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Longer Average Blood Storage Duration is Associated With Increased Risk of Infection and Overall Morbidity Following Radical Cystectomy

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Abstract

Background—Bladder cancer patients undergoing radical cystectomy experience high rates of perioperative blood transfusions and morbidity. The aim of this study was to evaluate the impact of blood storage duration on the risk of adverse perioperative outcomes in this high-risk patient population.

Materials and Methods—In a retrospective review of radical cystectomy patients from 2010–2014 that received perioperative blood transfusions, the average storage duration for all units transfused was used to classify patients as receiving older blood using three different definitions (< 21 days, 21–28 days, and ≥ 28 days). Multivariable Poisson regression models were used to determine the adjusted relative risk of perioperative infections and overall morbidity in those given older blood compared to fresher blood.

Results—A total of 205/451(45%) patients undergoing radical cystectomy received non-irradiated, perioperative blood transfusions. In multivariable modeling, increasing average blood storage duration, as a continuous variable, was associated with an increased risk of infections (RR=1.08 per day, 95%CI 1.01–1.17) and overall morbidity (RR=1.08 per day, 95%CI 1.01–1.15). Furthermore, ≥ 28 day blood storage (vs. <28) was associated with increased infections (RR=2.69, 95%CI 1.18–6.14) and morbidity (RR=2.54, 95%CI 1.31–4.95), and ≥ 35 day blood storage (vs.

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<35) was also associated with increased infections (RR=2.83, 95%CI 1.42–5.66) and morbidity (RR=3.35, 95%CI 1.95–5.77).

Conclusions—Although blood is stored up to 42 days, storage >28 days may expose radical cystectomy patients to increased perioperative infections and overall morbidity compared to storage <28 days. Prospective cohort studies are warranted in cystectomy and other high-risk surgical oncology patients, to better determine the impact of blood storage duration.

Keywords

Blood transfusion; Infection; Cystectomy; Bladder cancer; Postoperative complications

1. Introduction

During the 42-day allowed shelf life for blood storage prior to transfusion, red blood cells (RBCs) undergo biochemical and structural changes, which may impair their ability to deliver oxygen.^{1,2} Moreover, storage of blood increases levels of pro-inflammatory cytokines and oxidative stress experienced by RBCs.^{1,3} This phenomenon, termed the “storage lesion,” is the pathophysiological mechanism fueling investigations into the effects of RBC storage duration on clinical outcomes following perioperative blood transfusion (PBT).⁴

Retrospective studies in surgical cohorts have shown PBT of older blood compared to fresher blood is associated with increased morbidity and mortality following surgery.^{5–8} However, large randomized clinical trials (RCTs) conducted on this topic demonstrate no difference in clinical outcomes for patients receiving fresh vs. older blood.^{9–12} A recent meta-analysis concluded these RCTs have used very conservative definitions of old blood, and as a result, have not fully investigated the effect of blood stored 4–6 weeks, which is commonly transfused in clinical practice.¹³ Moreover, three of these RCTs were conducted in non-surgical cohorts. Therefore, generalizing these RCT findings to surgical oncology patients may not be appropriate.

Among surgical oncology patients, bladder cancer patients undergoing radical cystectomy (RC) experience higher than average rates of readmission and perioperative complications.^{14,15} Approximately 33–67% of patients undergoing RC for bladder cancer receive PBTs.¹⁶ RC patients innately experience high rates of PBT (exposure of interest), perioperative morbidity, and readmissions (outcomes of interest). Therefore, RC patients represent an inherently high-risk population to study the impact of RBC average storage duration on perioperative outcomes.

In RC patients, current literature on PBT has focused on comparing clinical outcomes in patients that received PBTs to patients that did not, including a previous study from our institution focused on neoadjuvant chemotherapy (NAC) patients.^{16–18} While these studies provide important clinical knowledge, recent retrospective surgical series in non-RC cohorts have shown RBC storage duration is an important determinant of clinical outcomes.^{5–8} To date, only one retrospective study addressed the effect of blood storage duration on outcomes following RC.¹⁹ While they found no difference between fresh vs. old blood

transfusions, this study was underpowered due to its small sample size and conservative definition of older blood (>14 days). As a result, additional studies to investigate the effect of RBC storage duration on clinical outcomes in RC patients are warranted.

We sought to determine the impact of RBC average storage duration on perioperative infectious complications and overall morbidity in RC patients, a high-risk patient population, using clinically relevant definitions of older blood. We hypothesize PBTs with blood stored for longer average duration are associated with higher rates of perioperative morbidity in RC patients.

2. Materials and Methods

2.1 Patient Cohort

With approval from the Johns Hopkins Medical Institutions (Baltimore, MD, USA) institutional review board, patients undergoing RC for bladder cancer at Johns Hopkins Hospital between January 2010 and December 2014 was analyzed using blood storage duration data obtained from a web-based intelligence portal (IMPACT Online, Haemonetics, Braintree, MA), and data from our anesthesia information management system (Metavision, iMdSoft, Dedham, MA). Use of these databases and quality control methods were described previously.^{20,21} Of the 451 patients that underwent RC during this time period, 52% (233/451) received PBTs. The standard of care at Johns Hopkins Hospital is to transfuse with leukoreduced PBTs. The “perioperative” time period was defined as any blood transfusion throughout the hospital stay during which the RC took place including intraoperative transfusions. Among the 233 transfused patients, 28 (12% [28/233]) were excluded because they received irradiated blood, which alters the expiration date (28-day instead of 42-day maximum storage). The remaining 205 patients was the cohort used for storage duration analyses. During the study time period there was no strict institution-wide hemoglobin trigger for PBT. For purposes of risk-adjustment, collected data included the use of NAC, pathologic staging (T and N stage), Charlson comorbidity index (CCI), American Society of Anesthesiologists (ASA) classification score, and casemix index (MSDRGWt), a comprehensive surrogate marker of overall disease severity and complexity of hospital procedures.^{22,23}

2.2 RBC Storage Duration

A previous RCT used 21 days as the definition of old blood, but since blood is stored up to 42 days we sought to investigate the graded effect of using higher cutoffs for defining old blood.¹¹ We stratified patients using the average storage duration of all PBTs received into the following groups: <21 days versus 21 days, <28 days versus 28, and <35 days versus 35 days.

2.3 Complications

Primary outcomes were infection and composite morbidity during the hospitalization in which the RC was performed. Infection was chosen because it is a common complication following RC and pathophysiologic mechanisms exist to support an association between longer blood storage duration and increased infection rates.^{24–26} Infection was defined as

any of the following: *C. difficile*, sepsis, surgical-site infection, pyelonephritis, or drug-resistant infection. Morbid events were defined as (1) infection, (2) thrombotic event (deep venous thrombosis, pulmonary embolus, or disseminated intravascular coagulation), (3) renal event (acute renal failure, oliguria/anuria, or urinary tract infection), (4) respiratory event (pneumonia or respiratory failure), and (5) ischemic event (myocardial infarction, transient ischemic attack, or cerebrovascular accident), which is consistent with previous studies.^{20,21} Data to classify morbid events were obtained through the hospital's billing database, using ICD-9 codes as a validated, prospective method to collect information on in-hospital complications.^{22,23} Conditions flagged as present on admission were not considered to be "in hospital/acquired" morbid events. Secondary outcomes assessed for all causes were 90-day readmission and mortality rates.

2.4 Statistical Analysis

Baseline characteristics were compared between fresh vs. old blood using all three predetermined definitions of old blood (21 days, 28 days, 35 days) using the student's t-test or Wilcoxon rank-sum test for continuous variables and chi-squared or Fischer's exact test for categorical variables. Next, univariable and multivariable Poisson regression models with robust variance estimates were calculated to determine predictors of infection and overall morbidity.²¹ Poisson regression models were used since the prevalence of both primary outcomes was >10%. It was determined a priori age, sex, average blood storage duration, and additional covariates significant on univariable analysis would be entered into the multivariable Poisson regression models to determine risk-adjusted, independent predictors of infection and overall morbidity. The adjusted relative risk was also calculated treating average blood storage duration as a continuous variable. Appropriate statistical comparison tests were used with $p < 0.05$ to define significance for all tests. Analyses were generated with JMP version 9.0.2 (SAS Institute, Inc., Cary, NC) and STATA version 12.0 (College Station, TX).

3. Results

The rate of PBT was similar ($p=0.4$) for patients with muscle invasive (pT2 stage, 46.2% [61/132]) and non-muscle invasive bladder cancer (<pT2 stage, 50.3% [159/316]). Controlling for age, sex, MSDRGWt, BMI, and NAC, PBTs were associated with increased morbidity (RR=2.20, 95%CI 1.28–3.78), but did not meet traditional levels of significance for infectious complications (RR=1.84, 95%CI 0.98–3.48) compared to patients that did and did not receive PBTs. Of the 205 patients that received PBTs, 41% (84/205) received transfusions intraoperatively. The median average storage duration of PBTs was 29 days [IQR 14–40]. Baseline characteristics are listed in Table 1, and the rates of each type of complication are listed in Table 2.

3.1 Mean Storage Duration as Continuous Variable

Multivariable modeling showed mean blood storage duration, as a continuous variable, was predictive of a higher risk of infectious complications (RR=1.08 per day, 95%CI 1.01–1.17, Table 3) and overall morbidity (RR=1.08 per day, 95%CI 1.01–1.15, Table 4).

3.2 21-day cutoff

Using a definition of 21 days for the average age of transfused RBC units to define older blood, 27 (13%) individuals received fresh blood and 178 (87%) that received old blood. There were no differences in baseline characteristics (Table 1). Multivariable modeling showed PBTs with older blood was not associated with higher risk of infection (RR=10.02, 95%CI 0.51–196.33, Table 3, Figure 1) or overall morbidity (RR=4.48, 95%CI 0.68–29.59, Table 4, Figure 1). Of note, the RRs for the different cutoffs presented in figure 1 should not be compared to each other, but compared to the null value of RR=1. Notably on univariable modeling, N+ disease (RR=1.53, 95%CI 0.69–3.39 and RR=1.34, 95%CI 0.69–2.60), muscle invasion (RR=1.52, 95%CI 0.65–3.56 and RR=1.43, 95%CI 0.72–2.81), NAC (RR=0.71, 95%CI 0.35–1.44 and RR=0.73, 95%CI 0.41–1.29), and intraoperative transfusions (RR=0.68, 95%CI 0.32–1.44 and RR=0.86, 95%CI 0.48–1.54) were not significant predictors of infectious complications or morbidity, respectively. Ninety-day mortality (0% [0/27] vs. 3.4% [6/178], $p=0.99$) and readmission (33.3% [9/27] vs. 24.1% [43/178], $p=0.3$) rates were comparable in the fresh and old blood groups respectively (Table 2).

3.3 28-day cutoff

Using a definition of 28 days for the average age of transfused RBC units to define older blood, 110 (54%) individuals received fresh blood and 95 (46%) received old blood. There were no differences in baseline characteristics (Table 1). Multivariable modeling showed transfusions with older blood was predictive of a higher risk of infection (RR=2.69, 95%CI 1.18–6.14, Table 3 and Figure 1) and overall morbidity (RR=2.54, 95%CI 1.31–4.95, Table 4 and Figure 1). Ninety-day mortality (2.1% [2/95] vs. 3.6% [4/110], $p=0.7$) and readmission (24.2% [23/95] vs. 26.4% [29/110], $p=0.8$) rates were comparable in the fresh and older blood groups respectively (Table 2).

3.4 35-day cutoff

Using a definition of 35 days for the average age of transfused RBC units to define older blood, 177 (86%) individuals received fresh blood and 28 (14%) received old blood. Patients receiving older blood were transfused fewer units on average (2.2 vs. 2.9, $p=0.003$) than patients receiving fresher blood (Table 1). Multivariable modeling showed transfusions with older blood was predictive of higher risk of infectious complications (RR=2.83, 95%CI 1.42–5.66, Table 3 and Figure 1) and overall morbidity (RR=3.35, 95%CI 1.95–5.77, Table 4 and Figure 1). Ninety-day mortality (2.8% [5/177] vs. 3.6% [1/28], $p=0.6$) and readmission (26.0% [46/177] vs. 21.4% [6/28], $p=0.8$) rates were comparable in the fresh and older blood groups respectively (Table 2).

3.5 Infectious Complications

Of the 28 individuals that experienced post-operative infectious complications, there were 17 (61%) surgical-site infections, 11 (39%) *C. difficile* infections, 4 (14%) cases of sepsis, 1 (4%) drug-resistant infection, and 1 (4%) case of pyelonephritis.

4. Discussion

In this study, we investigated the effect of average storage duration of transfused blood on complications in a surgical cohort at a high risk of perioperative morbidity - bladder cancer patients following RC. We demonstrate in the continuous model, PBT with blood of longer average storage duration is associated with increased risk of infection and overall morbidity. As the average storage duration cutoff used to define older blood increased, the risk of both infection and morbidity increased, suggesting a causal relationship between older blood and increased infection and overall morbidity as this biological gradient relationship is one of the Bradford Hill criteria for causation.

The increased risk of both infection and composite morbidity was present at the 28-day and 35-day cutoffs. The only previous study investigating the effect of RBC storage duration in RC patients found no difference in complication rates between patients that received fresh vs. old blood.¹⁹ However, their sample size (n=163) along with their conservative definition of older blood (>14 days) most likely resulted in this study being underpowered to detect differences in complication rates. In the present study, we did not see differences in risk of infectious complications or overall morbidity when using a 21-day cutoff to define older blood. This is most likely because the adverse effects of RBC storage start to become significant around 21 days.¹⁻³ Of note, the group sample sizes for the 21 and 35-day cutoff were quite uneven leading to large confidence intervals for the 21-day RR. The null result at the 21-day cutoff should be investigated further in a cohort with a larger sample size for fresh blood with the 21-day cutoff. Previous RCTs investigating the effect of blood storage duration in other surgical specialties have used these conservative, shorter duration cutoffs (14 and 21 days) for categorizing blood as old.⁹⁻¹¹ This has resulted in the median storage duration of transfused units for old blood in these studies to be quite low (14.6, 22.0, and 28 days). However, since RBC units are deemed to be acceptable for transfusion until the end of the 6th week of storage (42 days), these studies did not assess the effect of truly old RBC units that are transfused frequently in some hospitals. The most recent RCT used a more liberal definition of old blood (25-35 days) resulting in median storage duration of 32 days in the old group, but this still excluded PBTs transfused in the 6th week of storage.¹² In this study, we used multiple pre-defined cutoffs that were higher than the cutoffs in the RCTs, which allowed us to investigate the effect of RBC storage duration with a more clinically relevant approach.

To our knowledge, there is only one previous study investigating the effect of storage duration 35 days, which was conducted at our institution.²⁰ However, this study excluded patients that received a mixture of fresh and older units and only included patients that received exclusively fresh or old blood. This approach is similar to the previous retrospective study in RC patients and the RCTs in non-RC cohorts, which also excluded patients who received a mixture of both fresh and old blood from their analyses. This was most likely done to maximize the potential to see a difference in outcomes between groups. We believe our study represents a more clinically relevant approach as we defined older blood by the average storage duration of all RBC units received. We would expect using the average storage duration instead of analyzing patients that received exclusively fresh vs. exclusively old blood to underestimate the impact of storage duration on the risk of infection and overall

morbidity. However, in the current study we were still able to detect significant differences in clinical outcomes between the two groups using average storage duration. This would suggest the increased risk of infection and morbidity in patients that received exclusively old blood may be even higher than the increased risk found in our study using average storage duration. Moreover, in clinical practice most patients do not receive only fresh blood or only old blood, and often receive a mixture of fresh and older blood increasing the clinical relevance of our study to “real-world” practice in hospitals.

Support for a causal relationship of older blood leading to increased infections and overall morbidity comes from the fact that the risk of infection and morbidity increased as the cutoff for the definition of old blood increased as this biological gradient relationship is one of the Bradford Hill criteria for causation. Moreover, when analyzed as a continuous variable our results show an 8% increased risk of infection and composite morbidity for each additional day of blood storage. Further support for this causal relationship comes from the “iron hypothesis” which provides a plausible pathophysiological mechanism for this effect.²⁸ As blood is stored, the proportion of RBCs that experience the storage lesion increases. When RBCs with storage lesions are transfused, they are more likely to be engulfed by macrophages in the reticuloendothelial system due to their structural changes. Once taken up by the macrophages, the breakdown of hemoglobin in the RBC results in the release of iron (Fe). Normally Fe is carried in the blood bound to transferrin, but the very high load of Fe associated with older PBT can eclipse the body’s supply of transferrin resulting in non-transferrin bound iron (NTBI) to be present in blood. Several studies have shown NTBI is associated with increase rates of infections, especially of ferrophilic bacteria.^{29,30} Additionally, higher levels of total Fe and NTBI are found in units stored for longer durations.³¹ Therefore, the iron hypothesis is a potential mechanism by which older PBTs can lead to increased rates of infection.

The findings of this study have potential implications for PBT policy in high-risk patients, such as those undergoing RC. Among surgical oncology procedures, RC has one of the highest rates of morbidity with approximately 20% of patients experiencing a complication during the index admission and more than 33% of patients experiencing hospital readmission.^{14,15} Our findings suggest longer storage duration of RBC units given to RC patients result in a significant increase in infectious complications and overall morbidity rates. However, larger prospective cohort studies are needed to confirm this finding. While urologists do not have control over the storage duration of PBTs given to a patient, we hope this study will bring increased awareness to the potential harms of PBTs and spark important dialogues between urologists, anesthesiologists, pathologists, and individuals in laboratory medicine about the importance of blood storage duration. Our findings further highlight the importance of appropriate guideline-based PBT in bladder cancer patients undergoing cystectomy and should be a stimulus for institutions to have additional dialogue about the adverse effects of overuse of PBT.^{32–33} Moreover, a restrictive strategy for hemoglobin transfusion triggers should be strongly considered in RC patients to reduce unnecessary transfusions. While previous RCTs did not find a significant difference in the primary clinical outcomes, they did not specifically study cancer patients who have received systemic chemotherapy or those given blood near the end of the 42-day shelf life.

It is important to note we did not control for preoperative hemoglobin, intraoperative fluid management, or estimated blood loss because these variables are not expected to be associated with the exposure of interest (storage duration of PBTs) in RC patients, and therefore cannot be confounders of the relationship between blood storage duration and the risk of infection or morbidity. Moreover, we show in Table 1 that intraoperative fluid management, intraoperative blood loss, nadir hemoglobin, and last hemoglobin are comparable between fresh vs. old blood in for each cutoff providing further support for these variables to be unlikely confounders of the relationship between blood storage duration and the risk of infection or overall morbidity.

There are several limitations of this study to note. This is a retrospective analysis of prospectively collected data from a single-institution, tertiary care center, which could limit the generalizability of the findings. However, the use of a previously validated method to ascertain complications with prospectively collected billing data is a strength that removes the biases associated with retrospectively collecting complication data.^{22,23} In addition, blood storage practices can differ at institutions across the country, which could reduce the generalizability of our results. Moreover, the observational nature of this study increases the potential of residual confounding due to unmeasured variables. However, our results coupled with the findings of previous retrospective studies, makes it unclear as to whether the clinical equipoise necessary to ethically conduct a RCT giving truly old blood units to patients (28 or 35 days) is still present. Additionally, the sample size was limited, and therefore this study was not adequately powered to detect differences in 90-day mortality or readmission rates. Finally, our aim was to address differences in perioperative morbidity and mortality, and therefore, this study does not investigate oncologic outcomes.

5. Conclusions

In conclusion, PBTs with RBC units of longer storage duration (28 days) are associated with an increased risk of infectious complications and overall morbidity in bladder cancer patients undergoing RC. Our findings suggest prospective blood storage duration cohort studies should be performed in high-risk, surgical oncology patient populations, such as RC patients, which were not specifically included in previous RCTs in order to better inform the debate of the importance of blood storage duration on clinical outcomes in surgical oncology cohorts.

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Figure 1. Relative risk and 95% confidence intervals (error bars) for composite morbidity and infection using 21, 28, and 35-day definitions of older blood calculated by multivariable Poisson regression with robust variance estimate models

Table 1

Patient characteristics stratified by average storage duration of RBC units transfused.

Characteristic	<21 days (n=27)	21 days (n=178)	p-value	<28 days (n=95)	28 days (n=110)	p-value	<35 days (n=177)	35 days (n=28)	p-value
Age (mean $\pm$ SD)	64 $\pm$ 10	67 $\pm$ 11	0.2	67 $\pm$ 9	66 $\pm$ 12	0.8	67 $\pm$ 10	65 $\pm$ 12	0.5
Gender male (%)	20 (74%)	136 (76%)	0.8	72 (76%)	84 (76%)	0.9	135 (76%)	21 (75%)	0.9
Average Units Transfused (mean $\pm$ SD)	2.3 $\pm$ 1.3	2.9 $\pm$ 2	0.052	2.6 $\pm$ 1.7	3 $\pm$ 2.1	0.2	2.9 $\pm$ 2	2.2 $\pm$ 1.1	0.003
Median Average Units Transfused [IQR]	2 [2, 2]	2 [2, 4]	0.14	2 [2, 4]	2 [2, 4]	0.2	2 [2, 4]	2 [1.5, 2.5]	<0.001
Mean Average Storage Duration	17.1 (2.7)	29.9 (4.7)	<0.001	22.7 (4.1)	33.0 (3.2)	<0.001	26.8 (5.5)	37.2 (2.0)	<0.001
Median Average Storage Duration [IQR]	18 [15, 19]	30 [26, 34]	<0.001	25 [20, 26]	33 [30.3, 35]	<0.001	27 [24.4, 31]	36.5 [35.5, 38.4]	<0.001
MSDRGWt (mean $\pm$ SD)	3.3 $\pm$ 3	3.1 $\pm$ 1.3	0.8	3.3 $\pm$ 1.97	3.1 $\pm$ 1.3	0.3	3.2 $\pm$ 1.7	3.2 $\pm$ 1.4	0.99
CCI (mean $\pm$ SD)	3.6 $\pm$ 1.6	4 $\pm$ 2	0.2	3.8 $\pm$ 1.9	4 $\pm$ 2	0.45	3.8 $\pm$ 1.9	4.7 $\pm$ 2.2	0.056
ASA score (mean $\pm$ SD)	2.7 $\pm$ 0.5	2.7 $\pm$ 0.5	0.8	2.7 $\pm$ 0.5	2.7 $\pm$ 0.6	0.9	2.7 $\pm$ 0.5	2.53 $\pm$ 0.6	0.2
BMI (mean $\pm$ SD)	28.3 $\pm$ 5.7	27.5 $\pm$ 4.9	0.5	27.7 $\pm$ 5	27.6 $\pm$ 5.1	0.9	27.6 $\pm$ 4.9	27.6 $\pm$ 5.8	0.98
NAC (%)	13 (48%)	85 (48%)	0.97	45 (47%)	53 (48%)	0.9	84 (47%)	14 (50%)	0.8
Adjuvant Chemotherapy (%)	1 (4%)	8 (5%)	0.99	5 (5%)	4 (4%)	0.7	7 (4%)	2 (7%)	0.4
Pathologic T stage									
- pT1 or less	10 (37%)	48 (27%)	0.3	26 (28%)	32 (29%)	0.9	50 (29%)	8 (29%)	0.99
- pT2	17 (63%)	128 (73%)		67 (72%)	78 (71%)		125 (71%)	20 (71%)	
Pathologic N stage									
- N0	20 (74%)	138 (78%)	0.8	71 (75%)	87 (79%)	0.6	136 (77%)	22 (79%)	0.98
- N1	3 (11%)	15 (8%)		8 (8%)	10 (9%)		16 (9%)	2 (7%)	

Characteristic	<21 days (n=27)	21 days (n=178)	p-value	<28 days (n=95)	28 days (n=110)	p-value	<35 days (n=177)	35 days (n=28)	p-value
- N2/3	2 (7%)	18 (10%)		12 (13%)	8 (7%)		17 (10%)	3 (11%)	
- Nx	2 (7%)	7 (4%)		4 (4%)	5 (5%)		8 (5%)	1 (4%)	
Intraoperative Estimated Blood Loss in ml (mean $\pm$ SD)	1031 $\pm$ 109	1047 $\pm$ 44	0.9	1053 $\pm$ 57	1036 $\pm$ 58	0.8	1044 $\pm$ 43	1055 $\pm$ 125	0.9
Intraoperative Colloids in ml (mean $\pm$ SD)	197 $\pm$ 61	156 $\pm$ 25	0.5	163 $\pm$ 32	160 $\pm$ 33	0.96	156 $\pm$ 24	206 $\pm$ 70	0.5
Intraoperative Crystalloids in ml (mean $\pm$ SD)	5352 $\pm$ 576	4766 $\pm$ 234	0.3	4985 $\pm$ 304	4707 $\pm$ 310	0.5	4819 $\pm$ 231	5091 $\pm$ 657	0.7
First measured Hgb * (mean $\pm$ SD)	11.1 $\pm$ 0.4	11.3 $\pm$ 0.1	0.6	11.4 $\pm$ 0.2	11.2 $\pm$ 0.2	0.6	11.3 $\pm$ 0.1	11.6 $\pm$ 0.4	0.4
Nadir Hgb during hospitalization (mean $\pm$ SD)	7.7 $\pm$ 0.2	7.8 $\pm$ 0.1	0.6	7.9 $\pm$ 0.1	7.8 $\pm$ 0.09	0.7	7.8 $\pm$ 0.1	7.8 $\pm$ 0.2	0.7
Last Hgb during hospitalization (mean $\pm$ SD)	9.0 $\pm$ 0.2	9.4 $\pm$ 0.1	0.06	9.3 $\pm$ 0.1	9.4 $\pm$ 0.1	0.3	9.3 $\pm$ 0.1	9.2 $\pm$ 0.2	0.5

* This is the first measured hemoglobin during hospitalization in which RC took place.

SD- standard deviation

MSDRGWt- casemix index

CCI- Charlson comorbidity index

ASA- American Society of Anesthesiologist

BMI- body mass index

NAC- neoadjuvant chemotherapy

Hgb- hemoglobin

Table 2

Incidence of outcomes stratified by average storage duration of RBC units transfused.

Outcomes	<21 days (n=27)	21 days (n=178)	<28 days (n=95)	28 days (n=110)	<35 days (n=177)	35 days (n=28)	Any PBT (n=205)	No PBTs (n=218)
Overall	3	37	12	28	28	12	40	17 (7.8%)
Morbidity	(11.1%)	(20.8%)	(12.6%)	(25.5%)	(15.8%)	(42.9%)	(19.5%)	14 (6.4%)
- Infectious	2 (7.4%)	26	9 (9.5%)	19	20	8	28	1 (0.5%)
- Renal	0 (0%)	(14.6%)	1 (1.0%)	(17.3%)	(11.3%)	(28.6%)	(13.7%)	2 (0.9%)
- Thrombotic	1 (3.7%)	6 (3.4%)	3 (3.2%)	5 (4.5%)	4 (2.3%)	2 (7.1%)	6 (2.9%)	1 (0.5%)
- Ischemic	0 (0%)	7 (3.9%)	0 (0%)	5 (4.5%)	7 (4.0%)	1 (3.6%)	8 (3.9%)	1 (0.5%)
- Respiratory	0 (0%)	2 (1.1%)	1 (1.1%)	2 (1.8%)	2 (1.1%)	0 (0%)	2 (1.0%)	
		2 (1.1%)		1 (0.9%)	1 (0.6%)	1 (3.6%)	2 (1.0%)	
90-Day	9	43	23	29	46	6	52	42
Readmission	(33.3%)	(24.2%)	(24.2%)	(26.4%)	(26.0%)	(21.4%)	(25.4%)	(19.3%)
90-Day	0 (0%)	6 (3.4%)	2 (2.1%)	4 (3.6%)	5 (2.8%)	1 (3.6%)	6 (2.9%)	5 (2.3%)
Mortality								

Table 3

Relative risk (old vs. fresh blood) of infectious complication * based on average storage duration of RBC units transfused

	21-day cutoff		28-day cutoff		35-day cutoff		Mean Storage Duration (No Cutoff)	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Age								
- Female	1.003 (0.97–1.04)	0.9	1.01 (0.97–1.05)	0.6	1.002 (0.96–1.05)	0.9	1.004 (0.97–1.04)	0.8
- Male								
MSDRGWt								
- Female	Reference		Reference		Reference		Reference	
- Male	1.66 (0.57–4.82)	0.4	1.75 (0.14–4.80)	0.3	1.58 (0.54–4.59)	0.4	1.63 (0.58–4.57)	0.3
BMI								
- Female	1.43 (1.18–1.75)	<0.001	1.32 (1.20–1.44)	<0.001	1.28 (1.18–1.38)	<0.001	1.33 (1.21–1.48)	<0.001
- Male	1.11 (1.05–1.17)	<0.001	1.11 (1.04–1.18)	0.001	1.10 (1.03–1.16)	0.001	1.10 (1.04–1.17)	0.001
Average Storage Duration								
- <21 days	Reference		Reference		Reference		Reference	
- 21 days	10.02 (0.51–196.33)	0.1	2.69 (1.18–6.14)	0.02	2.83 (1.42–5.66)	0.003	1.08 (1.01–1.17)	0.03
- <28 days								
- 28 days								
- <35 days								
- 35 days								
Continuous variable (per day)								

* Infectious complication defined as any of the following: *C. difficile*, sepsis, surgical-site infection, pyelonephritis, or drug-resistant infection.

MSDRGWt- casemix index

BMI- body mass index

Table 4
Relative risk (old vs. fresh blood) of composite morbidity* based on average storage duration of RBC units transfused

	21-day cutoff		28-day cutoff		35-day cutoff		Mean Storage Duration (No Cutoff)	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Age								
- Female	Reference		Reference		Reference		Reference	
- Male	1.42 (0.71–2.83)	0.3	1.49 (0.77–2.90)	0.2	1.48 (0.72–3.05)	0.3	1.46 (0.75–2.84)	0.3
Mean units of blood transfused								
- Female	1.07 (0.997–1.15)	0.06	1.07 (1.006–1.15)	0.03	1.13 (1.05–1.20)	0.1	1.10 (1.02–1.17)	0.008
MSDRGWt								
- Female	1.30 (1.14–1.49)	<0.001	1.25 (1.15–1.36)	<0.001	1.21 (1.12–1.31)	<0.001	1.26 (1.15–1.38)	<0.001
BMI								
- Female	1.07 (1.01–1.12)	0.01	1.07 (1.01–1.12)	0.045	1.05 (1.01–1.11)	0.02	1.06 (1.01–1.11)	0.01
Average Storage Duration								
- <21 days	Reference		Reference		Reference		Reference	
- 21 days	4.48 (0.68–29.59)	0.1	2.54 (1.31–4.95)	0.006	3.35 (1.95–5.77)	<0.001	1.08 (1.01–1.15)	0.02
- <28 days								
- 28 days								
- <35 days								
- 35 days								
Continuous variable (per day)								

* Composite morbidity defined as any of the following: (1) infection, (2) thrombotic event, (3) renal event, (4) respiratory event, (5) ischemic event.

MSDRGWt- casemix index

BMI- body mass index