Perioperative blood transfusion predicts short term morbidity after nephrectomy

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Introduction: *To assess 30-day morbidity and mortality following partial nephrectomy (PN) and radical nephrectomy (RN) with relation to the administration of perioperative blood transfusions PBT).*

Materials and methods: *The National Surgical Quality Improvement Program was queried for patients with malignant renal tumors (International Classification of Diseases Ninth Revision codes 189-189.2) who underwent RN (Current Procedure Terminology codes 50220, 50225, 50230, 50234, 50236, 50545, 50546, 50548) or PN (50240, 50543) between 2005-2013. Patients were stratified by transfusion status and assessed for postoperative outcomes both separately and in composite, including morbidity, mortality, infectious complications, and pulmonary complications. Univariate and multivariate analyses were performed to identify significant independent predictors of these composite outcomes.*

Results: *The overall transfusion rates were 15.8% and 8.2% for RN and PN, respectively. On multivariate analysis, PBT was associated with increased morbidity (RN: OR 2.147, 95% CI 1.687-2.733; PN: OR 2.081, 95% CI 1.434-3.022), mortality (RN: OR 2.308, 95% CI 1.159-4.598; PN: OR 5.166, 95% CI 1.207-22.12), infectious complications (RN: OR 1.656, 95% CI 1.151-2.383; PN: OR 1.945, 95% CI 1.128-3.354) and pulmonary complications (RN: OR 3.040, 95% CI 2.125-4.349; OR 3.771, 95% CI 2.108-6.746).*

Conclusions: *For patients undergoing RN or PN there is a significant association between receipt of PBT and 30-day postoperative outcomes, specifically overall morbidity, mortality, infectious complications, and pulmonary complications. The mechanism that underlies these effects has not been elucidated, but it most likely involves immunomodulation and acute lung injury. Future research should focus on formulating comprehensive transfusion guidelines for oncologic-related nephrectomies.*

Key Words: blood transfusion, kidney cancer, nephrectomy, complications

Introduction

Kidney cancer is among the top ten most common cancers for both men and women with an estimated 62,700 new cases and 14,240 deaths in 2016.[1] Survival at 5 years is very favorable for localized disease at approximately 80%-90% when treated with extirpative surgery by either radical nephrectomy (RN) or partial nephrectomy (PN).[2,3]

Perioperative blood transfusion (PBT), either during the operation or soon after, is used relatively frequently in both RN and PN with rates reported in the literature as high as 21% in large studies.[9,10] PBT has been associated with poor oncologic outcomes - increased risk of recurrence and poor cancer specific survival - after surgery for intestinal, hepatic, gynecologic and esophageal malignancies, as well as most urologic malignancies (bladder and prostate).[11-14]

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Surgical outcomes – postoperative complications, readmission – have also been shown to be associated with PBT among various cancer operations.[15-17]

Although the precise reason for this effect has yet to be fully understood it has been attributed to immunomodulation and the proinflammatory response induced by blood transfusions.[18,19] In addition, there is a definite role of the immune system in the natural history of renal cell carcinoma (RCC) as is evident by the limited, but sometimes dramatic effect of cytokine therapy or cytoreductive surgery for metastatic disease.[4-6]

Despite sharing a common theme of immune modulation, the effect of PBT on long term outcomes following extirpative surgery for RCC is unclear.[10,20-22] There are no reports to our knowledge with information on short term morbidity and/or mortality that might be attributable to PBT following RN or PN. Thus, we conducted a study using the National Surgical Quality Improvement Program (NSQIP) database to assess the effect of PBT on 30-day postoperative outcomes in both PN and RN for kidney cancer.

Materials and methods

The American College of Surgeons NSQIP database was retrospectively reviewed for all patients who underwent PN or RN from 2005 to 2013. The ACS-NSQIP includes data from over 400 participating academic, public and private hospitals. The database is maintained by trained surgical clinical reviewers from each participating institution who receive continuing education and are audited to ensure data reliability. Preoperative, intraoperative and postoperative patient factors are recorded and are reliable as has been described previously.[23]

The 2005-2013 ACS-NSQIP Participant Use Files were queried for all patients with the International Classification of Diseases Ninth Revision (ICD-9) codes for kidney cancer (189-189.2) and matched with the Current Procedure Terminology codes for PN (50240, 50543) and RN (50220, 50225, 50230, 50234, 50236, 50545, 50546, 50548). Perioperative transfusion status was then used to stratify patients and was defined as at least 1 unit of packed or whole red blood cells given during surgery or up to 72 hours postoperatively. Emergency procedures were excluded.

Outcomes

Our primary outcome was 30-day postoperative morbidity as defined as one or more of the following: acute renal failure, stroke, coma for greater than 72 hours, unplanned intubation, pulmonary embolism (PE), ventilation for greater than 48 hours, peripheral neurologic deficit, cardiac arrest, myocardial infarction, progressive renal insufficiency, graft/prosthesis/flap failure, wound dehiscence, urinary tract infection (UTI), deep vein thrombosis (DVT), sepsis, superficial surgical site infection, deep incisional site infection, organ space surgical site infection or pneumonia. Secondary outcomes were 30-day mortality, readmission, length of stay, all infectious complications (UTI, pneumonia, superficial surgical site infection, deep incisional site infection, organ space surgical site infection and wound dehiscence) and pulmonary complications (pneumonia, unplanned intubation, ventilator > 48 hours and PE).

Demographics and risk factors

Patient level data included age, sex, body mass index (BMI), race (non-Hispanic white, black, other), smoking status, alcohol use, American Society of Anesthesiologists (ASA) physical status, dependent functional status, steroid use and prior operation in the past 30 days. Comorbid conditions included type 2 diabetes, dialysis, ascites, disseminated cancer, resting leg pain/gangrene, acute renal failure, esophageal varices, open wound infection, bleeding disorders, preoperative transfusion, weight loss, chemotherapy in past 30 days, radiotherapy in past 90 days and sepsis. Respiratory diseases were categorized as including chronic obstructive pulmonary disease (COPD), pneumonia, ventilator dependence or dyspnea (at rest or with moderate exertion). Heart disease included congestive heart failure, peripheral vascular disease, angina, history of myocardial infarction, previous percutaneous coronary intervention (PCI), previous cardiac surgery and hypertension. Neurologic diseases included CNS tumor, cerebrovascular accident, coma, previous transient ischemic attack, impaired sensorium and hemi/para/quadriplegia.

Statistical analysis

Analyses were performed separately on RN and PN patients and these groups were further divided into those who received transfusions and those who did not. Demographics, comorbidities and postoperative complications were compared on univariate analysis using the chi-square test for categorical variables with a p value of < 0.05 considered significant and the Student's t-test for normally distributed continuous variables. Logistic regression models were used to control for confounders and determine independent predictors of each outcome variable (morbidity, mortality, infectious complications, pulmonary complications). All analyses were performed using SPSS 23.0. Our institutional review board determined that our retrospective study was exempt.

TABLE 1. **Comparison of demographics and comorbidities between transfused versus non-transfused patients**

Variable	Radical nephrectomy			Partial nephrectomy		
	No transfusion % (n = 5711)	Transfusion % (n = 1014)	p value*	No transfusion % (n = 3970)	Transfusion % (n = 348)	p value*
Age (mean yrs)	64.0 ± 12.2	66.6 ± 11.5	< 0.001	59.1 ± 12.1	63.7 ± 12.2	< 0.001
Female	35.8 (2043)	36.1 (366)	0.844	61.8 (2453)	62.1 (216)	0.918
Body mass index			0.007			0.064
Underweight (< 18)	1.1 (60)	1.7 (17)		0.7 (26)	1.7 (6)	
Normal (18-29.9)	19.7 (1101)	23.3 (230)		15.5 (599)	18.4 (63)	
Overweight (30-39.9)	35.0 (1953)	35.3 (349)		33.3 (1290)	32.7 (112)	
Obese (> 40)	44.2 (2465)	39.7 (293)		50.6 (1960)	47.2 (162)	
Race			0.532			0.233
White	81.6 (2994)	82.1 (752)		81.9 (2858)	78.1 (246)	
Black	8.2 (404)	7.2 (66)		8.7 (302)	10.2 (32)	
Other	10.2 (499)	10.7 (98)		9.4 (328)	11.7 (37)	
Smoking history	21.8 (1246)	13.7 (139)	< 0.001	21.8 (865)	15.5 (54)	0.006
Dependent functional status			< 0.001			0.002
Independent	98.0 (5572)	96.0 (965)		99.1 (3919)	97.4 (337)	
Partially or totally dependent	2.0 (116)	4.0 (40)		0.9 (35)	2.6 (9)	
Steroid use	3.1 (179)	3.2 (32)	0.971	2.7 (106)	4.0 (14)	0.141
American Society of Anesthesiologist class			< 0.001			< 0.001
1-2	36.3 (2072)	21.4 (217)		45.0 (1785)	29.2 (101)	
3	57.6 (3284)	66.1 (670)		52.7 (2090)	67.1 (232)	
> 4	6.1 (349)	12.4 (126)		2.3 (91)	3.8 (13)	
Type 2 diabetes mellitus	20.2 (1153)	26.1 (265)	< 0.001	19.3 (768)	25.9 (90)	0.003
Resting leg pain/gangrene	0.1 (2)	0.0 (0)	0.562	0.0 (0)	1.2 (1)	< 0.001
Acute renal failure	0.4 (20)	0.4 (4)	0.828	0.1 (3)	1.1 (4)	< 0.001
Dialysis	3.2 (182)	3.5 (35)	0.660	0.1 (2)	0.9 93)	< 0.001
Ascites	0.1 (8)	0.5 (5)	0.018	0.1 (3)	0.9 (3)	< 0.001
Disseminated cancer	6.0 (345)	15.9 (161)	< 0.001	1.7 (69)	3.7 (13)	0.009
Open wound infection	0.8 (45)	1.0 (10)	0.518	0.3 (13)	1.1 (4)	0.019
Weight loss	2.6 (146)	8.8 (89)	< 0.001	1.0 (38)	1.7 (6)	0.172
Bleeding disorders	2.5 (142)	6.1 (62)	< 0.001	1.8 (70)	6.6 (23)	< 0.001
Hx CT in 30 days	1.8 (36)	6.9 (23)	< 0.001	0.2 (2)	1.2 (1)	0.061
Hx RT in 90 days	0.6 (12)	0.6 (2)	0.984	0.2 (2)	1.3 (1)	0.052
SIRS, sepsis or septic shock	0.8 (44)	2.8 (28)	< 0.001	0.3 (12)	0.6 (2)	0.391
Respiratory disease[a]	6.5 (373)	7.5 (76)	0.257	4.6 (184)	9.8 (34)	< 0.001
Heart disease[b]	66.7 (3811)	72.2 (732)	0.001	60.8 (2415)	74.1 (258)	< 0.001
Neurologic disease[c]	2.6 (150)	2.6 (26)	0.909	1.3 (53)	2.6 (9)	0.06
Any comorbidity[d]	72.2 (4123)	83.5 (847)	< 0.001	63.7 (2530)	79.6 (277)	< 0.001
Prior operation within 30 days	1.3 (27)	2.1 (7)	0.302	0.3 (4)	2.4 (2)	0.008

[a]respiratory disease = history of any chronic obstructive pulmonary disease, ventilatory dependence, pneumonia, dyspnea at rest or with moderate exertion; [b]heart disease = history of myocardial infarction, congestive heart failure, angina, previous cardiac surgery, previous PCI, hypertension, peripheral vascular disease; [c]neurologic disease = prior transient ischemic attack, CVA with or without neurologic deficit, CNS tumor, coma, hemi/para/quadriplegia or impaired sensorium; [d]any comorbidity = presence of any comorbidity listed as listed above.

*p values derived from chi-square tests for categorical variables and student's t-test for continuous variables.

Results

Between 2005 and 2013, 6725 and 4208 patients undergoing RN and PN, respectively, met inclusion criteria. A total of 15.0% (RN) and 8.3% (PN) received perioperative blood transfusion. Table 1 shows a comparison of patient demographics and comorbidities in the transfusion versus non-transfusion group stratified by operation type. Across both procedures, transfused patients were older, less likely to smoke, more likely to have disseminated cancer and more likely to have a history of bleeding disorders.

Preoperative variables in the transfusion versus non-transfusion groups are shown in Table 2. In both procedures, transfusion patients had higher mean creatinine, lower mean albumin, lower mean hematocrit and higher proportion of anemia. For procedure type, 28.3% versus 71.7% of minimally invasive versus open RN resulted in PBT while 36.5% versus 63.5% of minimally invasive versus open PN included PBT use.

Table 3 shows the univariate analysis for postoperative complications both separately and in composite. Overall, transfusion patients experienced more postoperative morbidity, higher mortality, more infectious complications, more pulmonary complications, higher readmission rate, longer hospital stays and longer operative time.

On multivariate analysis, four outcome measures were chosen: 30-day morbidity, 30-day mortality, all infectious complications and pulmonary complications. Significant predictors of each of these dependent outcomes are presented in Figures 1 and 2 for partial and radical nephrectomies respectively.

For partial nephrectomy, Figure 1, age and perioperative blood transfusion were significant across all four outcomes. In the morbidity model, ASA class 3 or > 4 and operative time were additional significant predictors. For mortality, only smoking status was an additional predictor. Female sex, ASA class 3 or > 4 and operative time were other significant predictors for infectious complications. Finally for pulmonary complications, smoking history and ASA class > 4 significantly predicted complications along with age and PBT.

For radical nephrectomy, Figure 2, age, operative time, ASA class > 4 and PBT were significant predictors for all four models. Minimally invasive approach was protective for all outcomes except mortality. For 30-day morbidity, additional predictors included smoking status, any comorbidities and contaminated or dirty/infected wounds predicted complications. Age was the only other independent predictor for 30-day mortality. For all infectious complications, female sex, smoking history, contaminated wound, dirty/infected wound were additional significant predictors. Finally for

TABLE 2. **Comparison of operative variables between transfused versus non-transfused patients**

Variable	Radical nephrectomy			Partial nephrectomy		
	No transfusion % (n = 5711)	Transfusion % (n = 1014)	p value*	No transfusion % (n = 3966)	Transfusion % (n = 354)	p value*
Preoperative lab values						
Creatinine	1.3 ± 1.3	1.4 ± 1.2	0.004	1.0 ± 10.4	1.2 ± 0.6	< 0.001
Albumin	4.0 ± 0.5	3.6 ± 0.7	< 0.001	4.2 ± 0.4	4.0 ± 0.6	< 0.001
INR	1.0 ± 0.2	1.1 ± 0.2	< 0.001	1.0 ± 0.3	1.0 ± 0.3	0.139
White blood cell count	7.7 ± 2.7	8.1 ± 3.9	< 0.001	7.3 ± 2.4	7.1 ± 2.2	0.107
Platelet count	249.9 ± 90.7	277.9 ± 117	< 0.001	236.6 ± 68.4	234.3 ± 89.3	0.576
Hematocrit	39.8 ± 5.0	34.8 ± 5.6	< 0.001	41.4 ± 4.3	38.2 ± 5.4	< 0.001
Anemia[a]	38.6 (2114)	76.4 (752)	< 0.001	22.9 (866)	51.5 (175)	< 0.001
Procedure types						
Minimally invasive	67.7 (3867)	28.3 (287)		61.0 (2420)	36.5 (127)	
Open	32.3 (1844)	71.7 (727)	< 0.001	39.0 (1550)	63.5 (221)	< 0.001
Wound classification						
Clean or clean/ contaminated	98.7 (5634)	96.8 (982)	< 0.001	99.4 (3948)	99.7 (347)	0.512
Contaminated or dirty/infected	1.3 (77)	3.2 (32)		0.6 (22)	0.3 (1)	

[a]anemia = presence of anemia based on preoperative hematocrit adjusted for sex (< 36.1% for females and < 40.7% for males)
*p values derived from chi-square tests for categorical variables and student's t-test for continuous variables

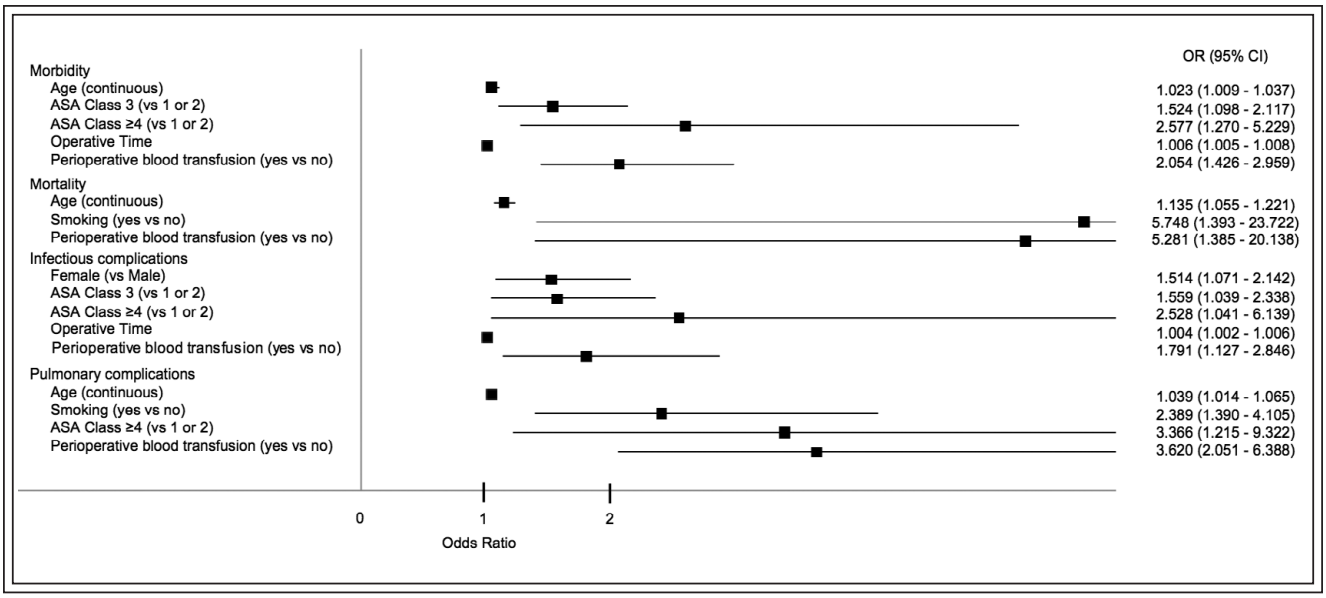

Figure 1. Forest plots displaying multivariate logistic regression analysis for partial nephrectomy composite outcomes - morbidity, mortality, infectious complications and pulmonary complications. Independent significant adjusted odds ratios and 95% confidence intervals from multivariate analysis.

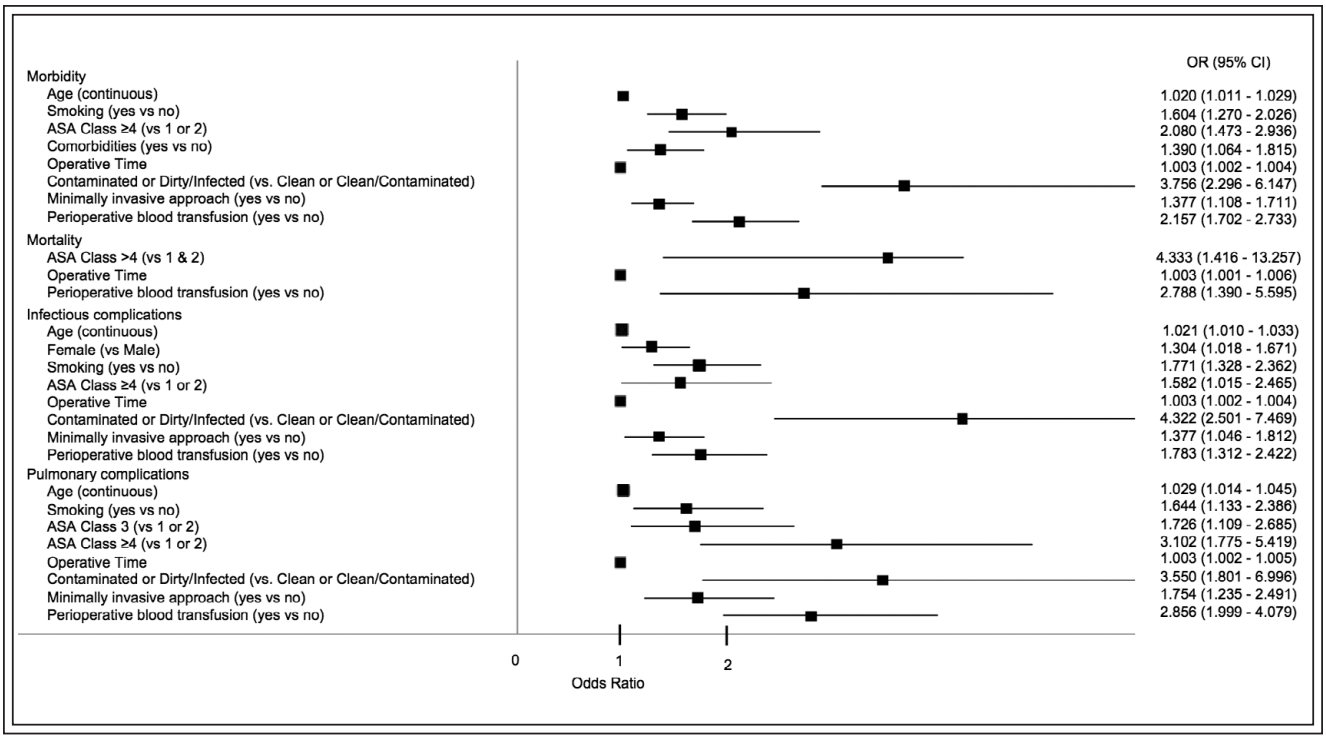

Figure 2. Forest plots displaying multivariate logistic regression analysis for radical nephrectomy composite outcomes - morbidity, mortality, infectious complications and pulmonary complications. Independent significant adjusted odds ratios and 95% confidence intervals from multivariate analysis.

TABLE 3. **Unadjusted postoperative outcomes between transfused versus non-transfused patients**

Variable	Radical nephrectomy			Partial nephrectomy		
	No transfusion % (n = 5738)	Transfusion % (n = 1028)	p value*	No transfusion % (n = 3966)	Transfusion % (n = 3354)	p value*
Postoperative complications						
Pneumonia	1.0 (58)	4.6 (47)	< 0.001	1.0 (39)	3.2 (11)	< 0.001
Unplanned intubation	1.0 (57)	4.4 (45)	< 0.001	0.4 (16)	5.5 (19)	< 0.001
Pulmonary embolism	0.4 (22)	1.9 (19)	< 0.001	0.4 (14)	0.3 (1)	0.843
On ventilator > 48 hours	0.4 (23)	5.1 (52)	< 0.001	0.2 (8)	2.6 (9)	< 0.001
Progressive renal insufficiency	0.7 (39)	2.9 (29)	< 0.001	0.6 (23)	4.0 (14)	< 0.001
Acute renal failure	0.6 (35)	3.4 (34)	< 0.001	0.4 (17)	2.6 (9)	< 0.001
Urinary tract infection	1.9 (107)	2.9 (29)	0.04	1.3 (51)	3.7 (13)	< 0.001
Stroke/CVA	0.2 (12)	0.8 (8)	0.002	0.1 (5)	0.3 (1)	0.438
Coma > 24 hrs	0.0 (0)	0.1 (1)	0.018			
Peripheral nerve injury	0.0 (1)	0.1 (1)	0.167	0.0 (1)	0.0 (0)	0.767
Cardiac arrest requiring CPR	0.3 (17)	1.2 (12)	< 0.001	0.2 (7)	2.3 (8)	< 0.001
Myocardial infarction	0.6 (33)	1.5 (15)	0.002	0.4 (15)	2.0 (7)	< 0.001
Graft/prosthesis/flap failure						
DVT requiring therapy	0.6 (34)	2.6 (26)	< 0.001	0.5 (19)	1.1 (4)	0.099
Sepsis	0.7 (42)	2.7 (27)	< 0.001	0.6 (22)	3.2 (11)	< 0.001
Superficial incisional SSI[a]	1.1 (64)	2.8 (28)	< 0.001	0.7 (27)	1.4 (5)	0.115
Deep incisional SSI[a]	0.2 (9)	0.7 (7)	0.001	0.3 (11)	0.3 (1)	0.972
Organ/space SSI[a]	0.4 (21)	1.3 (13)	< 0.001	0.3 (11)	1.7 (6)	< 0.001
Wound dehiscence	0.3 (19)	0.7 (7)	0.091	0.3 (11)	0.6 (2)	0.331
Composite outcomes						
Morbidity[b]	7.7 (437)	21.7 (220)	< 0.001	5.7 (225)	19.3 (67)	< 0.001
Mortality	0.5 (27)	2.7 (27)	< 0.001	0.2 (9)	2.0 (7)	< 0.001
Infectious complications[c]	4.7 (268)	11.9 (121)	< 0.001	3.6 (144)	10.9 (38)	< 0.001
Pulmonary complications[d]	2.3 (133)	11.0 (112)	< 0.001	1.5 (61)	7.8 (27)	< 0.001
Readmission	4.7 (267)	9.4 (95)	< 0.001	4.2 (167)	9.5 (33)	< 0.001
Operative time (min, mean ± SD)	177.1 ± 82.2	246.1 ± 117.3	< 0.001	187.8 ± 70.4	230.7 ± 95.2	<0.001
Length of stay (days, mean ± SD)	4.3 ± 3.8	8.0 ± 7.2	< 0.001	3.5 ± 2.5	6.0 ± 5.0	< 0.001

[a]SSI = surgical site infection; [b]morbidity = any complication; [c]infectious complications = UTI, pneumonia, superficial SSI, deep incisional SSI, organ space SSI, wound dehiscence; [d]pulmonary complications = pneumonia, unplanned intubation, ventilator > 48 hrs, pulmonary embolism

pulmonary complications smoking history, ASA class 3, any comorbidities and contaminated wound were also significant predictors.

Discussion

Using a national, validated database, we have shown PBT to be significantly associated with short term postoperative outcomes of overall morbidity, mortality, infection, and pulmonary complications, for both RN and PN.

Previous work on this topic has focused on the effect of PBT on survival and recurrence after RN or PN. In an early series from 1973-1985, 126 nephrectomies were identified and no significant difference in 5 year overall survival was shown in those receiving PBT.[21] During the same time period another institutional study examined a smaller cohort of 80 patients, 55 of whom received PBT, to also show no significant difference in overall survival.[24] Far from clarifying earlier results, more recent studies continue to provide mixed results. In a study of 258 patients, 208 of whom were transfused, no

survival difference found between transfused versus non-transfused patient undergoing surgery for RCC.[20] Edna et al, however, reviewed a group of 201 patients, 77% of which received a PBT, and found that transfusion of greater than 4 units was associated with decreased 2 year survival.[22] Lastly, Linder et al's retrospective review of 498 PN and RN cases reported that PBT resulted in cancer-specific survival (68% versus 92% at 9.1 years, $p < 0.05$) on univariate analysis and decreased 5 year overall survival (HR 1.23, $p = 0.02$) on multivariate analysis.[10]

To our knowledge, we are the first to report increased rates of pulmonary related complications in both PN and RN and its relation to PBT. A recent analysis using the NSQIP database for colorectal cancer surgery also found that PBT was a significant predictor of pneumonia (OR 2.70, 95% CI 1.84-3.97).[15] If there is direct causality between PBT and postoperative pneumonia then it could be associated with the pathophysiology of transfusion-related acute lung injury (TRALI). Tuinman et al. present evidence from patients undergoing cardiac surgery in whom they collected blood samples and bronchoalveolar lavage fluid postoperatively.[25] Their findings suggest that the mechanism of this relationship may be mediated by the activation of systemic inflammatory pathways via elevation of IL-1b, IL-8 and TNFa which in turn stimulates the coagulation cascade in the pulmonary vasculature, resulting in acute lung injury. Another proposed mechanism, called the "two-hit" model, suggests that patients with comorbid conditions, such as malignancy, leads to neutrophil sequestration in the lungs which can then promote localized tissue damage and subsequent lung injury after exposure to plasma and lipids from packed red blood cells.[26,27]

There have been several randomized controlled trials favoring restrictive over liberal transfusion protocols. A lower transfusion threshold of hemoglobin 7 mg/dL versus 10 mg/dL was shown to reduce the risk of MI and pulmonary edema in a randomized controlled trial of 838 ICU patients.[28] Villanueva and colleagues randomized 225 patients to restrictive versus liberal transfusions and found better overall survival at 6 weeks (95% versus 91%, $p = 0.02$) if the more restrictive cut off of 7 g/dL was used instead of 9 g/dL.[29] Several more RCTs have shown non-inferiority of restrictive transfusions when considering morbidity and mortality.[30,31] When this evidence is considered in the context of our findings of increased short term postoperative morbidity and mortality following PBT it seems to suggest that there may be a causal relationship between blood transfusion and pulmonary outcomes following surgery.

A notable limitation of our study was that the NSQIP database does not include tumor specific information such as tumor size, anatomic complexity or TNM staging information, which is likely, associated with postoperative morbidity and transfusion utilization. Relative value units (RVUs) in addition to operative time have been studied extensively in this database and have been used to control for surgical complexity.[16,32-35] Two non-oncologic studies on short term morbidity in the orthopedic and general surgery literature did not find that RVUs was a significant predictor of postoperative outcomes. The most recent of these studies to use RVUs is by Prescott et al, on short term outcomes after surgery for gynecologic malignancies who found that PBT was a significant predictor of morbidity, surgical site infection and mortality.[16] This measure was included in our own multivariate analysis and was not a significant independent predictor of outcomes suggesting that PBT, independent of other surgical variables, is associated with poorer short term outcomes.

Our study has several other limitations: its retrospective design and lack of data on the timing of postoperative complications, the type of blood transfusion (autologous versus allogenic), demographic and hospital information (such as socioeconomic status, hospital size or surgeon volume). Additionally, common nephrectomy-specific complications, such as urinary fistulas or urinomas, perinephric abscesses, were not included in the database.

Conclusions

Receipt of at least 1 unit of blood before, during, or after RN or PN was associated with increased 30 day morbidity, mortality, infectious complications and pulmonary complications on multivariate analysis. This study is among the first to investigate the association of PBT and short term operative outcomes. Further research should focus on the restrictive use of PBT in urologic oncology surgeries with a focus on both short and long term outcomes. □

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