protocol, although this was not standardized across departments. All patients underwent complete ICUD, regardless of the type of urinary diversion performed (ileal conduit *vs* neobladder *vs* ureterocutaneostomy). Nasogastric tube was removed at the end of the procedure; early mobilization and oral feeding was encouraged for all patients, starting on postop day (POD) 1. Low-molecular-weight heparin was prescribed for 4 weeks following guidelines.[3] Ureteral catheters were removed on POD 7 to 14 and urethral catheter (in case of neobladder reconstruction) on POD 10 to 21.

Any deviation from the normal postoperative course occurring during the first 30 days after surgery was considered as a complication and reported prospectively in each local database by a senior urologist. Complications were reported according to the modified CDC[9] and further classified in minor (Clavien I–II) and major complications

(Clavien III–V). Any death following rehospitalization for any postsurgical complication was attributed to bladder cancer. For each patient, the CCI was calculated using the online tool available at assessurgery.com as follows:

Clavien I → CCI score 8.7 → wC1 = 300

Clavien II → CCI score 20.9 → wC1 = 1750

Clavien IIIa → CCI score 26.2 → wC1 = 2750

Clavien IIIb → CCI score 33.7 → wC1 = 4550

Clavien IVa → CCI score 42.4 → wC1 = 7200

Clavien IVb → CCI score 46.2 → wC1 = 8550

Clavien V → always results in a CCI = 100

The CCI is then calculated with the following formula:

$$CCI = \sqrt{\frac{(wC1 + wC2 + \ldots + wCx}{2}}$$

wc: Weight of Complication

As explained above, if the patient dies, the CCI will always yield a value of 100. If the patient is alive instead, even if multiple life-threatening complications are encountered, the score will never exceed 99.

We implemented the 14 points of the EAU quality criteria for accurate and comprehensive reporting of surgical outcomes. In particular, data were prospectively encoded in local databases by senior urologists; follow-up duration was 30 days after surgery; outpatient information was included; mortality and causes of death were illustrated; intra and postoperative complications were detailed separately; the CDC and CCI were used to score and classify complications; crude and adjusted logistic and linear regressions were performed to explore risk factors for overall, major complications and CCI; and readmissions were analyzed. Finally, follow-up at 30 days was available for all patients.

Categorical variables are reported as frequencies and proportions, and continuous variables as medians and interquartile ranges (IQR). To assess the differences of categorical variables between groups, Pearson's chi-square or Fisher's exact test, and for continuous variables, Mann–Whitney U test were used. Correlation between length of stay and CDC or CCI was analyzed using Spearman's test. Uni- and multivariable logistic regressions were performed, including risk factors for overall complications (any event) and major complications (CDC ≥III). We then performed crude and adjusted linear regressions to explore association between the same risk factors and CCI. Risk factors analyzed included age (continuous), sex (categoric), BMI (continuous), Charlson Comorbidity Index (continuous), smoking status (categoric), prior abdominal surgery (categoric), urinary diversion (categoric), and number of resected nodes (continuous). We finally performed a sample size calculation to properly evaluate the sensitivity of the CCI as primary endpoint in a hypothetical clinical trial, considering an expected overall complication rate of 50% and a major complication rate of 20%.

We assumed a difference of 10 points for the CCI, an absolute risk reduction of 20% for overall morbidity with the CDC, an absolute risk reduction of 10% in major complications with the CDC, a power of 80%, and an α-error of 0.05.

The difference of 10 points on the CCI scale was chosen because it reflects grade 1 difference in the established Clavien classification, whereas the 20% and 10% absolute risk reduction was based on previous propositions for radical cystectomy trials.[10] Statistical analyses were performed using Stata 14.1; p-value ≤0.05 was considered statistically significant.

Results

A total of 959 patients were included in the final analysis. Baseline characteristics, as well as pathologic data are shown in Table 1. Of note, 48% received neoadjuvant systemic therapy. Overall, we reported 885 postoperative complications, experienced by 507 patients (53%). Details of complications and organ-site are illustrated in Table 2. Four patients (0.5%) died (Clavien V, CCI = 100) postoperatively: two of pulmonary embolism, one of septic shock, and one of massive thrombosis of the abdominal aorta. There were 22/959 (2%) intraoperative complications, including 11 bowel injuries, 4 vascular lesions, 3 obturator nerve injuries, 1 ureteral injury, 2 hypotensive shocks requiring amines, and 1 anaphylactic shock. Three patients (0.3%) required conversion to open cystectomy.

Figure 1 plots every patient experiencing at least one complication, the morbidity score is presented with the CDC (blue line, only the highest-grade complication represented) and the CCI (orange line, comprehensive morbidity). As shown, for patients experiencing only one complication, the two lines correspond. The higher the number of postoperative events, the wider the gap between the two classification systems. The box and whisker plot (Fig. 2) illustrates CCI distribution across different CDC groups. When implementing the CCI score, 13% ($n = 121$) were upgraded to a superior category of CDC score. Indeed, major complications occurred in 17% if the CDC is used and in 23% if the CCI is used.

CDC and CCI both showed moderate correlation with length of stay (ρ CDC: 0.49; ρ CCI: 0.52, all $p < 0.001$).

On crude and adjusted logistic regression (Table 3), male sex, Charlson Comorbidity Index, neobladder reconstruction, and number of resected lymph nodes were significantly associated to an increased risk of overall complications (''a'' in Table 3). Similarly, male sex and neobladder reconstruction were associated to major complications (Clavien ≥III) (''b'' Table 3) on multivariable logistic regression and to a significant increase in CCI on adjusted linear regression (''c'' in Table 3).

When considering a hypothetical clinical trial, implementing the CCI would allow a net reduction of patients that need to be included to demonstrate a significant difference in complications rate (Table 4). Indeed, 80 patients would be needed to demonstrate a 10-point reduction in CCI, as opposed to 186 for a 20% absolute risk reduction in overall complications using the CDC (Table 4).

Discussion

This is the first study that specifically assessed the morbidity of RARC with ICUD using the CCI rather than the CDC. The CCI improved the definition of morbidity for patients experiencing more than one complication, making every complication count and capturing the global morbidity

TABLE 1. PREOPERATIVE, PERIOPERATIVE,
AND PATHOLOGIC CHARACTERISTICS
OF PATIENTS ($N = 959$)

Age (years)	
Median (IQR)	66 (59–73)
Mean ± SD	65 ± 10
Sex (M/F)	795/164 (83%/17%)
BMI	25.9 (23.6–28.4)
	26.2 ± 4.1
Smoking status	
Never	248 (27%)
Active	297 (33%)
Former	280 (30%)
Unknown	90 (10%)
ASA	
1	100 (10%)
2	607 (64%)
3–4	252 (26%)
Charlson comorbidity index	
2	222 (23%)
3	255 (27%)
4	209 (22%)
5	152 (16%)
6	76 (8%)
7	28 (3%)
8	17 (2%)
Neoadjuvant chemo or immunotherapy	
No	504 (52%)
Yes	455 (48%)
Previous abdominal surgery	271/959 (28%)
OR time (minutes)	
Median (IQR)	325 (285–401)
Mean ± SD	341 ± 90
Estimated blood loss (mL)	
Median (IQR)	300 (200–490)
Mean ± SD	379 ± 362
Intraoperative transfusion	45/935 (4.8%)
Urinary diversion	
Ileal conduit	489 (51%)
Neobladder	443 (46%)
Ureterocutaneostomy	27 (3%)
pT	
pT0	243 (25%)
pTis-1	262 (27%)
pT2	149 (16%)
pT3	233 (25%)
pT4	67 (7%)
pN	
pN0	741 (77%)
pN+	188 (20%)
pNx	30 (3%)
Surgical margins status	
Negative	886 (95%)
Positive	50 (5%)
Resected lymph nodes	
Median (IQR)	20 (14–29)
Mean ± SD	22 ± 13
Lymph node density (in %) in pN+	9% (5%–20%)

IQR = interquartile range.

TABLE 2. POSTOPERATIVE COMPLICATIONS

Complications according to CDC	
0	452 (47%)
I	62 (7%)
II	281 (29%)
IIIa	78 (8%)
IIIb	62 (6.5%)
Iva	15 (1.5%)
IVb	5 (0.5%)
V	4 (0.5%)
CCI (including patients with no complications	8.7 (0–22.6)
	14.3 ± 16.4
CCI (if at least one complication)	
Median (IQR)	22.6 (20.9–33.5)
Mean ± SD	27.1 ± 12.9
No. of postoperative complications	
0	452 (47%)
1	279 (30.4%)
2	143 (15%)
3	50 (6%)
4	19 (2%)
≥5	16 (1.6%)
Postoperative transfusion	115 (12%)
Readmission <30 days	128 (16%)
Type of complication	
Bleeding	118 (13%)
Ischemic	9 (1%)
Thrombotic	15 (1.5%)
Cardiac	26 (3%)
Infectious	275 (31%)
Gastrointestinal	188 (22%)
Urinary	132 (15%)
Lymphatic	29 (3%)
Pulmonary	16 (1.5%)
Miscellaneous	77 (9%)
Hospital stay (days)	
Median (IQR)	11 (8–15)
Mean ± SD	13 ± 9

CCI = Comprehensive Complication Index; CDC = Clavien–Dindo Classification.

of the postoperative course.[13] Furthermore, among studies evaluating complications after RARC with ICUD, this study encompasses one of the largest cohorts of patients ($n = 959$) reported in the literature to date, with only the International Robotic Cystectomy Consortium reporting on a higher number of patients ($n = 1094$).[15] We confirmed that the CDC can only give a limited vision of the patients' true postoperative morbidity, and 13% of the patients in the current study had an upgraded CDC score when the CCI is implemented. As an example, a patient experiencing pyelonephritis and deep venous thrombosis was classified as CDC II; however, his CCI is 29.6, which rather corresponds to a CDC IIIa.

The postoperative outcomes of our multicentric cohort are in line with previous studies,[4,10,15,16] either with extracorporeal urinary diversion,[4,10] ICUD,[17] or both.[16] Parekh and colleagues have demonstrated the noninferiority of RARC compared with open surgery in the RAZOR randomized controlled trial, with a complication rate of 67% for RARC, among which 22% were low-grade complications according
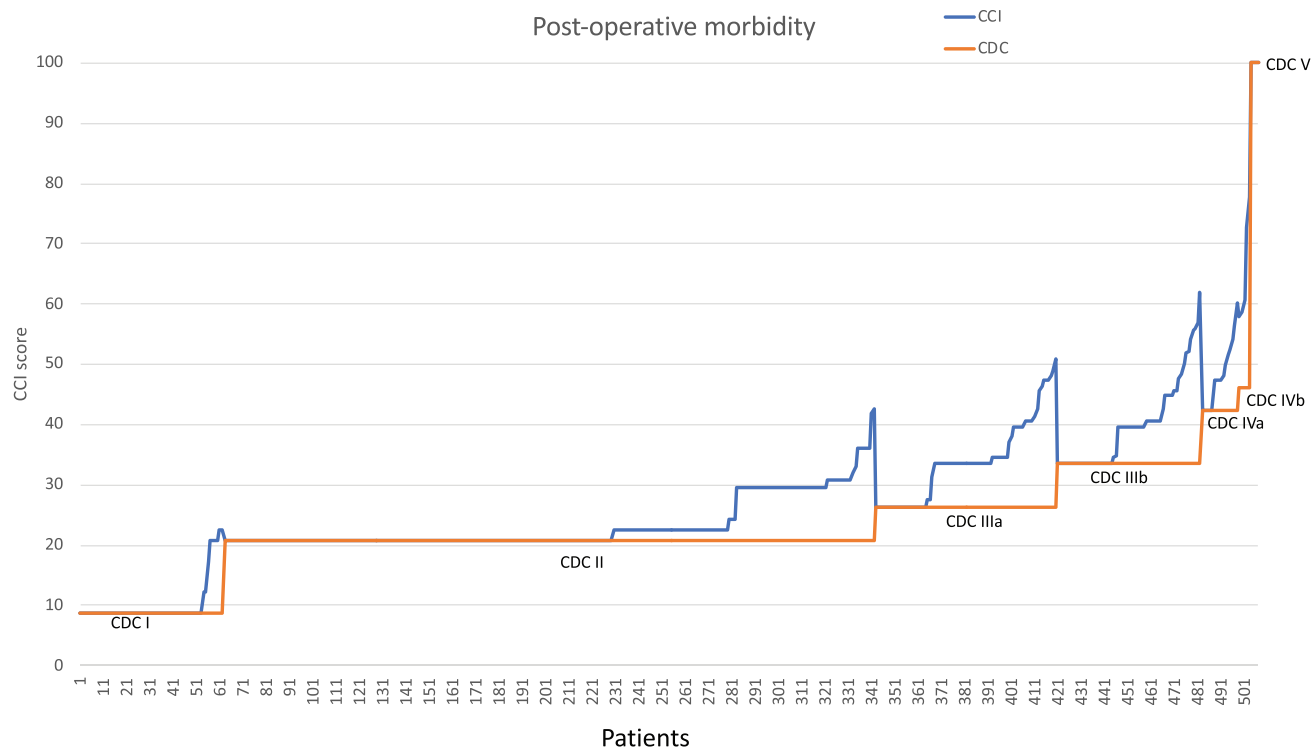
FIG. 1. The figure plots every patient experiencing at least one complication: the morbidity score is presented with the CDC (*blue line*, only the highest-grade complication represented) and the CCI (*orange line*, comprehensive morbidity). For patients experiencing only one complication, the two lines correspond. The higher the number of postoperative events, the wider the gap between the two classifications. CCI = Comprehensive Complication Index; CDC = Clavien–Dindo Classification. Color images are available online.

to the CDC.[4] Johar and associates have used the MSKCC grading system (modification of the CDC) for reporting complications in 939 patients undergoing RARC with mainly extracorporeal urinary diversion and reported an overall complication rate of 48%, mostly classified as low grade.[16] In their study, independent predictors of high-grade complications were age (categorical), receipt of neoadjuvant chemotherapy, and smoking status.[16]

Bochner and coworkers performed a randomized controlled trial comparing ORC with RARC with extracorporeal

FIG. 2. Box and whisker plot illustrating CCI distribution across different CDC groups.

urinary diversion in the MSKCC.[10] A total of 118 patients were randomized and the authors found no significant difference in terms of 90-day morbidity across the two techniques. The rate of grade 2 to 5 perioperative complications were 62% and 66% of RARC and open cystectomy patients, respectively. Hussein and colleagues published the results for patients undergoing RARC with ICUD within the International Robotic Cystectomy Consortium[17]: 57% overall morbidity and 13% of high-grade complications, as well as a median length of stay of 9 days.

Although it remains controversial whether each adverse event after radical cystectomy should be considered a complication, nonsevere complications can delay recovery and prolong rehabilitation, especially when more than one complication occurs in a single patient. This is why the CCI was developed, to account for multiple complications, condensed in a single formula, and each weighted according to its severity, allowing therefore to better understand cumulative morbidity.[13,18]

After its implementation in various oncologic surgeries,[19,20] CCI is becoming a more popular tool for evaluating complications in urological surgeries. For instance, CCI was assessed in a multiple of urological surgeries, including ORC, radical prostatectomy, and partial nephrectomy.[11] This study has shown an upgrade to a more severe complication grade in up to 32.4% of patients. CCI was demonstrated to be significantly more accurate than CDC in predicting length of hospital stay,[11] while our study has shown that both CDC and CCI were highly colinear with length of stay in RARC. Recently, two studies evaluated its utility in retrospective
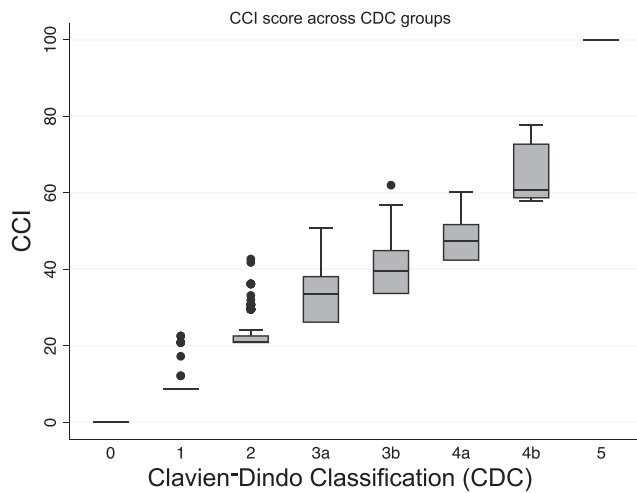
Table 3. Uni and Multivariable Logistic Regressions Exploring the Risk of Overall Morbidity (a), Major Complications (Clavien ≥III) (b), and Uni- and Multivariable Linear Regression Evaluating Risk of Morbidity Measured Through the Comprehensive Complication Index (c)

	Univariate			Multivariate		
Overall complications	OR	95% CI	p	OR	95% CI	p
(a)						
Age	1.01	0.99–1.02	0.07			
Sex (male vs female)	2.28	1.61–3.23	<0.001	2.14	1.39–3.20	<0.001
BMI (kg/m^2)	0.99	0.96–1.02	0.58			
Charlson Comorbidity Index	1.13	1.03–1.22	0.005	1.17	1.02–1.27	0.01
Smoking status						
Never	Ref.	Ref.	Ref.			
Active	0.96	0.69–1.34	0.83			
Former	1.38	0.98–1.94	0.07			
Prior abdominal surgery	1.24	0.93–1.65	0.14			
Continent urinary diversion	1.69	1.24–2.29	0.001	1.63	1.09–2.10	0.006
No. of resected lymph nodes	1.02	1.001–1.03	0.005	1.04	1.02–1.05	<0.001

	Univariate			Multivariate		
Major complications	OR	95% CI	p	OR	95% CI	p
(b)						
Age	1.01	0.99–1.02	0.63			
Sex (male vs female)	3.70	1.9–7.18	<0.001	2.50	1.21–5.15	0.013
BMI (kg/m^2)	0.99	0.95–1.04	0.75			
Charlson Comorbidity Index	1.06	0.96–1.18	0.26			
Smoking status						
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Active	1.17	0.71–1.93	0.53	0.96	0.58–1.60	0.88
Former	1.74	1.08–2.81	0.023	1.54	0.95–2.52	0.08
Prior abdominal surgery	1.13	0.78–1.64	0.50			
Continent urinary diversion	1.82	1.25–2.65	0.002	1.75	1.18–2.60	0.006
No. of resected lymph nodes	1.001	0.99–1.02	0.81			

	Univariate			Multivariate		
CCI	Coeff.	95% CI	p	Coeff.	95% CI	p
(c)						
Age	0.09	−0.01 to 0.2	0.079			
Sex (male vs female)	6.65	3.9 to 9.40	<0.001	5.30	1.95 to 8.65	0.002
BMI (kg/m^2)	−0.04	−0.30 to 0.23	0.78			
Charlson Comorbidity Index	0.97	0.28 to 1.66	0.006	0.86	−0.003 to 1.72	0.05
Smoking status						
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Active	0.56	−2.20 to 3.33	0.69	−1.33	−4.32 to 1.67	0.39
Former	2.89	0.07 to 5.70	0.044	2.77	−0.27 to 5.80	0.07
Prior abdominal surgery	2.14	−0.19 to 4.47	0.07			
Continent urinary diversion	4.81	2.38 to 7.24	<0.001	5.40	2.44 to 7.57	<0.001
No. of resected lymph nodes	0.05	−0.04 to 0.13	0.281			

Table 4. Sample Size Calculation for a Hypothetic Trial Using Clavien–Dindo Classification or Comprehensive Complication Index to Evaluate Postoperative Morbidity

	Assumption	Sample size
Any complication (yes vs no)	20% absolute risk reduction	186 patients
Major complications (CDC ≥ III)	10% absolute risk reduction	398 patients
CCI	Δ10 points	80 patients

cohorts of patients undergoing ORC and showed that the implementation of the CCI upgraded the severity of patient complications in up to 20%.[12,14] Although these studies are in line with our results, we are the first to use a prospective database created specifically to report all the intra and post-operative complications according to the CCI.

The present study reflects current practice across 15 centers, in which the vast majority (if not the totality) of patients scheduled for radical cystectomy are offered RARC with ICUD, thus limiting selection bias. The striking difference in the number of complications per patient (higher in the open

cystectomies cohort) should prompt a thorough comparison of the CCI between ORC and RARC+ICUD. Indeed, this underlines the need to radically change the way of reporting complications in future studies to better reflect the surgical outcomes of extremely complex major surgeries such as radical cystectomies. Hopefully, these findings would encourage the investigators of ongoing trials comparing RARC with ICUD to the open approach, such as the iROC trial[21] and NCT03434132, to implement the CCI when reporting the complication outcomes.

Implementing CCI has also other advantages. We have shown it reduced the sample size needed to establish a significant difference in postoperative morbidity in a hypothetical trial. This supports the results published in other surgeries that not only CCI helped to reduce sample size but also was more sensitive to show differences in surgical endpoints.[22–24] Moreover, compared with CDC, which is a rigid categorical variable, CCI is a continuous variable that could allow direct comparison between interventions and therefore offer a substantial flexibility in the interpretation of results using means. Future trials implementing the CCI should plan statistical analyses based on a continuous outcome variable, rather than the conventional fixed categoric CDC classification.

Finally, considering that CCI is a better predictor of postoperative morbidity than CDC, and given that complications are considered a crucial predictor of overall cost of hospital stay after major surgery,[25] it could be more accurate in predicting in-hospital costs than CDC as already demonstrated in other oncological surgeries.[25,26]

Our study is not devoid of limitations. First, our study included high-volume centers with experienced surgeons, which could explain the very low 30-day mortality rate of 0.5%. These outcomes might not be replicable in all urological centers. However, we should mention that centralization of bladder cancer treatment in high-volume centers, which is commonplace in many developed countries, was demonstrated to improve surgical outcomes and survival.[27] Second, given that this is a multi-institutional study, there is a significant variability across institutions in terms of surgical techniques and postoperative management.[28] Third, we are unable to account for anesthesiologist volume, which is associated to perioperative outcomes and transfusion rates.[29,30] Fourth, we are unable to define impact of the CCI on long-term oncologic outcomes; future research will explore this potential association. Finally, although our cohort is among the largest in the literature and all patients are encoded in prospective local registries, retrospective analyses are exposed to potential biases and further prospective studies are needed to confirm our findings.

Conclusion

This is the first study to introduce and validate the implementation of CCI in RARC with ICUD. Compared with the CDC, CCI appeared more accurate to evaluate postoperative morbidity by taking into account the cumulative aspect of complications and by capturing the global morbidity of the postoperative course. Moreover, our results showed that implementation of CCI may help to reduce the sample size required for demonstrating a significant difference in complication rates in upcoming clinical trials exploring the morbidity of radical cystectomy.

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30. Re: Vetterlein MW, Klemm J, Gild P, et al. Improving estimates of perioperative morbidity after radical cystectomy using the European Association of Urology Quality Criteria for Standardized Reporting and Introducing the Comprehensive Complication Index. Eur Urol 2019;77:55–65. Eur Urol 2020;77:e10–e11.

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Abbreviations Used

CCI = Comprehensive Complication Index
CDC = Clavien–Dindo Classification
ICUD = intracorporeal urinary diversion
IQR = interquartile range
ORC = open radical cystectomy
POD = postoperative day
RARC = robot-assisted radical cystectomy

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AU4: Please check if the edit made to the sentence is okay, ''The study aimed to adopt the CCI for the evaluation of complications in patients undergoing robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) and explore its advantages in the analysis of the morbidity of RARC with ICUD.''

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