



Perioperative complications and in-hospital mortality in radical cystectomy patients with heart-valve replacement

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ABSTRACT

Purpose: To assess in-hospital mortality and complication rates after radical cystectomy (RC) in patients with history of heart-valve replacement.

Materials and methods: Using the National Inpatient Sample (2000–2019), non-metastatic bladder cancer patients undergoing RC were stratified according to history of heart-valve replacement. Regression models (RM) predicted hospital outcomes.

Results: Of 25,535 RC patients, 250 (1.0%) harbored history of heart-valve replacement. Heart-valve replacement patients were older (median 74 vs. 70 years), more frequently male (87.2 vs. 80.6%), and more frequently had Charlson comorbidity index ≥ 3 (26.8 vs. 18.9%). In RC patients with history of heart-valve replacement vs. others, 62 vs. 2634 (24.8 vs. 10.4%) experienced cardiac complications, 28 vs. 3092 (11.2 vs. 12.2%) intraoperative complications, 11 vs. 1046 (4.4 vs. 4.1%) infections, <11 vs. 594 (<4.4 vs. 2.3%) perioperative bleeding, <11 vs. 699 (<4.4 vs. 2.8%) vascular complications, 74 vs. 6225 (29.6 vs. 24.7%) received blood transfusions, 37 vs. 3054 (14.8 vs. 12.1%) critical care therapy (CCT), and in-hospital mortality was recorded in <11 vs. 463 (<4.4 vs. 1.8%) patients. In multivariable RM, history of heart-valve replacement independently predicted cardiac complications (odds ratio 2.20, 95% confidence interval 1.62–2.99; $p < 0.001$). Conversely, no statically significant association was recorded between history of heart-valve replacement and length of stay, estimated hospital cost, intraoperative complications, perioperative bleeding, vascular complications, infections, blood transfusions, CCT use, and in-hospital mortality.

Conclusions: Radical cystectomy patients with history of heart-valve replacement exhibited a 2.2-fold higher risk of cardiac complications, but no other complications, including no significantly higher in-hospital mortality.

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1. Introduction

Radical cystectomy (RC) is guideline-recommended standard treatment in non-metastatic muscle-invasive bladder cancer patients [1–3]. Some RC candidates may have a history of heart-valve replacement which may predispose them to potentially longer length of stay, higher estimated hospital cost, higher intraoperative and postoperative complications as well as to higher in-hospital mortality. However, actual complication and mortality rates after RC in heart-valve replacement patients are unknown.

We addressed this knowledge gap and hypothesized that length of stay, estimated hospital cost, perioperative complication, and in-hospital mortality rates after RC do not differ between patients with vs. without history of heart-valve replacement. To test this hypothesis, we relied on a large-scale population-based cohort of non-metastatic bladder cancer patients undergoing RC within the United States.

2. Materials and methods

2.1. Data source

To test for length of stay, estimated hospital cost, perioperative complications, and in-hospital mortality after RC, we relied on discharge data from the National Inpatient Sample (NIS 2000–2019). The NIS is a set of longitudinal hospital inpatient databases included in the Healthcare Cost and Utilization Project and formed by the Agency for Healthcare Research and Quality through a Federal-State-Industry partnership [4]. All diagnoses and procedures were coded using the International Classification of Disease (ICD) 9th revision Clinical Modification (ICD-9-CM), ICD 10th revision Clinical Modification (ICD-10-CM), as well as ICD 10th revision Procedure Coding System (ICD-10-PCS).

2.2. Study population

We focused on patients with a primary diagnosis of bladder cancer (ICD-9-CM codes 188.0–188.6, 188.8, 188.9, and ICD-10-CM codes C67.0–C67.6, C67.8, C67.9) aged ≥ 18 years. Only patients treated with radical cystectomy were included according to previously reported methodology [5,6]. Patients with a diagnosis of lymph node invasion or metastatic stage (ICD-9-CM codes 196. x, 197. x, 198. x, and ICD-10-CM codes C77. x, C78. x, C79. x) were excluded [6]. Additionally, patients were stratified according to history of heart-valve replacement (ICD-9-CM codes V42.2, V43.3, and ICD-10-CM codes Z95.2–Z95.4) [7].

2.3. Definition of variables for analyses

Study endpoints consisted of length of stay, intraoperative and postoperative complications (bleeding, cardiac complications, vascular complications, infections, and transfusions) [6,8,9], in-hospital mortality, and use of critical care therapies (CCT), defined as invasive mechanical ventilation, insertion of percutaneous endoscopic gastrostomy tube, dialysis for acute kidney failure, total parenteral nutrition, and tracheostomy identified by ICD-9 and ICD-10 codes according to previously established methodology [10–12]. Additionally, estimated hospital cost were calculated relying on total hospital charges provided by the NIS. Converting total hospital charges into estimated hospital cost was performed using HCUP Cost-to-Charge Ratios which were based on hospital accounting reports, according to NIS methodological guidelines [4,6]. All calculations were adjusted to 2019 United States dollar relying on the overall Consumer Price index [13]. To account for comorbidities, the Deyo modification of Charlson comorbidity index (CCI) was used [14], according to coding algorithms for defining comorbidities in ICD-9-CM and ICD-10-CM codes by Quan et al. [15]. Covariates consisted of patient characteristics including age at admission (years, continuously coded), sex (female vs. male), and CCI (0 vs. 1 vs. 2 vs. ≥ 3),

as well as hospital characteristics including hospital region (West vs. Midwest vs. Northeast vs. South), and teaching hospital status (non-teaching vs. teaching).

2.4. Statistical analyses

First, patient and hospital characteristics as well as perioperative length of stay, estimated hospital cost, perioperative complications, and in-hospital mortality rates were tabulated. Medians and interquartile ranges (IQR) were recorded for continuously coded variables. Frequencies and proportions were recorded for categorical variables. Wilcoxon rank sum test, Pearson's Chi-square test, and Fisher's exact test were applied. Second, estimated annual percentage changes (EAPC) were assessed with the least squares linear regression. Third, univariable and multivariable Poisson regression models predicting length of stay and estimated hospital cost, as well as logistic regression models predicting perioperative complications and in-hospital mortality were fitted after adjustment for clustering at the hospital level using generalized estimating equation methodology [11,12]. To account for multiple testing, additional Bonferroni correction was applied ($n = 10$).

All analyses and their reporting followed the NIS reporting guidelines [4]. Due to NIS data reporting agreement, only sample sizes of at least eleven patients could be reported. In consequence, for sample sizes of less than eleven observations, counts and associated proportions were reported as less than eleven. Nevertheless, all reported p-values are based on exact patient numbers within the NIS. Due to the anonymously coded design of the NIS, study-specific ethics approval was waived by the institutional review board. All tests were two sided, with a significance level set at $p < 0.05$. R software environment was used for statistical computing and graphics (R version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) [16].

3. Results

3.1. Descriptive characteristics of the study population

Within the NIS, we identified 25,535 non-metastatic bladder cancer patients who underwent radical cystectomy between 2000 and 2019. Of those, 250 (1.0%) patients had a history of heart-valve replacement (Table 1). Over time, the proportion of patients with history of heart-valve replacement ranged from 0.5 to 1.7% per year without a detectable increase or decrease (EAPC +1.9%, 95% confidence interval [CI] -0.4 to $+4.4\%$; $p = 0.1$). Patients with history of heart-valve replacement were older (median age 74 vs. 70 years; $p < 0.001$), more frequently male (87.2 vs. 80.6%; $p < 0.001$), and more frequently had CCI ≥ 3 (26.8 vs. 18.9%; $p < 0.001$). According to hospital characteristics, patients with history of heart-valve replacement were less frequently treated in the South (24.0 vs. 35.1%; $p = 0.003$), and in non-teaching hospitals (16.4 vs. 22.2%; $p = 0.03$).

3.2. Length of stay, estimated hospital cost, perioperative complications, and mortality rates

In RC patients with history of heart-valve replacement vs. others, median length of stay was 8 vs. 8 days (IQR 6–12 vs. 6–11 days; $p = 0.2$; Table 2). Estimated median hospital cost were 90,504 vs. 78,940 \$USD (IQR 58,908–133,905 vs. 54,214–121,643 \$USD; $p = 0.03$). Regarding perioperative complications, 62 vs. 2634 (24.8 vs. 10.4%; $p < 0.001$) experienced cardiac complications, 28 vs. 3092 (11.2 vs. 12.2%; $p = 0.6$) intraoperative complications, 11 vs. 1046 (4.4 vs. 4.1%; $p = 0.8$) infections, < 11 vs. 594 (< 4.4 vs. 2.3%; $p = 0.4$) perioperative bleeding, < 11 vs. 699 (< 4.4 vs. 2.8%; $p = 0.5$) vascular complications, 74 vs. 6255 (29.6 vs. 24.7%; $p = 0.08$) received blood transfusions, and 37 vs. 3054 (14.8 vs. 12.1%; $p = 0.2$) received CCT. In-hospital mortality was recorded in < 11 vs. 463 (< 4.4 vs. 1.8%; $p = 0.5$) patients (actual counts and actual proportions are not shown due to NIS reporting rules).

Table 1

Descriptive characteristics of 25,535 non-metastatic bladder cancer patients, undergoing radical cystectomy, stratified according to history of heart-valve replacement.

Characteristic	Heart-valve replacement, n = 250 (1.0%)	No heart-valve replacement, n = 25,285 (99.0%)	p-value ^a
Age at admission, median (IQR in years)	74 (68, 78)	70 (62, 76)	< 0.001
Male sex, n (%)	218 (87.2%)	20,386 (80.6%)	< 0.001
Charlson comorbidity index, n (%)			< 0.001
0	70 (28.0%)	10,002 (39.6%)	
1	49 (19.6%)	5533 (21.9%)	
2	64 (25.6%)	5059 (20.0%)	
≥3	67 (26.8%)	4691 (18.9%)	
Hospital region, n (%)			0.003
West	54 (21.6%)	4845 (19.2%)	
Midwest	80 (32.0%)	6669 (26.4%)	
Northeast	56 (22.4%)	4891 (19.3%)	
South	60 (24.0%)	8880 (35.1%)	
Teaching hospital status, n (%)			0.03
Large (≥400 beds)	178 (71.2%)	17,835 (70.5%)	
Medium (200–399 beds)	47 (18.8%)	4806 (19.0%)	
Small (<200 beds)	25 (10.0%)	2537 (10.0%)	

^a Wilcoxon rank sum test; Pearson’s Chi-squared test. Abbreviation: IQR = Interquartile range.

Table 2

Perioperative length of stay, complications, and in-hospital mortality rates after radical cystectomy in 25,535 non-metastatic bladder cancer patients, stratified according to history of heart-valve replacement.

Characteristic	Heart-valve replacement, n = 250 (1.0%)	No heart-valve replacement, n = 25,285 (99.0%)	p-value ^a
Length of stay, median (IQR in days)	8 (6, 12)	8 (6, 11)	0.2
Estimated hospital cost, median (IQR in \$USD)	90,504 (58,908, 133,905)	78,940 (54,214, 121,643)	0.03
Intraoperative complications, n (%)	28 (11.2%)	3092 (12.2%)	0.6
Perioperative bleeding, n (%)	<11 (<4.4%)	594 (2.3%)	0.4
Postoperative complications			
Cardiac complications, n (%)	62 (24.8%)	2634 (10.4%)	< 0.001
Vascular complications, n (%)	<11 (<4.4%)	699 (2.8%)	0.5
Infections, n (%)	11 (4.4%)	1046 (4.1%)	0.8
Blood transfusions, n (%)	74 (29.6%)	6255 (24.7%)	0.08
Critical care therapy, n (%)	37 (14.8%)	3054 (12.1%)	0.2
In-hospital mortality, n (%)	<11 (<4.4%)	463 (1.8%)	0.5

^a Wilcoxon rank sum test; Pearson’s Chi-squared test; Fisher’s exact test. Abbreviation: IQR = Interquartile range.

3.3. Multivariable regression models

In multivariable regression models, history of heart-valve replacement independently predicted cardiac complications (multivariable odds ratio [OR] 2.20, 95% CI 1.62–2.99; $p < 0.001$; Table 3). Conversely, no statically significant association was recorded between history of heart-valve replacement and length of stay ($p = 0.7$), estimated hospital cost ($p = 0.2$), intraoperative complications ($p = 0.3$), perioperative bleeding ($p = 0.4$), vascular complications ($p = 0.3$), infections ($p = 0.7$), blood transfusions ($p = 0.2$), CCT use ($p = 0.7$), and in-hospital mortality ($p = 0.9$) after RC. Even after Bonferroni correction for multiple testing that consisted of ten multiple models addressing ten different endpoints, the association between history of heart-valve replacement and cardiac complications remained statistically significant (Bonferroni-corrected $p = 0.00000044$ vs. prior to Bonferroni correction $p = 0.0000044$).

4. Discussion

In non-metastatic bladder cancer patients undergoing RC, the association between history of heart-valve replacement and length of stay, estimated hospital cost, perioperative complications, as well as in-hospital mortality is unknown. To address this knowledge gap, we relied on a 20-year comprehensive population-based cohort within the

Table 3

Univariable and multivariable regression models addressing perioperative length of stay, complications and in-hospital mortality according to history of heart-valve replacement (reference no history of heart-valve replacement) in 25,535 non-metastatic bladder cancer patients undergoing radical cystectomy after adjustment for clustering at the hospital level using generalized estimating equation methodology.

Outcome of interest	Univariable		Multivariable ^a	
	RR/OR (95% CI)	p-value	RR/OR (95% CI)	p-value
Length of stay	1.00 (0.93, 1.08)	1.0	1.03 (0.89, 1.20)	0.7
Estimated hospital cost	1.02 (0.93, 1.13)	0.7	0.86 (0.68, 1.10)	0.2
Intraoperative complications	0.90 (0.62, 1.31)	0.6	0.83 (0.57, 1.22)	0.3
Perioperative bleeding	0.69 (0.25, 1.86)	0.5	0.63 (0.23, 1.71)	0.4
Postoperative complications				
Cardiac complications	2.81 (2.10, 3.75)	0.000000000024	2.20 (1.62, 2.99)	0.00000044^b
Vascular complications	0.73 (0.31, 1.73)	0.5	0.62 (0.26, 1.48)	0.3
Infections	1.08 (0.60, 1.93)	0.8	0.90 (0.50, 1.63)	0.7
Blood transfusions	1.25 (0.97, 1.62)	0.08	1.20 (0.91, 1.58)	0.2
Critical care therapy	1.25 (0.89, 1.77)	0.2	1.08 (0.75, 1.54)	0.7
In-hospital mortality	1.33 (0.60, 2.96)	0.5	1.06 (0.46, 2.41)	0.9

Abbreviations: CI = confidence interval; RR = rate ratio; OR = odds ratio.
^a Adjusted for age at admission, sex, comorbidities (Charlson comorbidity index), hospital region, and teaching hospital status.
^b After Bonferroni correction: $p = 0.0000044$.

NIS and made several important findings.

First, we identified important differences in descriptive characteristics between RC patients with vs. without history of heart-valve replacement. Specifically, patients with history of heart-valve replacement were older (median age 74 vs. 70 years; $p < 0.001$), and sicker (CCI ≥ 3 26.8 vs. 18.9%; $p < 0.001$). As expected, such patients more frequently underwent RC in teaching hospitals (83.6 vs. 77.8%; $p = 0.03$). Based on these differences, analyses addressing adverse in-hospital outcomes, such as the current analyses, require detailed multivariable adjustment for baseline patient and institutional variables, as was done in the present study.

Second, we postulated that adverse in-hospital outcomes will not be significantly higher in heart-valve replacement patients than other RC patients. The most important adverse outcome consists of in-hospital mortality. Testing for in-hospital mortality rates revealed no significant differences (<4.4 vs. 1.8%; $p = 0.5$). Furthermore, multivariable models predicting in-hospital mortality failed to identify history of heart-valve replacement as an independent predictor of this outcome ($p = 0.9$). This observation is extremely important in medical decision-making regarding use of RC relative to RC alternatives, such as trimodal therapy (TMT) or its derivatives, namely radiotherapy without chemotherapy or chemotherapy without radiotherapy after transurethral resection of the bladder (TURB). Specifically, clinicians may reassure patients with history of heart-valve replacement that the risk of in-hospital death should not discourage them from considering RC as the gold standard option for muscle-invasive bladder cancer.

Third, we also tested for differences in nine remaining adverse in-hospital outcomes between history of heart-valve replacement vs. other RC patients. Of those nine comparisons, only one revealed higher complication rates. Specifically, the rate of cardiac complications was 24.8 vs. 10.4% ($p < 0.001$). After multivariable adjustment for patient and hospital characteristics, patients with history of heart-valve replacement exhibited a 2.2-fold higher cardiac complication rate than other RC patients. The importance of this multivariable observation remained statistically significant even after strictest adjustment for multiple testing using the Bonferroni correction (after vs. prior to Bonferroni correction: $p = 0.0000044$ vs. $p = 0.0000044$). Conversely, none of the remaining eight adverse endpoints, namely length of stay ($p = 0.7$), estimated hospital cost ($p = 0.2$), intraoperative complications ($p = 0.3$), perioperative bleeding ($p = 0.4$), vascular complications ($p = 0.3$), infections ($p = 0.7$), blood transfusions ($p = 0.2$), and CCT use ($p = 0.7$), neither demonstrated differences in proportions prior multivariable adjustment nor exhibited statistical significance after multivariable testing.

Taken together, RC patients with history of heart-valve replacement harbor less favorable patient characteristics, such as older age and higher comorbidity burden (CCI ≥ 3). Despite these baseline disadvantages, heart-valve replacement patients were not at higher risk of in-hospital mortality or other eight standard in-hospital outcomes, such as length of stay, estimated hospital cost, intraoperative complications, perioperative bleeding, vascular complications, infections, blood transfusions, and CCT use. However, heart-valve replacement patients exhibited a higher rate of cardiac complications than other RC patients. This rate translated into a 2.2-fold higher multivariable rate of such complications. Despite the presence of this untoward association with one of the examined adverse endpoints, patients with history of heart-valve replacement requiring RC may be reassured that such procedure does not expose them at a significant higher risk of in-hospital mortality and any other standard adverse in-hospital outcomes. These observations are essential to convey to RC candidates at medical decision-making and counselling prior to definitive therapy assignment.

The present study has inherent limitations. First and foremost, due to the retrospective nature of the NIS, selection and reporting biases may have remained. This limitation applies to the current study as well as to all previous analyses relying on the NIS [6,8,9,17] or other large-scale retrospective databases, such as the Surveillance Epidemiology and

End Results database [18,19], and the National Cancer Database [20]. Second, despite its very large size, NIS still offers information about a very limited number of patients with history of heart-valve replacement due to the rarity of this condition, especially in RC patients. In consequence, sample size prevented specific subgroup analyses according to type of heart-valve replacement, namely prosthetic vs. xenogenic vs. other. Third, ICD-9 and ICD-10 codes within the NIS may systematically underestimate some perioperative complication rates. However, the inherent biases associated with this methodology are equally applicable to both patients with vs. without history of heart-valve replacement. Fourth, the NIS does not allow the calculation of certain hospital-specific variables after 2011. Therefore, performing state-level specific analyses and calculating conflating hospitalization cost were not possible. Due to patient-specific considerations, the reported perioperative outcomes are not meant to be related to the general population of the United States. Therefore, weighting according to discharge was not applied in the current analyses. Additionally, the amount of detail included in the current analysis was also limited due to the nature of the NIS. For example, timing, duration, and dose of anticoagulation as well as disease process-specific variables were not available. Moreover, although cardiac complications were reported, the amount of detail regarding their nature was limited. Last but not least, the NIS exclusively provides in-hospital data. Unfortunately, data after the index admission are not available. Nevertheless, the present study provides important and new insights into the perioperative risks of RC patients with history of heart-valve replacement.

5. Conclusions

Radical cystectomy patients with history of heart-valve replacement exhibited a 2.2-fold higher risk of cardiac complications, but no other complications, including no significantly higher in-hospital mortality.

CRedit authorship contribution statement

Carolyn Siech: Conceptualization, Conception and design, Data curation, Funding acquisition, Data acquisition, Data curation, Data analysis and interpretation, Writing – original draft, Drafting the manuscript, Formal analysis, Statistical analysis. **Andrea Baudo:** Conceptualization, Conception and design, Writing – review & editing, Editing and review the manuscript, Formal analysis, Statistical analysis. **Mario de Angelis:** Conceptualization, Conception and design, Writing – review & editing, Editing and review the manuscript, Formal analysis, Statistical analysis. **Letizia Maria Ippolita Jannello:** Conceptualization, Conception and design, Writing – review & editing, Editing and review the manuscript, Formal analysis, Statistical analysis. **Francesco Di Bello:** Conceptualization, Conception and design, Writing – review & editing, Editing and review the manuscript, Formal analysis, Statistical analysis. **Jordan A. Goyal:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript, Formal analysis, Statistical analysis, All authors read and approved the final manuscript. **Zhe Tian:** Data acquisition, Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript, Formal analysis, Statistical analysis. **Fred Saad:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Shahrokh F. Shariat:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Nicola Longo:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Luca Carmignani:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Ottavio de Cobelli:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Alberto Briganti:** Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Marina Kosiba:** Data curation, Writing – review & editing,

Editing and review the manuscript. **Philipp Mandel**: Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Luis A. Kluth**: Data curation, Data analysis and interpretation, Writing – review & editing, Editing and review the manuscript. **Felix K.H. Chun**: Conceptualization, Conception and design, Writing – review & editing, Editing and review the manuscript. **Pierre I. Karakiewicz**: Data curation, Data acquisition, Writing – review & editing, Editing and review the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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