ORIGINAL RESEARCH

The association between patient body mass index and perioperative outcomes following radical cystectomy: An analysis using the American College of Surgeons National Surgical Quality Improvement Program database

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Abstract

Introduction: Radical cystectomy is a highly morbid procedure, with 30-day perioperative complication rates approaching 50%. Our objective was to determine the effect of patients' body mass index (BMI) on perioperative outcomes following radical cystectomy for bladder cancer.

Methods: We identified 3930 eligible patients who underwent radical cystectomy for non-metastatic bladder cancer using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. The primary exposure was preoperative BMI, categorically operationalized in four strata according to the World Health Organization criteria: <18.5 kg/m^2, 18.5–25 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2. Our primary outcome was major perioperative complication comprising mortality, re-operation, cardiac event, or neurological event.

Results: BMI was significantly associated with rates of major complications (p=0.003): major complications were experienced by 17.0% of patients with BMI <18.5 kg/m^2, 7.8% of patients with BMI 18.5–25 kg/m^2, 7.9% of patients with BMI 25–30 kg/m^2, and 10.8% of patient with BMI >30 kg/m^2. Following multivariable adjustment for relevant demographic, comorbidity, and treatment factors, compared to patients with BMI 18.5–25 kg/m^2, patients with BMI <18.5 kg/m^2 (odds ratio [OR] 2.28, 95% confidence interval [CI] 1.07–4.78) and BMI >30 kg/m^2 (OR 1.59, 95% CI 1.17–2.16) were significantly more likely to experience a major complication in the 30 days following cystectomy. Among the secondary outcomes, significant differences were identified in rates of pulmonary complications (p=0.003), infectious complications (p<0.001), bleeding requiring transfusion (p=0.01), and length of stay (p=0.001).

Conclusions: Patients who are outside of a normal BMI range are more likely to experience major complications following radical cystectomy for bladder cancer.

Introduction

Radical cystectomy (RC), together with cisplatin-based neo-adjuvant chemotherapy, is a mainstay in the treatment of muscle-invasive bladder cancer (MIBC). However, the complexity of the procedures and the inherent patient characteristics of those with MIBC have resulted in perioperative complication rates of over 50%.[1] The risk of perioperative morbidity is subject to influence from numerous factors, including oncological, technical, and patient-derived.

Body mass index (BMI) is an important patient factor that is associated with numerous comorbidities, including cardiovascular disease, dyslipidemia, and diabetes. Obese patients undergoing RC have increased risk of positive soft tissue margins, which may be a surrogate for technical difficulty.[1] Furthermore, increased BMI has been shown to worsen postoperative outcomes in a number of other urological procedures.[2,3] Conversely, low BMI (underweight patients may be a marker for frailty and poor nutrition) and performance status are factors that have been show to be associated with the risk of perioperative complications following RC.

To date, there has been conflicting data regarding the effect of BMI on oncological outcomes following RC.[1,3,4] Data regarding the effect of BMI on perioperative complications are sparse, with some evidence that patients with a low BMI have increased risk perioperative complications, possibly relating to disease severity or poor nutrition.[5]

Due to the conflicting data currently available, we sought to assess the association between patient BMI and morbidity and mortality associated with RC. To do so, we used the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database, a large, multi-insti-

tutional, validated registry that has been shown to perform better than administrative databases or institutional series in capturing intraoperative and postoperative complications.[6]

Methods

Study subjects

We used the participant use files of the ACS NSQIP to identify patients undergoing RC (Common Procedural Terminology code 51590, 51595, 51596) with a postoperative diagnosis of bladder cancer (ICD-9 code 188.x) between January 1, 2007 and December 31, 2014. We excluded 180 patients with disseminated disease and 33 patients for missing data on important covariates or outcomes: American Society of Anesthesiologists (ASA) physical status classification (n=9), height (n=15), weight (n=11), and length of stay (n=4).

Outcomes

Our primary outcome was major perioperative complication comprising mortality, re-operation, cardiac event, or neurological event. Secondary outcomes included pulmonary and infectious complications, venous thromboembolism, bleeding requiring transfusion, and prolonged length of stay (>7 days).

Exposure

The primary exposure was preoperative BMI, categorically operationalized in four strata according to the World Health Organization criteria: <18.5 kg/m^2, 18.5–25 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2.

Covariates

Standard demographic and clinical information abstracted for all patients included age, race, ASA physical status class (categorised as class 1–2 vs. class 3–4), history of cardiac disease, history of neurological disease, history of chronic obstructive pulmonary disease (COPD), history of diabetes (requiring oral agent or insulin), end-stage renal disease (ESRD) requiring dialysis, current smoking status (active smoker within one year), use of preoperative chemotherapy (within 90 days of surgery), use of preoperative radiotherapy (within 90 days of surgery), chronic steroid use, and functional status prior to surgery (independent vs. partially or totally dependent). We further characterized the type of urinary diversion using CPT codes (51590 and 51595 = ileal conduit; 51596 = continent).

Statistical analysis

Descriptive statistics were used to compare baseline demographic factors; frequencies and proportions were calculated for categorical variables and medians and interquartile ranges (IQR) for continuous variables, respectively. We compared proportions and medians for patients across the categories of BMI using the Chi-squared test (Fisher's exact test where appropriate) and Wilcoxon rank sum test, respectively. For categorical variables, we further used the Cochrane-Armitage test for trend to assess for trends across the BMI categories.

We then examined the proportion of cases resulting in a complication in each of our prespecified categories. We compared the proportions of patients experiencing a complication among each of the BMI categories using Fisher's exact test and tested for trends using the Cochrane-Armitage test for trend. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for each complication category were calculated using multivariable logistic regression modelling. We adjusted for a priori variables selected based on literature review to identify relevant patient and operative characteristics. These included patient age, gender, ASA category, history of cardiac disease, history of diabetes, smoking history, history of COPD, history of neurological disease, history of ESRD, exposure to chronic steroids, baseline functional status, and type of urinary diversion.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.).

Results

We identified 3930 patients in the NSQIP database who underwent RC for bladder cancer during the study interval. Of these patients, 59 (1.5%) had BMI <18.5 kg/m^2, 988 (25.1%) had BMI 18.5–25 kg/m^2, 1522 (38.7%) had BMI 25–30 kg/m^2, and 1361 (34.6%) had BMI >30 kg/m^2. BMI was significantly associated with patient age, gender, comorbidity as assessed using ASA score, history of diabetes, history of COPD, active smoking, functional status, and urinary diversion type (p<0.0001–0.007) (Table 1). Rates of continent urinary diversion increased as patient BMI increased (Table 1).

BMI was significantly associated with rates of major complications (p=0.003, p for trend=0.06) (Table 2); major complications were experienced by 17.0% of patients with BMI <18.5 kg/m^2, 7.8% of patients with BMI 18.5–25 kg/m, 7.9% of patients with BMI 25–30 kg/m^2, and 10.8% of patient with BMI >30 kg/m^2. Among the secondary outcomes, significant differences were identified in rates of pulmonary complications (p=0.003), infectious complications (p≤0.001), bleeding requiring transfusion (p=0.01), and prolonged length of stay (p=0.001) (Table 2). There was no difference in venous thromboembolism (p=0.37) (Table 2).

Table 1. Baseline characteristics of patients undergoing radical cystectomy, stratified by BMI category

	BMI <18.5 kg/m²	BMI 18.5–25 kg/m²	BMI 25–30 kg/m²	BMI >30 kg/m²	p	p for trend
Age (median, IQR)	69, 57–75	71, 63–78	70, 63–76	67, 60–74	<0.0001	
Sex (n, %)						
Male	33, 55.93	764, 77.33	1313, 86.27	1131, 83.10	<0.0001	<0.0001
Female	26, 44.07	224, 22.67	209, 13.73	230, 16.90		
Race (n, %)					0.27	n/a
Caucasian	52, 88.14	827, 83.70	1315, 86.40	1182, 86.85		
African American	2, 3.39	48, 4.86	49, 3.22	51, 3.75		
Other/unknown	5, 8.47	113, 11.44	158, 10.38	128, 9.40		
ASA category (n, %)					<0.001	<0.001
1–2	9, 15.25	293, 29.66	418, 27.46	288, 21.16		
3–4	50, 84.75	695, 70.34	1104, 72.54	1073, 78.84		
Cardiac history (n, %)	2, 3.39	41, 4.15	65, 4.27	74, 5.44	0.37	0.11
Neurologic history (n, %)	2, 3.39	11, 1.11	18, 1.18	16, 1.18	0.48	0.71
History of COPD (n, %)	13, 22.03	91, 9.21	110, 7.23	123, 9.04	0.0004	0.26
Diabetes (n, %)	0, 0.00	118, 11.94	274, 18.00	400, 29.39	<0.0001	<0.0001
Dialysis (n, %)	0, 0.00	3, 0.30	5, 0.33	0, 0.00	0.13	0.12
Active smoking (n, %)	35, 59.32	315, 31.88	349, 22.93	272, 19.99	<0.0001	<0.0001
Preoperative chemotherapy* (n, %)	1, 1.69	22, 2.23	56, 3.68	42, 3.09	0.20	0.25
Preoperative radiotherapy* (n, %)	0, 0.00	1, 0.10	1, 0.07	2, 0.15	0.14	0.65
Chronic steroid use (n, %)	2, 3.39	40, 4.05	40, 2.63	47, 3.45	0.26	0.55
Functional status (n, %)					<0.0001	0.0004
Independent	52, 88.14	968, 97.98	1495, 98.23	1346, 98.90		
Partially/totally dependent	7, 11.86	20, 2.02	27, 1.77	15, 1.10		
Urinary diversion					0.007	0.0009
Ileal conduit	52, 88.14	812, 82.19	1188, 78.06	1053, 77.37		
Continent diversion	7, 11.86	176, 17.81	334, 21.94	308, 22.63		

*Note: Preoperative chemotherapy and radiotherapy must have occurred within 90 days of surgery to be recorded in the National Surgical Quality Improvement Program database. ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IQR: interquartile range.

Following multivariable adjustment for relevant patient demographics, comorbidities, and treatment details, compared to patients with a normal BMI (18.5–25 kg/m²), patients with BMI >30 kg/m² (OR 1.59, 95% CI 1.17–2.16) and BMI <18.5 kg/m² (OR 2.28, 95% CI 1.07–4.78) were significantly more likely to experience a major complication in the 30 days following cystectomy (Table 3). Regarding secondary outcomes, patients with BMI >30 kg/m² were at greater odds of a pulmonary and (OR 2.20, 95% CI 1.36–3.56) and infectious complication (OR 1.52, 95% CI 1.24–1.85) compared to patients with normal BMI. Interestingly, obese patients were less likely to have bleeding requiring transfusion (OR 0.83, 95% CI 0.70–0.99). Patients with underweight BMI (<18.5 kg/m²) were more likely to have an infectious complication (OR 2.27, 95% CI 1.31–3.95) and a prolonged length of stay (OR 2.99, 95% CI 1.62–5.52) compared to patients with normal BMI.

Discussion

Given the obesity epidemic in first-world countries, there is increasing interest in research pertaining to surgical outcomes among obese patients. In this study using the NSQIP database,

we found several differences in the complication rates of the patients with an underweight BMI (<18.5 kg/m²) and patients in the obese category (>30 kg/m²) when compared to normal weight patients (BMI 18.5–25.0 kg/m²). Both underweight and obese BMI groups were more likely to suffer major complications (mortality, re-operation, cardiac event, or neurological event). Obese patients were also more likely to have pulmonary and infectious complications compared to patients with normal BMI. The underweight BMI group was more likely to have a prolonged length of stay and infectious complications compared to patients with normal BMI. To our knowledge, this is the first large-scale study to demonstrate obesity as an independent risk factor for major complications following RC for bladder cancer.

The current literature demonstrates a complex relationship between obesity and bladder cancer. There is evidence to suggest that obesity leads to an increased risk of bladder cancer[7] and an increased risk of recurrence in patients with non-muscle-invasive disease.[8] This may be due to obese patients being more likely to have higher tumor grade and more positive surgical margins, subsequently leading to higher rates of disease recurrence.[1,3] However, other studies have not found that obesity is related to worse survival or

Table 2. Crude rates of complications during radical cystectomy

	BMI <18.5 kg/m²	BMI 18.5–25 kg/m²	BMI 25–30 kg/m²	BMI >30 kg/m²	p	p for trend
Sample size	59	988	1522	1361		
Major complication (n, %)	10, 16.95	77, 7.79	120, 7.88	147, 10.80	0.003	0.06
Mortality (n, %)	5, 8.47	18, 1.82	22, 1.45	32, 2.35	0.001	0.89
Reoperation (n, %)	4, 6.78	51, 5.16	77, 5.06	93, 6.83	0.17	0.10
Cardiac complication (n, %)	1, 1.69	21, 2.13	33, 2.17	39, 2.87	0.56	0.20
Neurologic complication (n, %)	0, 0.00	5, 0.51	6, 0.39	11, 0.81	0.45	0.23
Pulmonary complication (n, %)	4, 6.78	26, 2.63	50, 3.29	72, 5.29	0.003	0.004
Infectious complication (n, %)	24, 40.68	212, 21.46	363, 23.85	402, 29.54	<0.0001	0.0005
Sepsis (n, %)	11, 18.64	111, 11.23	184, 12.09	197, 14.47	0.04	0.064
Pneumonia (n, %)	8, 13.56	39, 3.95	47, 3.09	37, 2.72	<0.001	0.004
Urinary tract infection (n, %)	5, 8.47	70, 7.09	132, 8.67	153, 11.24	0.005	0.0007
Surgical site infection (SSI) (n, %)	10, 16.95	83, 8.40	175, 11.50	232, 17.05	<0.001	<0.001
Organ space SSI (n, %)	4, 6.78	38, 3.85	84, 5.52	80, 5.88	0.14	0.07
Deep incisional SSI (n, %)	0, 0.00	11, 1.11	26, 1.71	43, 3.16	0.002	0.0002
Superficial SSI (n, %)	6, 10.17	36, 3.64	72, 4.73	125, 9.18	<0.001	<0.001
Venous thromboembolism (n, %)	2, 3.39	41, 4.15	74, 4.86	77, 5.66	0.37	0.08
Deep vein thrombosis (n, %)	2, 3.39	25, 2.53	50, 3.29	48, 3.53	0.58	0.22
Pulmonary embolism (n, %)	0, 0.00	19, 1.92	32, 2.10	44, 3.23	0.073	0.02
Bleeding needing transfusion (n, %)	32, 53.24	413, 41.80	568, 37.32	515, 37.84	0.009	0.01
Prolonged length of stay (n, %)	44, 74.58	483, 48.89	731, 48.03	690, 50.70	0.0007	0.77

BMI: body mass index.

poor oncological outcomes;[9,10] one recent prospective study even found an improvement of overall survival in obese patients.[4] This likely highlights what has been termed the "obesity paradox" — overweight and early obese states are associated with improved survival among cancer patients.[11] The exact mechanism of this phenomenon has been debated, but has been hypothesized to be secondary to methodological (i.e,. detection bias and reverse causality) and clinical (i.e., less aggressive tumor biology and improved tumor response among obese patients) reasons.[11] The relationship between obesity and post-surgical complications is somewhat clearer, as several studies confer with our data that obesity is likely related to increased risk of immediate post-surgical complications in patients undergoing RC.[4,12,13] We found that obese patients were 59% more likely to suffer a major complication, 52% for infectious complications,

and had more than double (OR 2.20) the odds of pulmonary complications compared to normal weight patients. The protective factor of obesity and bleeding requiring blood transfusion is not supported by the current literature (even in robotic cystectomy cases)[10] and deserves future work to further clarify this association. Ultimately, these findings highlight the need for acute/intensive postoperative surgical care among obese patients and appropriate preoperative counselling regarding trimodality therapy in those that may be at already high surgical risk. Specifically, obese patients require aggressive pulmonary toilet, attentive wound management, and cardiac/neurological monitoring.

The underweight BMI patients, after adjusting for comorbidities, had significantly higher rates of major, pulmonary, and infectious complications, as well as greater transfusion requirements and prolonged length of stay compared to

Table 3. Multivariate logistic regression models, results presented as odds ratio (95% CI)

	BMI <18.5 kg/m²	BMI 18.5–25 kg/m²	BMI 25–30 kg/m²	BMI >30 kg/m²
Major complication	2.28 (1.07–4.78)	Referent	1.09 (0.80–1.47)	1.59 (1.17–2.16)
Pulmonary complication	2.63 (0.85–8.07)	Referent	1.32 (0.81–2.16)	2.20 (1.36–3.56)
Infectious complication	2.27 (1.31–3.95)	Referent	1.16 (0.95–1.41)	1.51 (1.24–1.85)
Venous thromboembolism	0.92 (0.21–3.94)	Referent	1.20 (0.81–1.78)	1.49 (1.00–2.23)
Bleeding requiring transfusion	1.54 (0.89–2.66)	Referent	0.85 (0.72–1.01)	0.83 (0.70–0.99)
Prolonged length of stay	2.99 (1.62–5.52)	Referent	1.02 (0.86–1.20)	1.18 (0.99–1.40)

Note: All models adjusted for effect of patient age, gender, American Society of Anesthesiologists category, history of cardiac disease, history of diabetes, smoking history, history of chronic pulmonary disease, history of neurologic disease, history of end-stage renal disease, exposure to chronic steroids, baseline functional status, and type of urinary diversion. BMI: body mass index; CI: confidence interval.

those of normal weight. Several previous studies also support worse outcomes among malnourished (underweight) patients undergoing RC.[14-17] Poor nutrition in the perioperative setting leads to poor wound healing, increased risk of infection, and an increase in both overall and disease-specific mortality. Although in our patient population the majority did not receive neoadjuvant chemotherapy, the use of neoadjuvant chemotherapy is now standard of care with MIBC treatment, which can further complicate issues of malnutrition.

Previous studies have assigned objective metrics to malnourishment and outcomes for patients undergoing RC. Arora et al[18] showed that hypoalbuminemia (<3.5 g/dL) was independently associated with worse postoperative outcomes in all BMI groups. Although underweight patients were most likely to have hypoalbuminemia, 10–20% of patients within the normal and obese categories were found to have preoperative hypoalbuminemia. Second, patients with sarcopenia undergoing RC have been shown to have worse five-year cancer-specific survival (49% vs. 72%, p=0.003) and overall survival (39% vs. 70%, p=0.003) compared to patients without sarcopenia.[19] Third, BMI stability has been shown in the colorectal cancer literature to be a prognostic metric. Patients who had significant preoperative weight loss were shown to have a poor prognosis.[20]

It is important for urologic oncologists to critically assess patient weight and nutritional status preoperatively, both with regards to intra- and postoperative planning, as well as when counselling patients and families. Enhanced Recovery After Surgery (ERAS) protocols frequently note the importance of perioperative nutrition. While many institutions may have specific protocols regarding preoperative lab work, routine consultation with nutritionists, immunonutrition supplementation, or preoperative carbohydrate or protein loading, there are no specific guidelines related to the best implementation of these measures to improve perioperative nutrition status.[21-23]

The strengths of the NSQIP database include the generalizability of the results and validated outcomes and exposures, however, there are limitations, particularly as it pertains to assessing oncological interventions. These arise due to the specified goal of NSQIP and resultant limitations in data abstraction. Importantly, NSQIP lacks information on tumor stage, grade, and histology. Second, identification of the receipt of interventions, such as chemotherapy or radiotherapy, is limited to 90 days preceding the operative date. As neoadjuvant chemotherapy or salvage cystectomy following radiotherapy may increase the risk of perioperative complications, the inability to accurately capture these may confound the observed relationship. Further, among those identified as having these preoperative factors, there were too few patients to allow for multivariable analysis. Third, in NSQIP, we are unable to ascertain treatment intent. For example, it is impossible to distinguish between a RC undertaken with curative intent and one preformed in a pal-

liative setting. Fourth, BMI is frequently used as a measure of obesity and malnutrition but does not fully represent the perioperative nutrition status of individual patients, nor does it represent actual adipose distribution or muscle density (i.e., sarcopenia), which may be stronger underlying factors in predicting patient outcomes.[15,19] Fifth, our sample size for underweight patients was particularly small and our findings herein require validation in larger cohorts. Finally, there is no validated methodology for reporting Clavien-Dindo complications within NSQIP and, as such, we reported complications according to severity and organ systems.

Conclusions

Patients who are outside of a normal BMI range are more likely to experience major complications, as well as pulmonary complications, infection, bleeding requiring transfusion, and prolonged length of stay following RC for bladder cancer. This likely highlights a higher degree of complexity intraoperatively among obese patients and poorer nutritional status compared to patients of normal weight. While this database has rich patient and comorbidity data, the strength of these conclusions is limited by sample size, selection bias inherent in observational data, and lack of specific oncological detail.

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