

The Comprehensive Complication Index. Proposed modification to improve estimates of perioperative morbidity after radical cystectomy. A pilot study

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Introduction The aim of this article was to compare the 30-day morbidity after radical cystectomy comparing the prevalent Clavien-Dindo Classification (CDC) and the novel Comprehensive Complication Index (CCI). Additionally, evaluated the correlation between particular clinical features and the severity of perioperative morbidity.

Material and methods To the study included 42 patients (33 men and 9 women) who underwent open radical cystectomy (RC) with bilateral lymphadenectomy for bladder cancer. The selection of complications was based on groundbreaking research on morbidity after RC. The assessment of perioperative complications was performed using the CDC and then the CCI.

Results The CCI was found to be a significant upgrade in capturing cumulative morbidity in comparison to the CDC when used as the only evaluational tool.

Conclusions Using only the CDC may underestimate the severity of perioperative complications. Unfavorable clinical features e.g. older age, chronic kidney disease (CKD), persistent nodal (pN+) disease, prior abdominal and pelvic surgeries as well as smoking are of significant importance for the increase of the severity of perioperative complications

Key Words: radical cystectomy ◊ perioperative morbidity ◊ Clavien-Dindo classification
◊ Comprehensive Complication Index

INTRODUCTION

Bladder cancer is the seventh most commonly diagnosed cancer in men all over the world and the eleventh in both sexes combined [1]. In Poland, it accounts for almost 7% of oncological cases in the male population and 2% in the female population [2]. Treatment based on radical cystectomy, which is one of the most difficult surgical procedures in urology, is characterized by complications in 58% to even 99% of cases in the 3-month-long postoperative period [3, 4, 5]. So far, the notion of surgical complications has not been clearly and objectively defined, which makes it difficult to evaluate the qual-

ity of the surgery. The subjective assessment of the surgeon seems to be insufficient in terms of identifying and defining perioperative morbidity. Precise and well-organized data collection with reproducible assessment of the complications is an important aspect of reporting outcomes. Differences in methodology of data collection and interpretation alongside the lack of a uniform definition of complications, have resulted in discrepancies in reporting [6, 7, 8]. Therefore, in 2002 Martin et al. proposed 10 criteria for comprehensive reporting of surgical complications and recommended to use a uniform, standardized methodology [9]. This concept found an application in urology [10] and was successfully adopted

by the European Association of Urology (EAU) within the framework of the guidelines for reporting postoperative complications [11]. In 1992, Clavien et al. proposed a classification of complications in which the main differentiating criterion was the necessity for surgical intervention. The authors described four grades, containing five levels of complications [12]. Twelve years later, Dindo et al. revised this classification by introducing five grades with seven levels of complications [13]. The above-mentioned studies led to the development of the Clavien-Dindo Classification (CDC) in order to standardize perioperative complications reporting and rank them in an objective, simple and reproducible manner [13, 14]. This classification has been included in the EAU guideline for many years. The CDC is used to denote any perioperative disorders and it is increasingly used in clinical practice and studies related to surgery [15]. However, some authors indicate certain limitations of this classification, as only the highest graded complications are evaluated. Its inability to show a patient's cumulative morbidity burden results in an underestimation of the frequency and specificity of perioperative complications. [4, 6]. Therefore, a breakthrough Comprehensive Complication Index (CCI) was proposed by Slankamenag et al. to quantify perioperative morbidity on the basis of different grades of CDC [17]. There are studies that confirm that the CCI is of important complementary value to the CDC in evaluating complications [4, 6]. However, there are only a few studies in this area and therefore the use of the CCI in urology is not widespread.

With the above in mind, the aim of our study was to compare the 30-day morbidity after radical cystectomy according to the CDC and the CCI. Another goal was to try to assess the association between selected clinical features and the severity of perioperative complications in patients.

The presented hypothesis herein is that the morbidity burden after RC is underestimated with the use of only the CDC in comparison to the complementary use of the novel CCI, which may reveal a greater extent of adverse events. A secondary hypothesis is that an unfavorable clinical status of the patient increases the severity of perioperative complications.

MATERIAL AND METHODS

Study group

Inclusion and exclusion criteria

In January 2020, we conducted a retrospective analysis of prospectively collected data on postoperative

morbidities of 42 patients (33 men and 9 women) from the Urological Department of the Holy Cross Cancer Center in Kielce. These patients had undergone open radical cystectomy with ileal conduit urinary diversion and bilateral pelvic lymph node dissection due to urothelial cancer of the bladder from January 1, 2018 to December 31, 2019. None of the patients received neoadjuvant chemotherapy or radiotherapy because of disqualification or lack of agreement.

Information on the clinical condition of the patients (Table 1) and their postoperative morbidity (Table 2) was collected. The selection of surgical complications was based on groundbreaking studies on post-RC morbidity [4, 5, 8, 18, 19].

Table 1. Clinical characteristics of 42 patients who underwent open radical cystectomy for carcinoma of the urinary bladder

Number of patients (%)	42			
Male	33 (78.6)			
Female	9 (21.4)			
Age, mean (SD)	66.69 (7.52)			
Male	68.30 (8.29)		t = 0.63;	
Female	70.11 (3.41)		p > 0.05	
BMI, mean (SD)	27.055 (4.92)			
Male	27.42 (4.89)		t = 0.95;	
Female	25.67 (5.10)		p > 0.05	
Smoking (%)	Male	Female		
Yes	10 (30.3)	5 (55.6)	$\chi^2 = 1.96;$	
No	23 (69.7)	4 (44.4)	p > 0.05	
Hb (g/dl); mean (SD).				
N = 41	12.22 (2.05)	t = 0.32;		
Male N = 32	12.16 (2.09)	p > 0.05		
Female N = 9	12.41 (2.01)			
GFR (ml/min/1.73 m ²)	Male	Female		
≤60	11 (33.3)	6 (66.7)	$\chi^2 = 3.26;$	
>60	22 (66.7)	3 (33.3)	p = 0.071	
pN+ (%)	Male	Female		
Yes	14 (42.4)	3 (33.3)	$\chi^2 = 0.24;$	
No	19 (57.6)	6 (66.7)	p > 0.05	
	All	Male	Female	χ^2
Pathological characteristics (%)				
pT0	0 (0)			
pTa	0 (0)			
pTis	0 (0)			
pT1	5 (11.9)	4 (12.1)	1 (11.1)	0.01
pT2	8 (19.0)	6 (18.2)	2 (22.2)	0.75
pT3	16 (40.5)	12 (36.4)	4 (44.4)	0.66
pT4	13 (31.0)	11 (33.3)	2 (22.2)	0.52
pN stage (%)				
pN0	25 (59.5)	19 (57.6)	6 (66.7)	1.22
pN+	17 (40.5)	14 (42.4)	3 (33.3)	0.24

SD – standard deviation; Hb – haemoglobin; GFR – glomerular filtration rate; pN+ – pathological positive nodes status; t – Student's t-test; N – number of patients

Table 2. Frequencies, proportions and grading of perioperative 30-day complications in 42 patients who underwent open radical cystectomy

Complications	CDC grading	Number of complications	% of complications
Gastrointestinal		13	31
Ileus (paralytic)	I	6	14.3
Small bowel obstruction (mechanical)	IIIb	1	2.4
Clostridium Difficile colitis	II	1	2.4
Emesis	I	3	7.1
Anastomotic bowel leak	IIIb	1	2.4
Diarrhea (no Clostridium difficile associated)	I	1	2.4
Infectious		10	23.8
Fever of unknown origin	I	1	2.4
Bacteriuria (>10 ⁵ CFU/ml, asymptomatic)	I	2	4.8
Urinary tract infections (>10 ⁵ CFU, symptomatic)	II	4	9.5
Abscess	IIIa	1	2.4
Sepsis (SIRS in response to infectious process)	IVb	1	2.4
Gastroenteritis	II	1	2.4
Wound		3	7.1
Wound infection	II	2	4.8
Fascial dehiscence/evisceration	IIIb	1	2.4
Genitourinary		30	71.4
Acute kidney injury	II	5	11.9
Hydronephrosis/ ureteral obstruction	I	13	31.0
Urinary leak/urinoma	IIIa	2	4.8
Urinary retention	I	6	14.3
Parastomal hernia	I	1	2.4
Hematuria	I	3	7.1
Cardiac		6	14.3
Hypertension (new onset)	II	1	2.4
(Acute) congestive heart failure	I	1	2.4
Angina (pectoris)	I	3	7.1
Hypotension	II	1	2.4
Pulmonary		3	7.1
Respiratory distress/dyspnea	I	2	4.8
Pneumothorax	IIIa	1	2.4
Bleeding		8	19
Anemia requiring transfusion	II	8	19.0
Thromboembolic		1	2.3
Deep vein thrombosis	II	1	2.4

Table 2. Continue

Complications	CDC grading	Number of complications	% of complications
Neurological		6	14.3
Peripheral neuropathy	I	5	11.9
Loss of consciousness/syncope	I	1	2.4
Intraoperative		1	2.3
Bowel injury		1	2.4
Miscellaneous		19	45.2
Psychological illness	I	4	9.5
Dermatitis	I	1	2.4
Acidosis	I	2	4.8
Decubitus ulcer	I	4	9.5
Hypokalemia	I	5	11.9
Lymphocele	I	3	7.1
Death	V	2	4.8

CDC – Clavien-Dindo Classification; SIRS – systemic inflammatory response syndrome; CFU – colony forming units

CDC and CCI Classification

The assessment of perioperative morbidities was done initially using the CDC and then the CCI. In the first stage of the study, complications within the first 30 days after surgery were identified for each patient (Table 3) and each complication was assessed according to the validated and adopted CDC [4, 13, 14]. This classification consists of 5 major grades, where the third and fourth grade are divided into two subclasses (a and b). Assessment of any complication was based on the therapy used to correct it. The grades and the corresponding definitions of postoperative complications according to the CDC, as well as the number of cases, are presented in Table 2. The CDC grade III b is the cut-off point above which the most severe complications are found [13].

In the following step, the 30-day CCI was calculated for each patient [4, 17], using an online calculator, which is available on www.assessurgery.com. This innovative CCI combines all postoperative complications with their severity on a scale from 0 (uneventful course) to 100 (death). The value of 33.7 is the cut-off point on the scale, above which the most severe complications are found [17]. The value of 33.7 on the CCI corresponds to grade IIIb in the CDC [4].

Statistical analysis

In order to estimate differences of values of a given parameter between two groups, the non-parametric Mann-Whitney U test was applied. The Spearman's

rank-order correlation was used to estimate the strength of association between two variables with non-normal distribution. The relationship between evaluated CDC and CCI categories and other parameters were analyzed by logistic regression analysis, where the dependent variables were the CDC and CCI in a dichotomous division into categories. The analysis of covariance in the generalized linear model with the logit link function was performed to reveal correlations between the CCI and the other variables. The significance of the influence of a given independent variable was estimated by the Wald chi-square test. For all analyses, a p-value of less than 0.05 was considered statistically significant. All calculations were performed using the Statistica 13.1 program [20].

RESULTS

As the clinical observations of the patients presented in Table 1 indicate, both men and women were overweight with a body mass index (BMI) range from 26 to 30. The smallest group of patients were those with a high number of comorbidities (age-adjusted Charlson Comorbidity Index [ACCI] >6). There were more women smoking (55.6%) than men (30.3%) among the patients. The average preoperative hemoglobin value in men was below the lower cut-off of the normal level, while in women it was normal. Normal baseline renal function assessed on the basis of the glomerular filtration rate (GFR) was observed in more men (66.7%) than women (33.3%), and the differences were almost of statistical significance ($p = 0.071$). Bladder cancer was more advanced in men (42.4%) than in women (33.3%), but the differences were statistically insignificant. The greatest differences between the sexes were observed at the highest stage of cancer advancement, i.e. pT4 stage. Only 9% of men and the majority of women, i.e. 56%, had had prior abdominal and pelvic surgery. The differences were statistically significant at a level of $p < 0.01$.

A detailed summary of the number and percentage of all registered complication types, categories and grades according to CDC is presented in Table 2. A total of 102 adverse complications were reported in 35 out of 42 bladder cancer patients. The most common types included: genitourinary (71%), gastrointestinal (31%) and infectious complications (23%). Pulmonary, wound-related, thromboembolic complications as well as intraoperative injuries were relatively rare.

Overall, 83% patients experienced one or more complications, whereas 5 or more adverse events were documented in 16.6% convalescents. 14% of patients suffered from the most serious complications requir-

ing intervention under general anesthesia, which corresponded to grade IIIb or higher in CDC. Patients with the highest number of complications were those corresponding to CDC IIIb grade (Figure 1).

The median CCI increased with almost each CDC grade, which was statistically significantly. 14% of patients in CDC, and 26% of patients in CCI obtained the status of having the most serious complications (Figure 2).

Logistic regression analysis, where the dependent variable was the CDC (Table 3) or the CCI (Table 4), indicated that only two independent variables had a significant impact on the risk of qualifying to the 2nd degree or above in the CDC or a median of 20.6 and above on the CCI. Patients with a GFR of 60 or less and a pN + stage had, in both cases, a more than

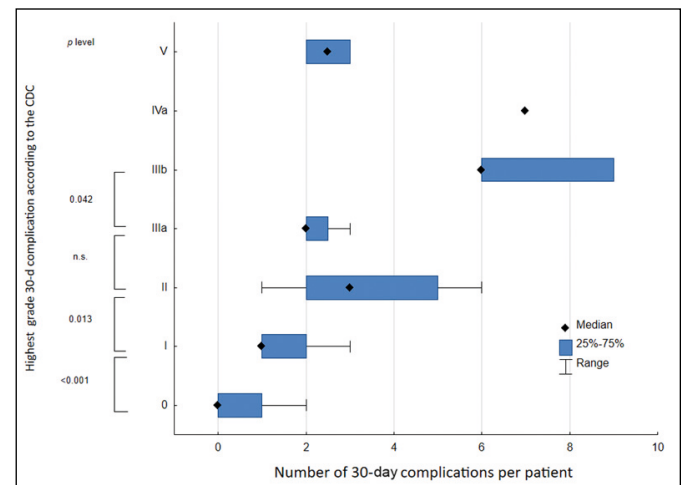


Figure 1. Median number and interquartile range of 30-day complications per patient according to the CDC (CDC – Clavien-Dindo Classification).

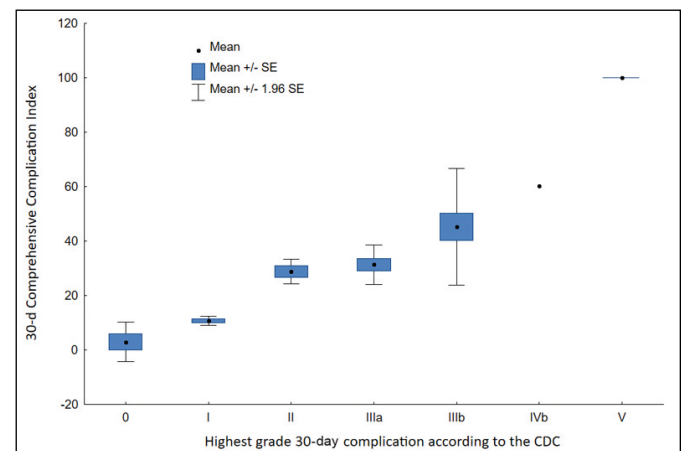


Figure 2. Median 30-day CCI per patient after RC stratified by the CDC (CDC – Clavien-Dindo Classification; CCI – Comprehensive Complication Index; SE – standard error).

10 times greater chance of qualifying to the second degree or above in the CDC (Table 3). With increases in the ACCI an increased number of postoperative complications were observed (described by CDC and CCI), (Tables 3 and 4).

Table 3. Multivariate logistic regression model identifying clinical characteristics associated with 30-day morbidity after open radical cystectomy according to the CDC. The CDC as a dependent variable (1 – 0 and I. 2 – the others)

	Wald's χ^2	p	OR	-95% CDC	+95% CDC
Age	0.45	n.s.	0.96	0.85	1.08
Sex					
Male reference					
Female	0.66	n.s.	2.43	0.26	22.49
BMI	0.09	n.s.	1.03	0.84	1.2
Smoking					
No reference					
Yes	0.17	n.s.	0.67	0.10	4.44
Hb (g/dl)	0.05	n.s.	0.94	0.56	1.58
GFR (ml/min /1.73 m ²)					
>60	4.73	<0.05	10.49	1.16	94.69
≤60 reference					
pN+					
No reference					
Yes	6.00	<0.05	10.47	1.48	73.62

CDC – Clavien-Dindo Classification; OR – Odds Ratio; BMI – Body Mass Index; Hb – Haemoglobin; GFR – Glomerular Filtration Rate; pN+ – pathological positive nodes status

Table 4. Multivariate logistic regression model detecting associations of clinical characteristics and short-term morbidity after RC using the CCI

	Wald's χ^2	p	OR	-95% CCI	+95% CCI
Age	0.11	n.s.e.	0.98	0.87	1.10
Sex					
Male reference					
Female	2.12	n.s.e.	4.91	0.3	45.23
BMI	0.56	n.s.e.	1.08	0.88	1.32
Smoking					
No reference					
Yes	0.21	n.s.e.	0.66	0.10	4.27
Hb (g/dl)	0.75	n.s.e.	0.80	0.48	1.35
GFR (ml/min /1.73 m ²)					
>60	4.77	<0.05	10.23	1.17	89.22
≤60 reference					
pN+					
No reference					
Yes	5.67	<0.05	9.15	1.38	60.68

CCI – Comprehensive Complication Index; OR – ODDS RATION; BMI – body mass index; Hb – haemoglobin; GFR – glomerular filtration rate; pN+ – pathological positive nodes status; p – the level of statistical significance; n.s.e. – no statistical existence

Table 5. Results of the analysis identifying impact of the co-variables on the CCI as a continuous dependent variable

	Degree of freedom	Wald's χ^2	p
Age	1	10.11	0.0015
BMI	1	2.46	0.1166
Hb (g/dl)	1	0.00	0.9970
Sex (female – 0. males – 1)	1	0.23	0.6290
Smoking no-0. yes – 1	1	23.10	0.0000
GFR (≥60 or <60 ml/min/1.73 m ²)	1	76.55	0.0000
pN+	1	110.27	0.0000

BMI – body mass index; Hb – Haemoglobin; GFR – glomerular filtration rate; pN+ – pathological positive nodes status

Spearman's rank-order correlation was used to estimate the relationship between age and the quantity of complications, but no statistical significance was observed. On the contrary, age was significantly associated with the severity of adverse events (Table 5). As the covariance results showed, the value of the CCI reflecting 30-d morbidity after RC was influenced by 3 major factors, including smoking, GFR and pN+ stage (Table 5).

DISCUSSION

We performed an evaluation of 30-day morbidity after open radical cystectomy in bladder cancer patients using the previously adopted Clavien-Dindo classification and the novel Comprehensive Complication Index. We found that most of the patients (83%) experienced at least one perioperative adverse incident. The obtained results correspond with other RC studies, in which the complication rate ranges from 82% to 99% [4, 16]. The most common complications we observed include genitourinary, gastrointestinal and infectious ones, which is consistent with the findings of other studies [4]. We suggest a more complementary assessment of perioperative complications using the CCI, which has the ability to capture cumulative morbidities. To our knowledge, the assessment of perioperative morbidity after RC by means of the CCI has not been frequently used by other authors [4, 16]. Both this study and previous papers confirm that the CCI is a significant upgrade in reporting perioperative morbidity. Like other authors, we found a significant increase in the recorded incidence of morbidity assessed by the CCI in relation to the CDC [4, 16]. In our study, the threshold for the most serious complications according to the CDC (from IIIb grade) was 14%, and in CCI, estimated from 33.7, was 12% 26%. Similarly, Furrer et al. [16] found fewer serious complications

assessed using the CDC in comparison to the CCI (27% vs 30.46%, respectively). However, the authors did not provide the exact number of complications referring to the cut-off point of 33.7 in the CCI.

The number of the most serious complications in the CCI, the 30.46% given in the above mentioned paper, includes patients above 35 points according to the CCI. Malte et al. [4] observed a similar association; according to the CDC, there were 11% of patients with the most serious complications (CDC grade \geq IIIb) and according to the CCI, 31%, i.e. 20% more (CCI \geq 33.7). Furrer et al. [12] pointed out that higher CCI results are of the utmost importance because ultimately the CCI is a significant predictor of mortality and severe complications, not only within the 30 days after surgery, but also during long-term follow-up of postoperative complications in the period from 91 to 365 days after surgery, which is important for patient counseling and follow-up.

In summary, the novel CCI evaluates cumulative morbidity and takes into consideration each complication and the required treatment specific for a given patient. In contrast, the CDC focuses only on one of the most severe complications. Referring to a particular example, if a patient suffered from pneumonia, symptomatic UTI and required blood transfusion, electrolyte balance compensation as well as analgesic and antipyretic treatment, he or she would receive a CDC grade II. At the same time, with a CCI score of 39.2, the threshold for serious complications would be exceeded. It should be emphasized that this is a pilot study and further evaluation will be carried out on a wider scale. On the basis of our own study, as well as other papers [21], it seems reasonable to recommend using the CCI in conjunction with the CDC. It is worthwhile to conduct similar research in other urological procedures as well to assess perioperative complications.

Observations should also be made to assess as many factors as possible that may increase perioperative morbidity. Our research confirmed the effect of a decreased GFR value and pN + stage on RC-related adverse events, while utilizing both the conventional CDC and the innovative CCI assessment. In our ana-

lysed group, similarly to previous studies, we did not find any correlation between BMI and the number of postoperative complications (described by CDC and CCI) [4]. BMI is used to assess probability of overweight and obesity. Diagnosis of obesity is based on adipometry in three localisations: on the shoulder, arm and abdomen. It can be reasoned that abdominal obesity would have the strongest correlation with postoperative complications following operations performed in abdomen and pelvis. This type of obesity is assessed by measuring the abdominal skin fold or Waist to Height Ratio (WHR). Future studies should take this variable into account.

As the authors of other CCI studies to date suggest, accurate documentation and reporting of complications do not imply treatment failure or inferior health care. On the contrary, it is part of a good quality control policy, which means that the medical center is able to ensure comprehensive outcome measurements and, as a consequence, it should be an integral part of the qualification process at a specialized, certified, referral center with urooncological expertise. In addition, in times of constantly increasing patient claims, it is important to inform patients preoperatively about the frequency and severity of complications [4].

CONCLUSIONS

Previously adopted hypotheses were confirmed regarding the following aspects:

1. Detailed analysis of perioperative morbidity using the additional CCI presents a higher complication rate in comparison to using the CDC alone. Therefore, the CDC as the only evaluation tool may underestimate the severity of postoperative complications.
2. Unfavorable clinical features e.g. older age, a baseline eGFR of less than 60, positive lymph nodes (pN+ stage), smoking or prior abdominal and pelvic surgeries increase the severity of perioperative complications.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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