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Article

Transfusion in Radical Cystectomy Increases Overall Morbidity and Mortality: A Retrospective Study Using Data from the American College of Surgeons—National Surgical Quality Improvement Program

Christian H. Ayoub, Nassib F. Abou Heidar, Alexandre K. Armache, Elia Abou Chawareb and Albert El Hajj *

Department of Surgery, Division of Urology, American University of Beirut Medical Center, Riad El Solh, P.O. Box 11-0236, Beirut 1107 2020, Lebanon; eaa35@aub.edu.lb (E.A.C.)
* Correspondence: ae67@aub.edu.lb; Tel.: +961-1-350000 (ext. 5246)

Abstract: Background: Radical cystectomy is a complex procedure imposing significant post-operation complications. **Objective**: Explore the impact of peri-operative pRBC transfusion on mortality and overall morbidity in a matched cohort. Methods: The American College of Surgeons—National Surgical Quality Improvement Program's (ACS-NSQIP) dataset was used to select patients who underwent RC in 2008–2019. Patients who witnessed pre-operative transfusion and emergency cases were excluded. Peri-operative pRBC transfusion was defined as an intra-operative or up to 24-h post-operative pRBC transfusion. We matched patients who underwent peri-operative pRBC transfusion to patients who did not receive transfusion. Length of stay, mortality, and overall morbidity were compared between the two matched cohorts. **Results**: The match cohort was matched on all pre-operative demographics and medical history variables and yielded 3578 matched patients. Patients who underwent peri-operative pRBC transfusion had a longer length of hospital stay (9.3 days) as compared to patients who did not undergo transfusion (8.13 days) ($p < 0.001$). Furthermore, patients who underwent transfusion also had higher odds of mortality (OR = 1.934) and overall morbidity (OR = 1.443) ($p < 0.03$). Specifically, patients who underwent transfusion had higher odds of organ space SSI, pneumonia, unplanned intubation, pulmonary embolism, failure to wean off of ventilator, renal insufficiency, urinary tract infections, stroke, myocardial infarction, cardiac arrest requiring CPR, deep vein thrombosis, and septic shock ($p < 0.047$). **Conclusion**: Peri-operative pRBC transfusion in RC was associated with longer hospital stays, significant morbidity, and mortality. For this reason, pre-operative patient optimization and possible alternatives to common pRBC practices should be considered in RC to circumvent complications.

Keywords: blood transfusion; cystectomy; surgical oncology; urinary bladder neoplasms; urology

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1. Introduction

Bladder cancer (BC) is the 10th most common cancer worldwide and the 9th leading cause of cancer death [1]. Radical Cystectomy (RC) is recommended for patients with localized muscle-invasive bladder cancer (MIBC), stage T2-T4a, and non-muscle-invasive bladder cancer that is unresponsive to intravesical therapy or cannot be controlled with a transurethral resection of the bladder (TURB) [2]. RC is considered a complex procedure that confers significant post-operative complications, reaching an incidence of 64% [3]. Post-operative complications may involve several organs and include paralytic ileus, pyelonephritis, small bowel obstruction, wound infection or dehiscence, pneumonia, cardiac arrythmias, and urinary tract infections [4,5].

Intra-operative events and operative characteristics can influence the outcome of RC, impacting the risk of morbidity and mortality. As an example, minimally invasive radical cystectomy has been associated with lower estimated blood loss, a shorter length of hospital

stays, and fewer 30-day overall complications [6]. Furthermore, the type of urinary diversion in RC could also influence the incidence of post-operative morbidity and mortality [7]. Another operative factor that could influence peri-operative morbidity and mortality is packed red blood cell (pRBC) transfusion intra-operatively or 24 h post-operatively.

Indications for peri-operative transfusion include anemia, blood loss, and inadequate oxygen delivery [8]. RC, known as a complex procedure, frequently entails intra- and post-operative pRBC transfusions, with rates ranging from 20.4% to 72.9% [9–11]. PRBC transfusion in RC has been associated with substantial morbidity; it can negatively impact oncologic outcomes and can decrease cancer-specific and overall survival [9–11]. For this reason, many studies have sought to determine pre-operative factors that could help predict the risk of transfusion post-radical cystectomy, hence aiming to optimize patient selection and provide alternatives to common pRBC transfusion practices [11–13]. Currently, the extent of the impact of pRBC transfusion on post-operative morbidity needs better elucidation. As such, the aim of this study is to explore the impact of post-operative pRBC transfusion on mortality and overall morbidity in RC using the National Surgical Quality Improvement Program's (NSQIP) database.

2. Materials and Methods

2.1. Study Design

The American College of Surgeons—National Surgical Quality Improvement Program's (ACS-NSQIP) dataset was used to select patients who underwent RC in the years 2008–2019. The following current procedural terminology (CPT) codes were used to select patients who underwent RC: 51570, 51575, 51580, 51585, 51590, 51595, and 51596. The dataset does not differentiate between open and minimally invasive (MIS) radical cystectomy. A total of 16,629 patients underwent RC in the years 2008–2019. Next, patients with pre-operative pRBC transfusion and emergency cases were excluded, as these served as major pre-operative confounders for post-operative pRBC transfusion. The final dataset included 15,588 patients who underwent RC, of which 4787 underwent peri-operative pRBC transfusion. The ACS-NSQIP database is a nationally validated, risk-adjusted, outcomes-based program. It encompasses 719 centers both inside and outside the United States. Data are collected by Surgical Clinical Reviewers (SCRs) who receive intensive training and follow-up support; in addition, data quality is ensured by an Intra-Rater Reliability Audit from participating sites.

2.2. Ethics Approval and Consent

Patient consent and Institutional Review Board (IRB) approval were not required since the data were de-identified, retrospectively collected, and did not include human subject research.

2.3. Data Availability

The (ACS-NSQIP) data are subject to a data use agreement. To access the dataset, a request to the ACS-NSQIP participant use form should be placed at the following link (https://www.facs.org/quality-programs/acs-nsqip/participant-use) accessed on 13 June 2022.

2.4. Patients, Variables and Outcome of Interest

We sought to compare demographics, medical history, and operative time among patients who received or did not receive peri-operative pRBC transfusion. Peri-operative pRBC transfusion was defined as the transfusion of pRBC intra-operatively or up until 24 h post-operatively. Patient demographics included age, body mass index (BMI), sex, and American Society of Anesthesiology (ASA) class. Patient medical history included diabetes, hypertension, pre-operative renal failure, chronic obstructive pulmonary disease (COPD), bleeding disorders, congestive heart failure (CHF), and chronic steroid use. Our outcomes of interest included the length of hospital stay, 30-day mortality, and overall major morbidity. Major morbidity was a composite outcome of superficial incisional surgical site

infection (SSI), deep incisional SSI, organ space SSI, wound disrupt, pneumonia, unplanned intubation, pulmonary embolism, failure to wean off of ventilator >48 h, renal insufficiency, renal failure, urinary tract infection (UTI), cerebrovascular accident (CVA), myocardial infarction (MI), cardiac arrest requiring cardiopulmonary resuscitation (CPR), deep vein thrombosis (DVT), sepsis, septic shock, and return to operating room (OR).

2.5. Statistical Analysis

To compare our outcomes of interest between patients who underwent peri-operative pRBC transfusion and patients who did not undergo transfusion, we decided to match the two groups in all pre-operative variables by propensity score matching. A 1:1 propensity score match was performed for all pre-operative demographics and medical history variables to produce a completely matched cohort. Categorical and continuous variables were analyzed using the chi-square test and independent *t*-test, respectively. Odds ratios for each outcome were then calculated using non-pRBC transfusion as a reference. IBM SPSS Statistics version 28 was used for the statistical analysis, and two-sided significance was set at 0.05.

3. Results

After propensity score matching, the matched cohort consisted of 3578 patients who were matched on operative time and all pre-operative demographics and medical history variables (Table 1).

Table 1. Demographics and medical history of patients who underwent radical cystectomy in the years 2008–2019, before and after propensity score matching.

***n* = 15,588**		**Before Propensity Score Matching *n* = 15,588**			**After Propensity Score Matching *n* = 3578**		
		No Transfusion *n* = 10,801	**Yes Transfusion *n* = 4787**	***p*-Value**	**No Transfusion *n* = 1789**	**Yes Transfusion *n* = 1789**	***p*-Value**
		***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**	
Demographics							
Age	<50	570 (5.3)	249 (5.2)	**<0.001 [a]**	90 (5)	88 (4.9)	0.750
	50–59	1608 (14.9)	622 (13)		219 (12.2)	245 (13.7)	
	60–69	3462 (32.1)	1411 (29.5)		536 (30)	518 (29)	
	70–79	3856 (35.7)	1815 (37.9)		704 (39.4)	706 (39.5)	
	>80	1305 (12.1)	690 (14.4)		240 (13.4)	232 (13)	
BMI	<25	2754 (25.5)	1457 (30.4)	**<0.001 [a]**	434 (24.3)	489 (27.3)	0.07
	25–29.9	4228 (39.1)	1747 (36.5)		724 (40.5)	683 (38.2)	
	30–34.9	2486 (23)	1021 (21.3)		419 (23.4)	388 (21.7)	
	35–39.9	882 (8.2)	361 (7.5)		148 (8.3)	144 (8)	
	>40	451 (4.2)	201 (4.2)		64 (3.6)	85 (4.8)	
Sex	Female	1713 (15.9)	1282 (26.8)	**<0.001 [a]**	263 (14.7)	279 (15.6)	0.456
	Male	9088 (84.1)	3505 (73.2)		1526 (85.3)	1510 (84.4)	

Table 1. *Cont.*

n = 15,588		Before Propensity Score Matching *n* = 15,588			After Propensity Score Matching *n* = 3578		
		No Transfusion *n* = 10,801	Yes Transfusion *n* = 4787	*p*-Value	No Transfusion *n* = 1789	Yes Transfusion *n* = 1789	*p*-Value
		n (%)	*n* (%)		*n* (%)	*n* (%)	
ASA	≤2	2718 (25.2)	866 (18.1)	**<0.001** [a]	357 (20)	360 (20.1)	0.900
	>2	8083 (74.8)	3921 (81.9)		1432 (80)	1429 (79.9)	
Diversion Type	IC or SB ± LND	8924 (82.6)	3987 (83.3)	0.309	1558 (87.1)	1483 (82.9)	<0.001
	Neobladder	1844 (17.1)	762 (15.9)	0.43	226 (12.6)	290 (16.2)	0.02
	USD or UCD + LND	5 (0.1)	1 (0)	0.075	2 (0)	0 (0)	0.99
Medical History							
Diabetes		2002 (18.5)	1044 (21.8)	<0.001 [a]	351 (19.6)	346 (19.3)	0.833
Hypertension		6302 (58.3)	2999 (62.6)	<0.001 [a]	1084 (60.6)	1088 (60.8)	0.891
Renal Failure		18 (0.2)	29 (0.6)	<0.001 [a]	2 (0.1)	1 (0.1)	0.564
COPD		764 (7.1)	377 (7.9)	0.076	124 (6.9)	135 (7.5)	0.478
Bleeding Disorder		288 (2.7)	207 (4.3)	<0.001 [a]	44 (2.5)	52 (2.9)	0.408
CHF		68 (0.6)	41 (0.9)	0.117	9 (0.5)	13 (0.7)	0.392
Steroid Use		316 (2.9)	226 (4.7)	<0.001 [a]	50 (2.8)	55 (3.1)	0.620
Operative Time (minutes)		329.8 ± 116.7	367 ± 130	<0.001 [a]	339.6 ± 110	336 ± 108	0.399

[a] Significant $p < 0.05$. BMI indicates body mass index (kg/m^2); ASA indicates the American Society of Anesthesiologists; Hypertension indicates hypertension requiring medication; COPD indicates chronic obstructive pulmonary disease; CHF indicates congestive heart failure. Ileal conduit (IC); Sigmoid bladder (SB); Lymph node dissection (LND); Ureterocutaneous diversion (UCD); Ureterosigmoid diversion (USD).

The matched cohort consisted of 1789 patients who underwent peri-operative transfusion (50%) and 1789 patients who did not (50%). In this matched cohort, patients who underwent peri-operative transfusion had a significant longer length of hospital stay (9.3 days) compared to those who did not undergo peri-operative transfusion (8.13 days) ($p < 0.001$) (Table 2). Furthermore, patients who underwent peri-operative pRBC transfusion also demonstrated higher rates of mortality and overall morbidity (OR = 1.934 and OR = 1.443, respectively) compared to patients who did not undergo peri-operative transfusion (p-value < 0.03) (Table 2). Specifically, patients who underwent peri-operative pRBC transfusion were found to have increased odds of organ space SSI (OR = 1.530), pneumonia (OR = 1.928), unplanned intubation (OR = 1.654), pulmonary embolism (OR = 1.655), failure to wean off of ventilator (OR = 1.941), renal insufficiency (OR = 1.961), UTI (OR = 1.286), CVA (OR = 2.442), myocardial infarction (OR = 2.072), cardiac arrest requiring CPR (OR = 1.88), DVT (OR = 2.172), and septic shock (OR = 1.953) compared to patients who did not undergo peri-operative pRBC transfusion (p-value < 0.047) (Table 2).

Table 2. Thirty-day length of hospital stay, mortality, and overall morbidity in patients who underwent peri-operative transfusion and patients who did not undergo transfusion in a matched cohort.

***n* = 3578 Matched Cohort**	**No Transfusion *n* = 1789** ***n* (%)**	**Yes Transfusion *n* = 1789** ***n* (%)**	**Odd's Ratio (95% CI)** **No Transfusion Reference**	***p*-Value**
Length of Stay	8.13 ± 8.9	9.3 ± 12.5	3.313 [0.492, 1.919]	<0.001 [a]
Mortality	31 (1.7)	59 (3.3)	1.934 [1.246, 3.002]	0.03 [a]
Major Morbidity [b]	515 (28.8)	659 (36.8)	1.443 [1.254, 1.660]	<0.001 [a]
Superficial Incisional SSI [c]	102 (5.7)	110 (6.1)	-	0.571
Deep Incisional SSI [c]	24 (1.3)	35 (2)	-	0.149
Organ space SSI [c]	110 (6.1)	163 (9.1)	1.530 [1.190, 1.967]	<0.001 [a]
Wound Disrupt	54 (3)	49 (2.7)	-	0.617
Pneumonia	37 (2.1)	70 (3.9)	1.928 [1.287, 2.888]	<0.001 [a]
Unplanned Intubation	38 (2.1)	62 (3.5)	1.654 [1.099, 2.491]	0.015 [a]
Pulmonary Embolism	25 (1.4)	41 (2.3)	1.655 [1.002, 2.733]	0.047 [a]
Failure to Wean [d]	24 (1.3)	46 (2.6)	1.941 [1.180, 3.193]	0.009 [a]
Renal insufficiency	29 (1.6)	56 (3.1)	1.961 [1.246, 3.086]	0.004 [a]
Renal failure	19 (1.1)	33 (1.8)	-	0.05
UTI	135 (7.5)	170 (9.5)	1.286 [1.016, 1.629]	0.037 [a]
CVA	7 (0.4)	17 (1)	2.442 [1.010, 5.904]	0.041 [a]
Myocardial Infarction	22 (1.2)	45 (2.5)	2.072 [1.239, 3.466]	0.005 [a]
Cardiac Arrest Requiring CPR	15 (0.8)	28 (1.6)	1.88 [1.001, 3.533]	0.046 [a]
DVT [e]	31 (1.7)	66 (3.7)	2.172 [1.410, 3.346]	<0.001 [a]
Sepsis	155 (8.7)	160 (8.9)	-	0.768
Septic shock	36 (2)	69 (3.9)	1.953 [1.298, 2.939]	<0.001 [a]
Return to OR	89 (5)	115 (6.4)	-	0.061

[a] Significant at alpha < 0.05. [b] Major morbidity is the composite outcome of postoperative incidence of major complications, which include superficial and deep surgical site infection, organ surgical infection, wound disturbance, pneumonia, unplanned intubation, pulmonary embolism, failure to wean off of ventilator > 48 h, renal insufficiency, acute renal failure, urinary tract infection, cerebrovascular accident, cardiac arrest requiring CPR, myocardial infarction, return to operating room, septic shock, or deep vein thrombosis. [c] SSI: Surgical site infection. [d] Failure to Wean indicates failure to wean off of ventilator > 48 h. [e] DVT indicates deep vein thrombosis.

4. Discussion

The significance of transfusion in radical cystectomy is frequently overlooked for several reasons. Firstly, much of the research has primarily focused on other endpoints, diverting attention from the impact of transfusion. Additionally, the limited sample sizes, statistical power, and lack of objectivity in perioperative transfusion data in available trials have hindered the ability to detect and assess the true influence of transfusion rates. It is essential to recognize that transfusion rates serve as valuable surrogates for surgical quality and can significantly drive the occurrence of postoperative complications [14]. Therefore, in this study, we sought to query data from a large nation-wide database (ACS-NSQIP) to explore the impact of pRBC transfusion on post-operative morbidity and mortality. Using a matched cohort, we observed a significant increase in hospital stay, major morbidity, and mortality in patients who underwent peri-operative transfusion during RC.

Peri-operative transfusion in RC has shown conflicting results in the literature with regard to its impact on outcomes including morbidity and mortality. On one hand, Kluth et al. investigated the effect of peri-operative transfusion in 2895 patients who underwent radical

cystectomy, and they were not able to demonstrate an impact of transfusion on oncological outcomes [15]. Similarly, Soubra et al., using the Surveillance, Epidemiology, and End Results (SEER) Medicare Database, were not able to demonstrate a significant association between transfusion and cancer-specific mortality or all-cause mortality in bladder cancer patients [16]. On the other hand, several studies have been able to demonstrate a detrimental effect of transfusion on survival outcomes. A recent systematic review showed that red blood cell transfusion is associated with worse overall survival, recurrence-free survival, and cancer-specific survival in bladder cancer patients [17]. Furthermore, other studies have also shown a dose-dependent relationship between the units transfused and cancer-specific mortality, as well as all-cause mortality [18]. More recently, a retrospective study by Diamantopoulos et al. showed that intra-operative blood transfusion was associated with poor overall and recurrence-free survival, as well as prolonged hospitalization [19].

Peri-operative transfusion was associated in our study with a prolonged length in hospital stay. Although a prolonged hospital stay after a peri-operative transfusion could be due to a more complex surgical procedure, we aimed to control for this variation by matching for operative time in an attempt to match complexity. Prolonged hospital stays have been shown to be important determinants for quality of care and a surrogate for overall post-operative morbidity [20]. Furthermore, prolonged hospital stays are associated with an increase in healthcare costs and further exposes patients to nosocomial infection and complications [21].

In addition to an increased length of stay, our study showed that peri-operative transfusion increased the odds of major morbidity and mortality. Specifically, it was shown that peri-operative transfusion increased the odds of infectious complications (surgical site infections, pneumonia, urinary tract infections, and septic shock), cerebrovascular and cardiopulmonary complications (deep venous thrombosis, pulmonary embolism, unplanned intubation, myocardial infarction, cardiac arrest, and cerebrovascular accident), and renal injury. These findings are in line with various studies showing that peri-operative transfusion is an independent predictor of morbidity or mortality in major abdominal surgeries, including hepatectomy [22], gastrectomy [23], colectomy patients [24], and pancreatectomy [24]. The more probable explanation for increased morbidity and infectious complications is the secondary immunosuppression that transfusions might prompt. The antigenic variability found in blood products might induce an immune response and create an overall increase in the body's inflammatory state. This was demonstrated by Jensen et al., who showed that blood transfusion led to an increase in inflammation-inducing cytokines (interleukin-2 and interleukin-6) [25]. With regard to the increase in deep vein thrombosis and pulmonary embolism, transfusions have been previously described as pro-thrombotic in the peri-operative period of pelvic fracture patients [26]. Furthermore, transfusions have also shown to increase thrombotic rates in colectomy patients [27]. In addition, peri-operative transfusion has also been found to be a predictor of increased cardiac and pulmonary complications in colorectal surgery [28].

Our findings, thus, emphasize the importance of adopting a conservative or restrictive approach towards blood transfusion in patients undergoing radical cystectomy [13]. These approaches may be incorporated as part of the Enhanced Recovery Pathway (ERAS), which aims to enhance a patient's preoperative status, maintain homeostasis, and reduce postoperative complications. Initially, selecting high-risk patients for peri-operative transfusion should be warranted by using risk prediction models to predict the need for pre-operative optimization [11]. Then, an emphasis should be made on different ways to increase red cell concentration (Supplementary Table S1). For example, treating anemia and iron deficiency pre-operatively has been proven to decrease transfusion rates and thus morbidity and mortality [29]. Alternatively, Warner et al. proposed that erythropoietin could be used to increase total red cell mass, hence decreasing the need for transfusion without negatively impacting surgical outcomes [30]. Furthermore, tranexamic acid was previously shown to reduce the need for blood transfusion without increasing the risk of venous thromboembolism (VTE) during open radical cystectomy [31]. Moreover, adopting the robot-assisted

approach instead of the open approach for radical cystectomy was proven to significantly lower perioperative transfusion rates [32]. Finally, other alternatives such as continuous norepinephrine administration combined with restrictive hydration have been shown to decrease intra-operative bleeding and, hence, the need for blood transfusion [12].

Despite our significant findings, this study has many limitations. First, due to the data's retrospective nature, many variables are absent, including hematocrit/hemoglobin levels at the time of transfusion. Another drawback is that the ACS-NSQIP data lack tumor-specific characteristics, such as tumor subtype and stage. In addition, the dataset does not differentiate between open and minimally invasive (MIS) radical cystectomy; thus, we could not adjust for the surgical approach in our analysis.

As a conclusion, our study showed that peri-operative transfusion was associated with longer hospital stays, greater overall morbidity, and mortality in patients undergoing radical cystectomy. For this reason, pre-operative patient optimization and possible alternatives to common transfusion practices should be considered in RC to circumvent complications.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/siuj5010008/s1, Table S1: Haemoglobin (Hb) thresholds for red blood cell transfusion or alternatives usage in adults.

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Informed Consent Statement: Patient consent was not required since the data were de-identified, retrospectively collected, and did not include human subject research.

Data Availability Statement: The (ACS-NSQIP) data are subject to a data use agreement. To access the dataset, a request to the ACS-NSQIP participant use form should be placed at the following link (https://www.facs.org/quality-programs/acs-nsqip/participant-use) accessed on 13 June 2022. The American University of Beirut Medical Center is enrolled in ACS-NSQIP as a participating center. As such, the data were made available by the ACS-NSQIP center and the AUBMC Department of Surgery after signing the data use agreement.

Conflicts of Interest: The authors declare no conflicts of interest.

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