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The Usefulness of the Modified Frailty Index for Muscle-Invasive Bladder Cancer Patients Treated with Radical Cystectomy

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Key Words
Bladder cancer • Cystectomy • Frailty Index • Postoperative complications

Abstract

Background: Radical cystectomy is still the gold standard for muscle-invasive bladder carcinoma (MIBC) treatment. In order to reduce postoperative complications, multimodality bladder-sparing therapies could be a good alternative. Studies in various malignancies have shown that the modified Frailty Index (mFI) may be more useful for identifying high-risk patients. ***Objectives:*** We investigated the possible correlation between the mFI in cystectomy patients with MIBC and serious complications 30 and 90 days postoperatively. ***Methods:*** Analysis of a prospective database of 109 consecutive MIBC patients who underwent a cystectomy between January 2012 and August 2017 was performed. The mFI was added retrospectively. Differences between groups were tested with independent t-tests, Mann-Whitney U tests, ANOVA, Kruskal-Wallis test, or Chi square tests as appropriate. Univariate and multivariate logistic regression analysis were performed to analyse the relation between the mFI and complications. ***Results:*** Patients with Clavien-Dindo ≥ 3 at 30 and 90 days postoperatively had a significantly higher mFI compared to patients with Clavien-Dindo < 3: the odds ratio of the mFI for serious complications within 30 days was 1.5 (95% confidence interval 1.1–2.1, p = 0.010) and for 90 days was 1.5 (95% confidence interval 1.1–2.1, p = 0.008). ***Conclusions:*** We found an association between a high mFI and postoperative complications and mortality. The mFI is therefore useful when discussing treatment options with MIBC patients.

Introduction

Worldwide there are 429,000 patients with bladder cancer, making it the 9th most common form of cancer for both sexes [1]. Bladder cancer is a disease that mainly occurs in elderly patients and due to the aging population in developed countries, this number is set to increase. In muscle-invasive bladder carcinoma (MIBC), radical cystectomy is still the gold standard treatment [2]. This procedure is associated with a high risk of morbidity and a mortality rate between 5.4 and 8.4% within 90 days [3–6]. With the aging of the population, the question is which patients do we still want to operate on and which do we want to offer a less invasive treatment. To reduce postoperative complications, multimodality bladder-sparing therapies could be a good alternative. In recent studies, patients were successfully treated with combinations of chemotherapy and radiotherapy [7]. No randomized studies have been performed to compare long-term results and complications of chemo-radiotherapy versus radical cystectomy.

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Table 1. Patient characteristics (n = 109)

	Values
Male, n (%)	79 (72.5)
Female, n (%)	30 (27.5)
Age, years	68.8 ± 8.5
CCI	3.4 ± 1.6
ASA, n (%)	
1	12 (11.0)
2	69 (63.3)
3	28 (25.7)
4	0 (0)
Median mFI (IQR)	1 (0.0–2.0)
mFI, n (%)	
0	39 (35.8)
1	28 (25.7)
2	25 (22.9)
3	8 (7.3)
4	6 (5.5)
5	2 (1.8)
6	1 (0.9)
11 items of the mFI, n (%)	
Diabetes mellitus	16 (14.7)
Congestive heart failure	8 (7.3)
Hypertension requiring medication	47 (43.1)
Transient ischemic attack or cerebrovascular accident	16 (14.7)
Functional status 2 (not independent)	0 (0.0)
Myocardial infarction	6 (5.5)
Peripheral vascular disease or rest pain	16 (14.7)
Cerebrovascular accident with neurological deficit	2 (1.8)
Chronic obstructive pulmonary disease or pneumonia	21 (19.3)
Prior percutaneous coronary intervention, precordial catch syndrome, or angina	10 (9.2)
Impaired sensorium	0 (0.0)

Currently the choice of treatment is being made using the Charlson Comorbidity Index (CCI), but also age and the American Society of Anesthesiologists (ASA) physical status classification system are still used [2]. However, in some studies there was no relationship between these scores and the postoperative mortality and morbidity in elderly patients [8]. Searching for a new possibility to identify those patients at risk for severe complications after surgery, the Canadian Study of Health and Aging Frailty Index was introduced in 2007 [9]. As a derivative of this, the modified Frailty Index (mFI) – consisting of 11 points, proved useful for identifying high-risk patients in various malignancies [10–13]. These studies wereall based on data from the National Surgical Quality Improvement Program. This database includes a large number of patients. However, not all complications are scored and parameters such as hospital volume and experience of the surgeon are lacking. The extrapolation of these results to clinical practice therefore remains difficult.

Our aim was to investigate the usefulness of the mFI in a low-volume hospital in order to identify patients who are at greater risk of serious complications 30 and 90 days after cystectomy.

Materials and Methods

Patients, Inclusion and Exclusion

All patients who underwent a radical cystectomy for bladder cancer between January 2012 and August 2017 were included. These procedures were all open cystectomies and performed by the same 2 urologists. After August 2017 our clinic switched to robot-assisted cystectomies, which were not included in this study. Cystectomies for a non-oncological reason were excluded to create a homogeneous group. All patients were allowed to eat until 4 hours before surgery and followed a fast-track protocol postoperatively. Antibiotics (cefazolin and metronidazole) were provided prophylactically prior to the procedure. Postoperative anti-emetics and laxatives were prescribed as usual. In addition, patients were mobilized as quickly as possible, mostly within 12 hours. Patients were monitored the first night in the 24-hour recovery ward.

The following variables were registered in a database: age, comorbidities, ASA classification, age adjusted CCI, surgical details, pathology reports, duration of stay in the hospital, and complications. Retrospectively, the records of all patients were again analyzed to calculate the mFI. The mFI consists of 11 patient characteristics. There are several, slightly different mFIs used in the literature, but we used the one described by Kim et al. [14]. Every variable is scored as 1 point. The scores range from 0 to 11, with a score of 0 representing no frailty and a score of 11 representing the highest degree of frailty. Complications were recorded using the Clavien-Dindo (CD) classification system, grade 1–5 [15]. Both the 30- and 90-day complication rates were collected. Based on postoperative documentation and outpatient clinic visits within this period, a CD score of 1 to 5 was given. If there were multiple complications for the same patient during this period, the highest score was used for the analysis. Because grade 1 and 2 complications are common and grade 3 and higher complications, in particular affect the patient, it was decided to make a cut-off point at grade 3 and higher.

Statistical Analysis

Continuous data are reported as mean ± SD, or in the case of non-parametric data as a median with the interquartile range (IQR). Categorical variables are reported as a number with a corresponding percentage. Differences between groups were tested with independent t-tests, Mann-Whitney U tests, ANOVA, Kruskal-Wallis test, or Chi square tests as appropriate. Univariate and multivariate logistic regression analyses were performed to analyze the relation between the mFI (treated as a continuous variable) and complications (CD 0–2 vs. ≥ 3). The following potential confounders were investigated ($p < 0.10$): gender, age, and ASA. CCI was not inspected as a potential confounder since the mFI and CCI have an overlap in their components and therefore, it was decided beforehand not to include CCI in the multivariate model. The area under the curve (AUC) of the receiver operating characteristic curve of both mFI and CCI (both treated as continuous

Table 2. Surgery and postoperative course (n = 109)

	Values	
Cutaneous diversion, n (%)	101 (92.7)	
Neo-bladder, n (%)	8 (7.3)	
Mean length of surgery, minutes	227.4 ± 55.4	
Median length of stay (IQR), days	13.0 (10.0–16.0)	
Median blood loss (IQR), ml	450 (300–750)	
Pathological T stage, n (%)		
T0	12 (11.0)	
Tis–T1	20 (18.3)	
T2	28 (25.7)	
T ≥ 3	49 (45.0)	
Pathological N stage, n (%)		
N0	85 (78.0)	
N1	13 (11.9)	
N ≥ 2	11 (10.1)	
Positive soft tissue margins, n (%)	9 (8.3)	
Complications, n (%)		
Ileus	28 (25.7)	
Urinary tract infection	15 (13.8)	
Bowel injury	2 (1.8)	
Fascial dehiscence	8 (7.3)	
Pulmonary	9 (8.3)	
Cardiac	15 (13.8)	
Renal dysfunction	7 (6.4)	
Delirium	8 (7.3)	
CD classification, n (%)	30-Day	90-Day
None	41 (37.6)	38 (34.9)
Grade 1	9 (8.3)	8 (7.3)
Grade 2	31 (28.4)	30 (27.5)
Grade 3	15 (13.8)	19 (17.4)
Grade 4	11 (10.1)	10 (9.2)
Grade 5	2 (1.8)	4 (3.7)

variables) was calculated. The Spearman correlation coefficient was calculated to measure the strength of association between mFI and CCI.

To determine a cut-off point for patients who are at risk for serious complications, a comparison of mFI groups was made: 0 versus 1 or higher, 0–1 versus 2 or higher, and 0–2 versus 3 or higher. In addition, a cut-off mFI ≥ 2 was chosen as it was previously set by Chappidi et al. [10]. We named the group of mFI < 2 'low risk' and mFI ≥ 2 'high risk'. Statistical analysis were performed using SPSS version 24 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

In our study period, 109 MIBC patients underwent a radical cystectomy with creation of a cutaneous diversion or neo-bladder. Of these patients 79 (72.5%) were male and age was 68.8 ± 8.5 years. CCI was 3.4 ± 1.6. Twelve patients (11.0%) had ASA 1, 69 patients (63.3%) ASA 2, 28 patients (25.7%) ASA 3, and there were no ASA 4 patients. The presence of the 11 items of the mFI are listed in table 1. Of all patients, 39 (35.8%) had a mFI of 0, 28 (25.7%) had a score of 1, 25 (22.9%) had a score of 2, and 17 (15.5%) had a score of ≥ 3.

Surgery and Postoperative Course

Of the 109 patients, 68 (62.4%) had a postoperative complication within 30 days and 28 of them (41.2%) had a CD ≥ 3. Within 90 days, 71 patients (65.1%) had a postoperative complication, of which 33 (46.5%) had a CD ≥ 3. Surgical details and the postoperative course including complications are presented in table 2. The most common complication was ileus (n = 28, 25.7%), followed by urinary tract infection (n = 15, 13.8%), and cardiac problems (n = 15, 13.8%).

mFI

Patients with CD ≥ 3 had a significantly higher mFI 30 days postoperatively compared to patients with CD < 3: the median (IQR) mFI of the patients with CD ≥ 3 was 1.5 (1.0–2.0) and of the patients with CD < 3 it was 1.0 (0.0–2.0) ($p = 0.007$). The odds ratio (OR) of the mFI for serious complications was 1.5 [95% confidence interval (CI) 1.1–2.1, $p = 0.010$]. After 90 days, we found the same results: patients with CD ≥ 3 had a significantly higher mFI compared to patients with CD < 3 : the median (IQR) mFI of patients with CD ≥ 3 was 1.85 (1.0–2.5) and of patients with CD < 3 it was 1.0 (0.0–2.0) ($p = 0.007$). The OR of the mFI for serious complications was 1.5 (95% CI 1.1–2.1, $p = 0.008$). For both 30 and 90 days, age and gender were not confounders for the relation between the mFI and the CD groups. ASA was a potential confounder: ASA was related ($p < 0.10$) with the mFI and with CD. However, due to an insufficient sample size ASA was not entered into the multivariate model. The receiver operating characteristic curve of the prediction model showed an AUC of 0.66 (95%CI 0.56–0.77) for complications after 30 days and an AUC of 0.66 (95%CI 0.55–0.76) after 90 days (both $p = 0.010$). No differences in CCI were found between the the CD < 3 and CD ≥ 3 groups after 30 and 90 days: 3.3 ± 1.6 vs. 3.8 ± 1.5 ($p = 0.096$), and 3.3 ± 1.6 vs. 3.7 ± 1.6 ($p = 0.147$) respectively. A moderate positive correlation was found between the mFI and CCI ($\rho = 0.68$, $p < 0.001$).

Cut-Off

A cut-off point for the mFI to classify patients at risk for serious complications after surgery could not be es-

Table 3. 90-Day complications and mortality (n = 109)

	mFI < 2 (n = 67)	mFI ≥ 2 (n = 42)	p
CD: all grades, n (%)	40 (59.7)	31 (73.8)	0.133
CD: grade 3 or higher, n (%)	17 (25.4)	16 (38.1)	0.159
Mortality, n (%)	0 (0)	4 (9.5)	0.020

tablished: no value was found above which there were significantly more complications (data not shown). The cut-off point was set at ≥ 2 as previously reported in the literature, which was also the median mFI score in the study population (median: 1.0). When setting the cut-off point at ≥ 2, 42 out of 109 patients (38.5%) were left in the 'high risk' group. After 30 days, 30 out of 42 patients (71.4%) in the 'high risk' group had a complication versus 38 out of 67 (56.7%) in the 'low risk' group (p = 0.123). There were noticeably more cardiopulmonary complications in the 'high risk' group: 18 out of 42 (42.9%) versus 6 out of 67 (9.0%) in the 'low risk' group. When we only took serious complications into account (CD ≥ 3), 14 out of 42 (33.3%) in the 'high risk' and 14 out of 67 (20.9%) in the 'low risk' had an event (p = 0.148). After 90 days we found almost the same results (table 3). We did, however, find a significant difference in mortality. After 30 days, 2 patients (4.8%) died in the 'high risk' group and after 90 days it was 4 patients (9.5%) versus 0 patient in the 'low risk' group (p = 0.020).

Discussion

With the increasing age of our MIBC population and new excellent treatment modalities, clinicians and especially urologists are looking for new ways to choose the right therapy for their patients [7, 16]. We believe that these choices can no longer be made based solely on a clinical view. Objective methods are of the utmost importance in helping both clinician and patient decide which treatment will be the best option for the patient. Traditionally, the CCI is a tool used to make a preoperative risk assessment, which is also advised by the European Urology Association guideline on MIBC [2]. The CCI is largely based on the chronological age of the patient. There are indications, however, that a biological age is more important than the chronological age. The occurrence of comorbidity will increase with the age of the patient, but this varies considerably per person. A study of Mitnitski et al. [17] showed that biological age was significantly more strongly associated with death than chronological age. This may also explain why the CCI in smaller cohorts is not related to poorer outcomes. A recent study of Atallah et al. [8] showed that there was no relationship between a high CCI and the incidence of morbidity and mortality in patients aged 75 years and older undergoing a cystectomy. In contrast to the CCI, the Canadian Study of Health and Aging Frailty Index and its derivative, the mFI, is not based on chronological age. In the present study, the CCI was not related to serious complications after 30 and 90 days. Furthermore, the mFI moderately correlated with the CCI.

In the literature many frailty indexes were proposed [9, 14, 18]. For colectomy patients, the mFI was successfully used recently in discriminating those patients at risk for severe complications and mortality [12]. Patients with a high mFI were more likely to be discharged to non-home care [19]. Lascano et al. [13] validated the mFI for urological malignancies. In a cohort of 2,679 patients, Chappidi et al. [10] found 30 days after a cystectomy a higher rate of CD grade 4 or 5 complications and a higher overall mortality rate in patients with an mFI ≥ 2. As we also found it relevant to prevent grade 3 complications, we included these in our analysis. With this broader definition of serious complications, we were also able to prove a relation between the mFI and the occurrence of serious complications (CD ≥ 3) within 30 and 90 days of cystectomy, even in a low-volume hospital. Patients with a CD ≥ 3 after 30 and 90 days had a significantly higher mFI at baseline than patients with a CD < 3.

However, there were major differences with Chappidi et al. [10]. In the National Surgical Quality Improvement Program database used by Chappidi et al. [10] gastrointestinal complications were not recorded. We think that registering these kinds of complications after a cystectomy is actually essential. In our study we found gastrointestinal complications that significantly contributed to our total complication rate in 25.7% of patients. Second, their follow-up was limited to 30 days postoperatively.

The 90-day period captures mortality from multiple causes and is therefore more valuable when providing information to patients before surgery [20]. In our study we observed a difference in mortality between 30 and 90 days follow-up. After 30 days, 2 patients from the 'high risk' group died and after 90 days this doubled to 4 patients. Within such a small group, this doubling is a number to take into account. Finally, Chappidi et al. [10] used a database where no information was available concerning hospital volume for cystectomies, type of urinary diversion, experience of the urologists, and whether the patient underwent neoadjuvant chemotherapy. In contrast, our population was homogenous and all surgery were performed by two experienced urologists together. Patients followed the same pre- and post-operative protocol and similar follow-up.

When using risk scores, it is important to determine a cut-off value in order to classify patients at risk. Due to an insufficient sample size, no cut-off value could be set in our study. Chappidi et al. [10] set the cut-off value of the mFI to 2 or higher. When this cut-off was applied to our data, no significant difference was seen in the rate of serious complications, except for mortality. This could be due to the small group of patients included in this study. However, only having a cut-off value is not enough since a choice for therapy cannot be made solely on the basis of this. In practice, the conversation between patient and urologist continues to be vitally important.

There are limitations in our study. First of all, we took CD grade 3 or higher as an endpoint. As mentioned before, we also considered a grade 3 complication to be a serious complication that should be prevented. As other endpoints have been chosen in the literature (grade 4 or higher), it is difficult to compare our results with these studies. In addition, as previously mentioned, the sample size was not sufficient to set a cut-off point for identifying high-risk patients.

In our study we just used clinical endpoints and did not measure the patient's quality of life because we used partly prospectively and partly retrospectively collected data. It would be interesting to prospectively collect data from this vulnerable patient population when the diagnosis of MIBC is set. Moreover, it would be valuable to measure the quality of life after radical cystectomy and to include this item in the decision tree as set by guidelines. When a decision is made for various treatment modalities, risk scores could then be taken into account. If these patients could then be tracked prospectively during the various treatments, both surgical and non-surgical, the actual usefulness of risk scores could be revealed.

Conclusion

We found a relationship between the mFI and the occurrence of serious complications within 30 and 90 days of cystectomy in patients with MIBC. In our cohort we could not define a cut-off value for the mFI. However, it seemed that patients with a mFI ≥ 2 are more likely to die within 90 days of surgery. The mFI appears to be a useful tool for discussing treatment options with MIBC patients. Further research into the value of the risk scores is required to confirm its potential.

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