

ASSOCIATION BETWEEN RISK FACTORS AND COMPLICATIONS IN RADICAL CYSTECTOMY PATIENTS

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Abstract: Radical cystectomy is considered first-line management in patients with muscle-invasive bladder cancer, and since radical cystectomy is associated with a high rate of complications, a comprehensive study to evaluate risk factors for this surgery is of utmost importance to optimize the treatment to the patient. In this single-center, retrospective cohort study, patients admitted for a Radical cystectomy from July 2016 to December 2019 had their demographics, lab parameters, and outcomes recorded. The study included 36 patients, of which 31(86%) were males. There was no significant association between gender, smoking status, comorbid, ASA score, and presence of CKD, pre-op hydronephrosis, and lymph node status. However, patients with pre-op serum albumin \leq 3.5 had 7.8 times higher odds of post-op complications than those with pre-op serum albumin >3.5, adjusting for chronic kidney disease. The p-value was statistically significant (p=0.03). Only low serum albumin was statistically associated with poor outcomes. Other factors studied were not significantly associated with an adverse result. There is still much controversy regarding the risk factors that increase the risk of complications after RC; as such, more studies are needed to establish them in the RC setting fully.

Keywords: Risk Factors, Complications, Chronic kidney disease, Radical Cystectomy

Introduction

Bladder cancer is the most frequently occurring malignancy of the urogenital system (Hollenbeck et al., 2005). It is the ninth most commonly occurring urinary system cancer, 7th in males and 17th in females (Ploeg et al., 2009). Various studies have established multiple risk factors for bladder cancer; smoking is the most common. Other identified risk factors include age, genetic predisposition, recurrent urinary tract infection, exposure to aromatic amines, schistosomiasis, and consumption of coffee, tea, and alcohol (Janković and Radosavljević, 2007).

Bladder cancer can be muscle-invasive or nonmuscle-invasive. Unfortunately, more than 30% of bladder cancer is muscle invasive at diagnosis (Pycha et al., 2008). The current gold standard of treatment for local control of muscle-invasive bladder cancer is the Radical Cystectomy with Pelvic lymph nodes dissection(Mannas et al., 2019). Radical cystectomy is an extensive surgery with many complications and is usually divided into early and late (Abrahamyan et al.). Different studies reported different rates of complications ranging from 25.7 to 64% (Hautmann et al., 2010).

There are multiple risk factors associated with complications following open radical cystectomy. They can be modifiable and non-modifiable risk factors. In various studies, the possible risk factors that increase the rate of complications after open radical cystectomy are divided into three groups, i.e., pre-operative (associated with patients' demographic and comorbid), per-operative (related to surgery) and post-operative risk factors (mainly associated with total length of stay in hospital and GI stimulation) (Bagrodia et al., 2009; Stimson et al., 2010).

Our study aims to determine the incidence of complications and identify potential risk factors that lead to complications after radical cystectomy.

Methodology

A single-center, retrospective cohort study using consecutive non-probability sampling was conducted

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in the Department of Urology, The Indus Hospital, Karachi, after the approval of the study from the Institutional Review Board. Previous data of all the patients who underwent Radical Cystectomy from July 2016 to December 2018 were analyzed. Their weight, height, comorbid, and other clinical and demographic variables were noted. Operative findings, number of transfusions, hospital stay, and post-operative recovery and infection were considered. Patients whose data are missing or incomplete will be excluded from the study.

All the collected data was entered in SPSS version 21.Mean ± Standard deviation calculated for continuous variables like age, weight, height, etc. Frequency & percentage were calculated for categorical variables. An Independent t-test or Fisher's exact test was used to compare continuous variables, and a chi-square test was used to compare categorical variables. $P \le 0.05$ will be considered significant.

Results

A total of 36 patients were enrolled in the study. Out of which, 31 (86.%) were males and only 5 (13.9%) were females, with median (IQR) age was 61(53.3-67.5) years. On average (±SD) height, weight and BMI of the patients was 158.4±11.2 cm, 57.4±12.5 kg and 22.8±4.3 Kg/m2 respectively

18 patients were found to have co-morbidities, out of which 5 (18.5%) were diabetic, 7 (25.9%) were hypertensive, 15 (55.6%) had CKD, 2 (7.4%) had IHD and 2 (7.4%) had respiratory disease. The majority (n=6, 16.7%) had an ASA score of I, 18 (50%) had ASA score of II, 9 (25%) had ASA score of III, 1 (2.8%) had ASA score of IV, and 2 (5.6%) had missing info. 21 (58.3%) had pre-op hydronephrosis. Of these 21 patients, 10 (47.6%) had bilateral hydronephrosis, 6 (28.6%) had left hydronephrosis, and 5 (23.8%) had hydronephrosis on the right side. Moreover, results showed no significant difference in age, BMI, pre-op serum creatinine, pre-op Hb, number of lymph nodes removed, duration of surgery, and length of stay in ICU between the patients who had post-op complications and those who had no post-

op complications (Table 1).

	ic of study populati			D 17 1	
Gender (Male/Female)	Mean±SD	Min-Max	Median(IQR)	P-Value	
Age (years)					
Male	61.7±11	30-86	62(54-69)	0.052 ^t	
Female	47.8±17.5	17-58	56(33.5-58)		
BMI					
Male	22.8±4.4	14.7-33.3	23.7(18.5-25.5)	0.818 ^I	
Female	23.2±4.3	18.1-27.7	25.6(18.6-26.7)		
Pre-operative Crea	atinine (mg/dl)		1	· · · · · ·	
Male	1.4±0.7	0.5-3.8	1.2(1-1.6)	0.876 [†]	
Female	1.3±0.3	1-1.7	1.4(1-1.6)		
Pre-operative Seru	ım Albumin				
Male	3.6±0.5	2.4-4.3	3.8(3.2-4)	0.494 [†]	
Female	3.4±0.7	2.8-4.4	3.4(2.8-4)		
Pre-operative Hb (mg/dl)				
Male	11±2	5.7-15.8	11(10.1-12.3)	0.383 ¹	
Female	11.8±1.2	10.9-13.8	11.6(11-12.9)		
operation duration	(hours)				
Male	6±1	4.3-8.3	6(5-6.8)	0.940 ¹	
Female	6±0.6	5.3-7	6(5.5-6.5)		
Number of lymph	nodes removed				
Male	17.4±5.8	9-27	16.5(12.5-22)	0.899 [‡]	
Female	17±5.4	10-25	16(13-21.5)		
duration of stay in	ICU				
Male	3.8±3.6	2-19	3(2-4)	0.372 ⁺	

Female	4±2.3	2-8	3(2.5-6)			
Post-operation duratio	Post-operation duration of stay in hospital					
Male	12±5.9	7-37	10(8-13)	0.872 [†]		
Female	12.2±7.4	6-25	10(7.5-18)			
Total duration of hospital stay						
Male	16.3±7.8	9-40	14(10-20)	0.695 [†]		
Female	15.2±7.3	10-28	12(11-21)			

Also, no significant association between gender, smoking status, comorbid, ASA score, pre-op hydronephrosis, lymph node status, intra-op transfusion, and post-op transfusion with post-op complications were seen. (Table 2&3).

Table 2: Comparison of Quantitative variables in patients who had complications with the non-complication	
group:	

Complications (Yes, NO)	Mean ±SD	Min-Max	Median(IQR)	P value	
Age (years)					
No	59.5±10	30-74	60(53.5-65.8)	0.877 ^I	
Yes	60.1±15.9	17-86	61(52.5-70.3)		
BMI					
No	23.8±4.6	14.7-33.3	24.9(21.3-26.2)	0.142 [†]	
Yes	21.6±3.8	15.5-28.4	21.7(18.4-24.4)		
Pre-operative Creatini	ne (mg/dl)				
No	1.2±0.4	0.5-2.5	1.1(1-1.5)	0.524 ⁺	
Yes	1.5±0.9	0.7-3.8	1.4(0.9-1.6)		
Pre-operative Serum A	lbumin (mg/dl)			I	
No	3.7±0.6	2.4-4.4	3.9(3.5-4.1)	0.030*1	
Yes	3.4±0.5	2.4-4.2	3.3(3.1-3.8)		
Pre-operative Hb (mg/	dl)				
No	11.5±2	5.7-15.8	11.2(10.6-12.5)	0.259 [±]	
Yes	10.7±1.8	7.5-15.4	11(9.5-11.5)		
operation duration (ho	ours)				
No	6.1±1	4.3-8.3	6(5.4-6.9)	0.597 ⁺	
Yes	5.9±1	4.5-8	6(5-6.3)		
Number of lymph node	es removed				
No	16.3±5.4	9-24	16(10-22)	0.225 [†]	
Yes	18.7±5.9	9-27	17.5(15-25.3)		
duration of stay in ICU	J				
No	2.8±0.8	2-4	3(2-3)	0.296 ^t	
Yes	5.1±4.8	2-19	3(2-7.3)		
Post-operative duratio	n of stay in hosp	oital			
No	9.9±2.4	6-16	10(8-10.8)	0.029* [†]	
Yes	14.8±7.9	7-37	13(9-18.8)		
Total duration of hosp	ital stay				
No	13.8±4.9	10-28	12.5(10-14.8)	0.056 [†]	
Yes	19.1±9.5	9-40	15(12-25.3)		

*P-value<0.05, **P-value<0.0001; I Independent sample T-test, I Mann Whitney U test

Complications (Yes, NO)	No n(%)	Yes n(%)	Total n(%)	P-Value
Gender				
Male	17(85)	14(87.5)	31(86.1)	1.000 ^t
Female	3(15)	2(12.5)	5(13.9)	
Smoking status				
No	8(42.1)	9(56.3)	17(48.6)	0.404 ^I
Yes	11(57.9)	7(43.8)	18(51.4)	
Comorbid				
No	6(30)	3(18.8)	9(25)	0.700^{1}
Yes	14(70)	13(81.3)	27(75)	_
CKD				
No	15(75)	6(37.5)	21(58.3)	0.023* ^I
Yes	5(25)	10(62.5)	15(41.7)	
ASA score				
I	3(15)	3(21.4)	6(17.6)	0.883 [†]
II	10(50)	8(57.1)	18(52.9)	
III	6(30)	3(21.4)	9(26.5)	
IV	1(5)	0(0)	1(2.9)	
Pre-operative hydronephrosis				
No	10(50)	5(31.3)	15(41.7)	0.257 [‡]
Yes	10(50)	11(68.8)	21(58.3)	
Lymph nodes status				
N	0(0)	1(6.3)	1(2.8)	0.761 ⁺
NO	10(50)	10(62.5)	20(55.6)	
N1	2(10)	1(6.3)	3(8.3)	
N2	7(35)	3(18.8)	10(27.8)	
Nx	1(5)	1(6.3)	2(5.6)	
Metastasis				
M0	18 (90)	16(100)	34(94.4)	0.492 [†]
Mx	2(10)	-	2(5.6)	
Total Intraoperative transfusion	20(100)	16(100)	36(100)	
No	8(40)	6(40)	14(40)	1.000 [±]
Yes			21(60)	1.000
Yes Post-operative transfusion	12(60)	9(60)	21(00)	
No	6(30)	6(37.5)	12(33.3)	0.635 [†]
Yes	14(70)	10(62.5)	24(66.7)	
Pre-operative Acute Kidney I	njury			
No	17(85)	10(62.5)	27(75)	0.146^{1}
Yes	3(15)	6(37.5)	9(25)	

Table 3: Comparison of Qualitative variables in patients who had complications with the non-complication	
group:	

*P-value<0.05, **P-value<0.0001, †Chis-square test, & Fisher exact test

Additionally, results revealed that those who had postop complications had significantly low pre-op serum albumin in comparison to those who did not develop post-op complications (Median: 3.3 vs 3.9, p=0.03).

Table 4. Multivariable binary logistic regression

	adjusted OR	95% CI	P-value
Albumin	7.8	1.31-98.97	0.03
CKD	5.9	0.927-37.180	0.06

Also, the length of post-op hospital stays and total duration of hospital stay was higher in patients who had post-op complication than those who did not (p=0.029 and 0.056, respectively, Table 1).

The multivariable logistic regression analysis included all the variables with p-value < 0.25 in the univariate analysis. The results showed that patients with pre-op serum albumin \leq 3.5 had 7.8 times higher odds of post-op complications than those with pre-op serum albumin >3.5, adjusting for chronic kidney disease. The p-value was statistically significant (p=0.03, Table 4). Also, data showed that patients who had chronic kidney disease had 5.9 times higher odds of post-op complication than those who had no CKD adjusting for pre-op serum albumin, though the result was not statistically significant (p=0.06, Table 4)

Discussion

Any surgery presents with its intra and post-operative complications, and the variation in patients adds to the complexity of the risk of the surgery. Radical cystectomy is currently the procedure for patients with high-risk and muscle-invasive bladder cancer, with one of the highest complication rates in urological practice(Peng et al., 2020; Schulz et al., 2018). For a complex surgery like radical cystectomy (RC), which is a real challenge to urologists worldwide, identifying pre-operative predictors of outcome is of utmost importance(D'Elia et al., 2017). Identifying these factors would greatly help in the preoperative counseling of patients on his/her risk and also minimize those modifiable factors which might enhance the outcome of the surgery(Mannas et al., 2019).

Our patients had ASA score I, 18 (50%) had ASA score II, 9 (25%) had ASA score III, 1 (2.8%) had ASA score IV, and 2 (5.6%) had missing info. However, there was no significant association between the ASA score and post-operative complications. Furrer et al. reviewed 912 patients but found no significant association with post-operative complications(Furrer et al., 2018). Mannas et al. also checked to see if ASA score was associated with postoperative complications and found that patients with ASA 3-4 had a significantly more prolonged hospital stay than patients with scores 1-2(Mannas et al., 2019). Schulz et al. concluded that patients with ASA>3 had about twice the risk of mortality and morbidity compared to patients with ASA 1-2 (Schulz

Nutritional status is considered a confounding factor in a cancer patient's response to surgical stress(Allaire et al., 2017). BMI is a modifiable risk factor that provides the basis for any lifestyle modification to decrease the chances of complications after surgery. Concerning Obesity, there has been some conflicting data, with some authors failing to find any adverse complications associated with Obesity(Gierth et al., 2018; Hirobe et al., 2018)- like our study did, with other studies proving the opposite(Chromecki et al., 2013; Johnson et al., 2015). Allaire et al. reviewed around 30 studies involving BMI, which mainly concluded that BMI >30 increases the risk of venous thromboembolism and adverse risk factors(Allaire et al., 2017). A recent study by Lenardis et al. reviewed the complication rate of 3930 patients. It concluded that patients who had a BMI above or lower than that of normal were more likely to experience major complications such as pulmonary complications (p=0.003), infectious complications (p<0.001), bleeding requiring transfusion (p=0.01), and length of stay (p=0.001)(Lenardis et al., 2020).

Our study showed that patients with pre-op serum albumin ≤3.5g/dl had 7.8 times higher odds of postop complications than those with pre-op serum albumin >3.5g/dl. This finding was echoed by many studies, namely Garg et al., which found that low albumin levels were associated with increased rates of complications in 90 days (Garg et al., 2014). Bhalla et al. also determined that a pre-op albumin level of <4g/dl was associated with increased hospital stay post-RC (Bhalla et al., 2017). Many studies also significantly associated A low albumin level with increased mortality (Chan et al., 2013; Marques Bernardino et al., 2018; Morgan et al., 2011). One thousand nine hundred sixty-eight patients were reviewed in a series by Lyon et al., with 112 requiring reoperation after radical cystectomy. The study revealed that an albumin<3.5g/dl was associated with an increased risk (odds ratio 2.15, 95% CI 1.28-3.59, P = 0.004) of reoperation (Lyon et al., 2019). A systematic review including 29 studies that looked into the effect of nutritional status on the outcome of RC revealed that an albumin level of <3.5g/dl increased the risk of 30-day complications (OR 1.56, 95% CI 1.07-2.35) and was a predictor of worse 3year overall survival (OS) (HR 1.86, 95% CI 1.32-2.66)(Ornaghi et al., 2020).

Of the 15 patients who suffered from CKD, 10 had post-operative complications (p=0.02). Similarly, Johnson et al. reported an increase in significant morbidity and mortality, with less than 15% overall survival at 5 years for dialysis patients undergoing RC(Johnson et al., 2015). Hamano et al. evaluated 215 patients who had CKD out of 581 patients who underwent RC. They also concluded that CKD patients had a much lower survival probability than

those without CKD(Hamano et al., 2017). Sefik et al. reviewed 132 patients, with 46 patients having glomerular filtration rate (GFR) <60ml/min/1.73m². Unfortunately, those patients' overall mortality was higher than those with a GFR>60ml/min/1.73m²(Sefik et al., 2020). These findings were again echoed in a study by Sefik et al. which found that patients having a GFR<60 ml/s had an overall higher mortality(Sefik et al., 2020).

Our study did not find any significant association between smoking and poor outcome after RC. Inhalation of tobacco smoke has many adverse effects on the human body, and given the diverse pathophysiological effects, a smoking history is a recognized factor of peri-operative morbidity and mortality across most surgical procedures(Sopori, However, the association 2002). between complications after RC and smoking has not been clearly defined (Gandaglia et al., 2014; Lavallée et al., 2014: Sood et al., 2017). Sathianathen et al. compared 850 smokers with 850 nonsmokers undergoing RC and found that the overall incidence of Clavien III-V complications was higher in smokers (13.1% vs 7.4%, p<0.001)(Sathianathen et al., 2018). Reese et al. reviewed 633 out of the 10,848 patients who underwent reoperation after RC. They found that smoking (OR1.34 [1.11–1.63], P < 0.01) was a definite risk factor contributing to reoperation(Reese et al., 2019).

Conclusion

Our results showed no significant association between gender, smoking status, comorbid, ASA score, pre-op hydronephrosis, and presence of CKD, lymph node status, intra-op transfusion, and post-op transfusion with post-op complications. However, low albumin levels were significantly associated with a risk of complications. There is still much controversy regarding the risk factors that increase the risk of complications after RC; as such, more and more studies are needed to establish them in the RC setting fully.

Conflict of interest

The authors declared absence of conflict of interest.

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