Title: Delayed blood transfusion is associated with mortality following radical cystectomy

Running title: Delayed transfusion increases cystectomy mortality

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ABSTRACT

Objectives:

To examine the temporal association between blood transfusion and 90-day mortality in patients with bladder cancer treated with radical cystectomy.

Methods:

This retrospective cohort study of patients treated with radical cystectomy within the Premier Hospital network between 2003-2015. Patients outcomes were stratified those who received early blood transfusion (day of surgery) vs delayed blood transfusion (postoperative day ≥1) during the index admission. Primary end point was 90-day mortality following surgery.

Results:

The median age of 12,056 patients identified was 70 years. A total of 7,201 (59.7%) patients received blood transfusion. Within 90 days following surgery, 57 (2.2%), 162 (5.9%) and 123 (6.7%) of patients in the early, delayed and both early and delayed transfused patients died respectively. Following multivariate logistic regression to account for patient (age and Charlson Comorbidity Index [CCI]) and hospital (surgeon volume, surgical approach and academic status) factors, delayed blood transfusion was independently associated with 90-day mortality (Odds ratio [OR], 2.64; 95% Confidence Interval [CI], 1.98-3.53; $p<0.001$). A sensitivity analysis defining early blood transfusion as <2 days postoperatively, increased 90-day mortality persisted in patients receiving delayed transfusion (OR, 2.20; 95% CI, 1.63-3.00; $p<0.001$). Older patients (≥77 years) with the highest CCI (≥2) had a 7% absolute increase in the predicted probability of 90-day mortality if they were transfused late compared to patients transfused early.

Conclusion:

Patient undergoing cystectomy may benefit from expedited transfusion to prevent subsequent clinical deterioration which may lead to patient mortality. Future work is needed to elucidate the optimal timing of blood transfusion.

Keywords: Blood transfusion, radical cystectomy, bladder cancer, mortality, timing

Introduction

The transfusion of blood products has risks and has been linked to higher infection rates, allergic reaction, immunosuppression, renal dysfunction, cost, mortality and even lower cancer specific survival [1-8]. The American Association of Blood Banks recommend a restrictive transfusion strategy which is associated with lower cost and is non-inferior to liberal blood transfusion based on randomized trials [9-11].

Blood loss of between 500-1000 ml following radical cystectomy (RC) is common and blood transfusion may be necessary [12,13]. A decrease in hematocrit results in lower oxygen carrying capacity and this has been associated with increased mortality [14]. For patients who already deconditioned, anemia attributed to acute blood loss may exacerbate fatigue and make postoperative convalescence difficult. It is established that preoperative anemia is associated with a higher perioperative mortality [15].

While the association between mortality and blood transfusion following RC has been established, the temporal association between when blood transfusion is administered has not been explored [16,17]. In patients with active bleeding, blood transfusion can be lifesaving. However, the decision of when to transfuse is more complex and clinicians must weigh the risks and benefits. Moreover, recent randomized data studying the use of minimally invasive RC has suggested decreased blood loss compared to open RC which in turn translates to a decrease in blood transfusion requirement [12,18].

In this study, we investigate if delayed blood transfusion is associated with a higher 90-day mortality following RC for bladder cancer. We hypothesize that early blood transfusion is associated with a lower risk of mortality in this patient cohort compared to a delayed blood transfusion.

Methods

Data source

Data was extracted from the Premier Hospital Database (Premier Inc., Charlotte, NC, USA), an all-payer hospital discharge database which allows for quality benchmarking and determination of healthcare utilization in the USA The Premier database encompasses over 700 academic and non-academic hospitals and contains admission information for 50 million patients representing 20% of inpatient discharges in the United States.

Patient selection

International Classification of Diseases, ninth revision (ICD-9) codes were used to identify adults aged ≥18 years who had RC for bladder cancer, between 2003-2015. All cases were performed electively.

Variable of interest

Transfusion of blood products were defined as transfusion of any blood products according to hospital charge description. Blood products were classified as packed red blood cells (PBRC), whole blood, fresh frozen plasma (FFP), platelets and cryoprecipitate. Early transfusion was defined as transfusion on the day of surgery and delayed transfusion defined as any transfusion from day one postoperative during the index admission. The following baseline patient variables were extracted: age (categorized by quartiles: ≤62 years, 63-69 years, 70-77 years, ≥77 years), sex (male, female), race (white, non-white), marital status (married, unmarried), insurance status (Medicare, Medicaid, private, other/unknown), and Charlson Comorbidity Index [CCI] (0, 1, ≥2). Clavian-dindo classification was defined using ICD-9 codes with major complications defined as grade III-V complications.

Hospital characteristics analyzed include: teaching hospital status (academic, non-academic), urban/ rural status (urban, rural) and geographical region (Northeast, Midwest, West, South). Surgical characteristics included: year of surgery (2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2015), annual surgeon volume (continuous) and surgical approach (open, minimal invasive). For patients undergoing radical cystectomy, type of diversion (continent orthotopic or cutaneous neobladder vs ileal or colonic conduit) and pelvic lymphadenectomy were also analyzed.

Outcomes

Patient who met the inclusion criteria were subdivided to those who received no blood transfusion vs those who had early blood transfusion vs those who had delayed blood transfusion. Primary endpoint was 90-day mortality following surgery.

Statistical analysis

Descriptive statistics for categorical variables were reported as frequencies and proportions and subgroups were compared using chi-square test. Continuous variables were reported as medians and interquartile ranges and Mann-Whitney U test was used to compared sub-groups. Regression models were adjusted for clustering. Multivariate logistic regression was used to adjust for confounding factors and used to test for interactions. Odds of 90-day mortality and type of complication following RC was adjusted for patient age, CCI, surgical volume, approach (minimally invasive vs. open) and academic hospital status was determined with early transfusion as a reference. A clinical issue may be the definition of what exactly constitutes an early vs. delayed transfusion. Hence, a sensitivity analysis was performed to define early blood transfusion as <48 hours following surgery vs delayed blood transfusion as >48 hours following surgery. Five-fold cross validation was performed to determine the accuracy of the regression model to avoid overfitting. Predicted probability for mortality was calculated based on a logistic regression model. A two-sided $p < 0.05$ was defined as statistically significant. Statistical analysis was performed using Stata version 15 (StataCorp, College Station, TX, USA).

Ethical approval of studies and informed consent

A waiver was obtained before commencement of the study by the Brigham and Women’s Hospital Institutional review board in accordance with institutional regulation when using deidentified previously collected patient data.

Results

A total of 12,056 patients who had an elective RC were included for analysis (Table 1). There was a decrease in both early and delayed blood transfusion over a 13-year period between 2003 and 2015. This coincided with an increase uptake of minimal invasive RC which increased from 8.5% in 2003 to 36.8% in 2015. Patients treated with minimal invasive RC had a greater decline in early, late and patients with both early and late blood transfusion over time compared to open RC cases (Figure 1). Median PRBC transfused was 1 (Interquartile range [IQR]: 0-2, range: 0-57). The median age of the patient cohort was 70 years (IQR, 63, 77). Delayed blood transfusion was not associated with patient age or comorbidity on multivariable analysis.

A total of 401 patients (3.3%) from the whole cohort died within 90-day of surgery with patients receiving early transfusion and delayed transfusion accounting for 57 (2.2%) and 162 (5.9%) of patients respectively. A total of 123 (6.7%) patients who received both early and delayed transfusion died. Patients who died within 90-days were significantly older (median age: 74 years vs 69 years, $p<0.001$) and had more comorbid conditions (CCI ≥2, 54.1% vs 30.0%; $p<0.001$).

Multiple factors were associated with a higher 90-day mortality on multivariate logistic regression analysis. Any transfusion requirement, regardless whether early (Odds ratio [OR], 1.56; 95% Confidence Interval [CI], 1.13-2.17; $p=0.007$), delayed (OR, 4.07; 95% CI, 3.09-5.36; $p<0.001$) or early and delayed (OR, 4.44; 95% CI, 3.26-6.06; $p<0.001$) were independently associated with a higher 90-day mortality compared to patients who did not receive a transfusion. Sensitivity analysis also confirms that any blood transfusion was independently associated with any 90-day complications (early

[OR, 1.16; 95% CI, 1.01-1.33; p=0.033], delayed [OR, 1.81; 95% CI, 1.62-2.02; p<0.001], early and delayed [OR, 2.09; 95% CI, 1.78-2.45; p<0.001]) and 90-day major complications (early [OR, 1.21; 95% CI, 1.02-1.43; p=0.032], delayed [OR, 2.83; 95% CI, 2.47-3.25; p<0.001], early and delayed [OR, 3.76; 95% CI, 3.16-4.47; p<0.001]) following multivariate regression analysis. Other factors include increasing age [70-76 years (OR,1.81; 95% CI, 1.16-2.83; p=0.009), ≥77 years (OR, 2.78; 95% CI, 1.86-4.16; p<0.001)], higher CCI [CCI 1 (OR, 1.53; 95% CI, 1.16-2.02; p=0.002), CCI ≥2 (OR, 2.68; 95% CI, 2.08-3.46; p<0.001)]. Finally, non-academic hospitals (OR, 1.30; 95% CI, 1.04-1.64; p=0.024) were associated with a higher 90-day mortality on multivariate logistic regression analysis.

Table 2 reports unadjusted and adjusted models on the influence of delayed transfusion with early transfusion as the reference standard. Even after adjusting for patient factors such as patient age and CCI as well as institutional factors such as surgeon volume, surgical approach and academic hospital status, delayed blood transfusion remained independently associated with increased 90-day mortality (OR, 2.64; 95% CI, 1.94-3.60; p<0.001) (Table 2).

Sensitivity analysis performed confirmed similar outcomes following adjustment for patient (age, CCI) and institutional factors (surgical volume, approach and academic hospital status) (OR, 2.20; 95% CI, 1.63-3.00; p<0.001) even when early blood transfusion as <48 hours following surgery vs delayed blood transfusion as >48 hours following surgery. Further, subsequent adjustment for patient and institutional factors patients receiving both early and delayed transfusion had an even higher odds ratio of 2.81 (95% CI, 2.13-3.70; p<0.001) compared to patients transfused early (Supplementary Table 1). When only patients who experienced bleeding as a complication perioperatively (n=4,668), delayed blood transfusion (>24 hours) was associated with a high odds ratio of 90-day mortality (OE, 2.62; 95% CI, 1.79-3.84; $p<0.001$) compared to early blood transfusion following adjustment for patient and institutional factors.

Table 3 report the odds ratio of delayed transfusion for type of complication following radical cystectomy in an unadjusted and adjusted model with early transfusion as a reference. Following adjustment for both patient and institutional factors, cardiovascular ($p<0.001$), infection ($p<0.001$), renal ($p<0.001$), venous thromboembolism ($p<0.001$) and wound/ soft tissue ($p<0.001$) related complications were associated with a delayed blood transfusion (Table 3). This was also similar in patients receiving both early and delayed transfusion (Supplementary Table 2). There was no difference in transfusion related reaction and timing of transfusion.

Interaction between patient age and CCI was tested and absolute differences in predicted probability of mortality between patients receiving a delayed transfusion vs early transfusion was calculated as shown in Figure 2. Older patients with greater comorbidities who received delayed transfusions had notable increases in the predicted probability of mortality. Patients with CCI ≥2 who were ≥77 years who had a delayed blood transfusion had a 7.0% absolute increase in predicted probability of 90-day mortality compared to early transfusion patients (Figure 2).

Discussion

We report that patients treated with RC receiving a delayed blood transfusion had a higher 90-day mortality compared to patients receiving early blood transfusion. This was most pronounced in patients who were older and those who had more comorbidities. Moreover, a sensitivity analysis examining a 48-hour cutoff to define early transfusion confirmed similar results. For patients undergoing RC, delayed blood transfusion was associated with higher odds of 90-day mortality (p<0.001) compared to patients receiving early blood transfusion and this was even higher in patients receiving both early and delayed blood transfusions (p<0.001).

Clinical guidelines support the use of restrictive transfusion strategies and recommend a hemoglobin threshold of <7 g/dL to trigger for blood transfusion for most patients and a hemoglobin of 8-10 g/dL for high-risk patients.[9] This strategy is supported by randomized data in cardiac surgery where restrictive transfusion (Hb <7.5 g/dL) was non-inferior to liberal transfusion (Hb <9.5 g/dL) at 6 months [10]. Randomized data from critical care patients also support the use of a hemoglobin threshold of <7 g/dL and <9 g/dL for high risk patients to trigger transfusion in euvolemic patients [11]. However, there remains no primary data in non-cardiac patients particularly in patients undergoing pelvic surgery.

In clinical practice, many physicians appropriately adopt a “wait and see” approach when patients are at the cusps of the transfusion threshold rather than initiate blood transfusion. This may be due to multiple factors such as worse outcomes associated with blood transfusion, risk of adverse transfusion events and cost [2,5-8]. Further, an analysis of 360 RC patients reported that intraoperative blood transfusion was associated with a higher cancer specific survival at 5 years which was hypothesized to be related to immunomodulation of the immune system [8].

The decision to transfuse is multi-factorial and dependent on the combination of patient comorbidity, clinical hydration and trending serial hemoglobin results. As such, blood transfusion may not be administered in a prompt manner. Our results support the use of early blood transfusion and this may be advantageous compared to a 'watch and wait approach' with the eventuality of a delayed transfusion. Patients undergoing RC are distinct from other complex surgery. Blood loss during RC is very common particularly in patients treated with open surgery [18]. The combination of prolonged operating times, insensible fluid loss and third spacing makes clinical assessment of intravascular hydration status difficult and often inaccurate. Moreover, complexity of fluid and electrolyte shifts due to the use of bowel for urinary diversion are exacerbated particularly during weaning from intravenous fluids to oral fluids [19]. This results in subsequent reduction in intravascular fluid which can be further compounded by acute blood loss anemia which is common. Hence, these patients are distinct from cardiac surgery patients who have continued invasive monitoring of intravascular volume status.

Given the non-inferiority between liberal vs restrictive transfusion in cardiac surgery, we would further expand this argument when examining RC patients [10]. The finding that liberal transfusion was not associated with higher mortality, particularly in the case of RC, may suggest that when in doubt about the requirement of transfusion in patients with borderline indications, the risk of an early transfusion outweighs the risk of a delayed transfusion in patients treated with RC. In fact, the decision to transfuse early may represent an opportunity to modify the risk of mortality in a comorbid elderly patient population with immutable risk factors following complex surgery.

For a morbid operation, such as cystectomy, searching for preventable sources of complications is appealing. The concept of pre-habilitation is gaining popularity in preparation of patients undergoing planned RC [20]. Candidates for RC are often anemic due to hematuria and addressing preoperative anemia as part of pre-habilitation by intravenous iron is an attractive approach [21,22]. Randomized data has confirmed that blood transfusion requirement following a robotic RC is significantly lower than open cystectomy [12,18]. However, further research is required to elucidate the complex interplay between preoperative anemia, timing and requirement of blood transfusion and surgical approach.

We acknowledge limitations within the current study. Data utilized were retrospectively collected and subjected to retrospective bias and unknown confounders. In addition, we cannot determine causality but only an association between blood transfusion and mortality. While we hypothesized that delayed transfusion lead to subsequent complication and death, it is plausible that other complications may result in the need for transfusion and the complications itself eventually lead to patient death. The Premier database does record preoperative hemoglobin results or preoperative transfusion. Hence, we are unable to determine what is the hemoglobin level where patients were prescribed a blood transfusion. However, historic studies would suggest that over 90% of patients would have transfusion at a hemoglobin concentration of 8.0 g/dL [23]. We do not have information on patient cancer stage and the use of chemotherapy which can affect hemoglobin levels and the requirement for transfusion. Lastly, we cannot capture clinician judgment in cases where transfusions were administered because they were deemed to be appropriate based on clinical decision-making which supersedes guidelines.

We report a temporal association between blood transfusion and 90-day mortality where RC patients transfused in a delayed fashion had significantly higher mortality compared to patients transfused early. While the principles of restrictive transfusion are helpful in guiding clinical practice, patient undergoing RC may benefit from expedited transfusion to prevent subsequent clinical deterioration which may lead to patient mortality. Further work is required to understand the optimal timing of blood transfusion in RC patients.

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Conflict of interest/ competing interests: The authors report no conflict of interest related to the current manuscript.

Ethical approval:

A waiver was obtained before commencement of the study by the Brigham and Women's Hospital Institutional review board in accordance with institutional regulation when using deidentified previously collected patient data.

Disclaimer: The Premier Hospital Database is the source of de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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Tables:

Table 1: Patient demographics and complications stratified by all patients, no blood transfusion, early transfusion, late transfusion and early and late transfusion.

Table 2: Unadjusted and adjusted odds ratio of 90-day mortality and delayed transfusion compared to early transfusion.

Table 3: Unadjusted and adjusted odds ratio for classification of 90-day complications and delayed transfusion compared to early transfusion.

Figures:

Figure 1: Trends of early and delayed transfusion for A) over and B) minimal invasive radical cystectomy over time

Figure 2: Predicted probability of mortality for patients with absolute differences based on fitting interactions effects of CCI and patient age in adjusted logistic regression model in patients receiving a delayed transfusion.

Supplementary Tables:

Supplementary Table 1: Unadjusted and adjusted odds ratio of mortality and patients with early and delayed transfusion compared to early transfusion only.

Supplementary Table 2: Unadjusted and adjusted odds ratio for classification of 90-day complication and early and late transfusion with early transfusion as a reference.

Table 1: Patient demographics and complications stratified by all patients, no blood transfusion, early transfusion, late transfusion and early and late transfusion.

Variable	All patients (n=12,056)	No blood products (n=4,855)	Early transfusion (n=2,614)	Late transfusion (n=2,753)	Early & late transfusion (n=1,834)	P value
Age quartiles, n (%)						
≤62 years	2,975 (24.7)	1,388 (28.6)	596 (22.8)	604 (21.9)	387 (21.1)	<0.001
63-69 years	2,767 (23.0)	1,204 (24.8)	566 (21.6)	592 (21.5)	405 (22.1)	
70-76 years	3,237 (26.8)	1,216 (25.0)	742 (28.4)	742 (27.0)	537 (29.3)	
≥77 years	3,077 (25.5)	1,047 (21.6)	710 (27.2)	815 (29.6)	505 (27.5)	
Sex, n (%)						
Male	2,124 (17.6)	4,351 (89.6)	2,102 (80.4)	2,148 (78.0)	1,331 (72.6)	<0.001
Female	9,932 (82.4)	504 (10.4)	512 (19.6)	605 (22.0)	503 (27.4)	
Race, n (%)						
White	9,618 (79.8)	3,963 (81.6)	2,075 (79.4)	2,154 (78.2)	1,426 (77.8)	<0.001
Non-white	2,438 (20.2)	892 (18.4)	539 (20.6)	599 (21.8)	408 (22.2)	
Marital status, n (%)						
Married	7,149 (59.3)	3,021 (62.2)	1,565 (59.9)	1,562 (56.7)	1,001 (54.6)	<0.001
Unmarried	4,907 (40.7)	1,834 (37.8)	1,049 (40.1)	1,191 (43.3)	833 (45.4)	
CCI, n (%)						
0	5,002 (41.5)	2,355 (48.5)	1,085 (41.5)	984 (35.7)	578 (31.5)	<0.001
1	3,346 (27.7)	1,369 (28.2)	723 (27.7)	774 (28.1)	480 (26.2)	
≥2	3,708 (30.8)	1,131 (23.3)	806 (30.8)	995 (36.2)	776 (42.3)	
Year of diagnosis, n (%)						
2003-2004	1,411 (11.7)	444 (9.1)	331 (12.7)	390 (14.2)	246 (13.4)	<0.001
2005-2006	1,511 (12.5)	485 (10.0)	370 (14.1)	397 (14.4)	259 (14.1)	
2007-2008	1,836 (15.2)	615 (12.7)	443 (17.0)	501 (18.2)	277 (15.1)	
2009-2010	2,043 (17.0)	709 (14.6)	505 (19.3)	492 (17.9)	337 (18.4)	
2011-2012	2,255 (18.7)	975 (20.1)	435 (16.6)	495 (18.0)	350 (19.1)	
2013-2015	3,000 (24.9)	1,627 (33.5)	530 (20.3)	478 (17.3)	365 (19.9)	
Annual surgeon volume, n (%)						<0.001
≤2	5,953 (49.4)	2,109 (43.4)	1,331 (50.9)	1,431 (52.0)	1,082 (59.0)	
≥3	6,103 (50.6)	2,746 (56.6)	1,293 (49.1)	1,322 (48.0)	752 (41.0)	
Surgical approach						<0.001
Open	9,271 (76.9)	3,413 (70.3)	2,126 (81.3)	2,238 (81.3)	1,494 (81.5)	
Minimal invasive	2,785 (23.1)	1,442 (29.7)	488 (18.7)	515 (18.7)	340 (18.5)	
Lymph node dissection						
Yes	9,390 (77.9)	3,980 (82.0)	2,034 (77.8)	2,031 (73.8)	1,345 (73.3)	<0.001
No	2,666 (22.1)	85 (18.0)	580 (22.2)	722 (26.2)	489 (26.7)	
Insurance status, n (%)						
Medicare	8,039 (66.7)	3,017 (62.1)	1,784 (68.2)	1,945 (70.7)	1,293 (70.5)	<0.001
Medicaid	491 (4.1)	198 (4.1)	99 (3.8)	125 (4.5)	69 (3.7)	
Private	2,954 (24.5)	1,386 (28.6)	616 (23.6)	564 (20.5)	388 (21.2)	
Other	572 (4.7)	254 (5.2)	115 (4.4)	119 (4.3)	84 (4.6)	
Region urban/ rural, n (%)						
Rural	733 (6.1)	265 (5.5)	171 (6.5)	165 (6.0)	132 (7.2)	0.040
Urban	11,323 (93.9)	4,590 (94.5)	2,443 (93.5)	2,588 (94.0)	1,702 (92.8)	
Academic center, n (%)						
Academic	7,286 (60.4)	2,909 (59.9)	1,626 (62.2)	1,689 (61.4)	1,026 (57.9)	0.020
Non-academic	4,770 (39.6)	1,946 (40.1)	988 (37.8)	1,064 (38.7)	772 (42.1)	
Region, n (%)						
Northeast	2,515 (20.8)	987 (20.3)	492 (18.8)	631 (22.9)	405 (22.1)	<0.001
Midwest	2,048 (17.0)	738 (15.2)	492 (18.8)	507 (18.4)	311 (17.0)	
South	5,568 (46.2)	2,339 (48.2)	1,216 (46.5)	1,198 (43.5)	815 (44.4)	
West	1,925 (16.0)	791 (16.3)	414 (15.9)	417 (15.2)	303 (16.5)	
Complications, n (%)						
No complications	6,006 (49.8)	2,572 (53.0)	1,410 (53.9)	1,266 (46.0)	758 (41.3)	<0.001
Any complications	6,050 (50.2)	2,283 (47.0)	1,204 (46.1)	1,487 (54.0)	1,076 (58.7)	
Major complications, n (%)						
No/ minor complications	10,362 (86.0)	4,446 (91.6)	2,357 (90.2)	2,202 (80.0)	1,357 (74.0)	<0.001
Major complications	1,694 (14.0)	409 (8.4)	257 (9.8)	551 (20.0)	477 (26.0)	

Table 2: Unadjusted and adjusted odds ratio of 90-day mortality and delayed transfusion compared to early transfusion.

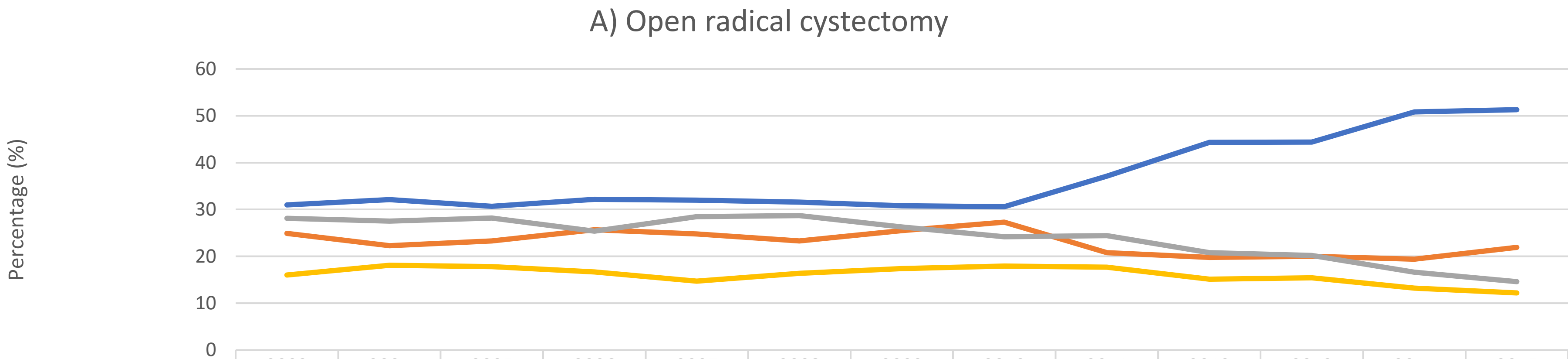
Complication	**Delayed transfusion (OR, 95% CI)**
Unadjusted	2.80 (2.08-3.78)
Adjusted for patient age	2.78 (2.06-3.74)
Adjusted for CCI	2.68 (1.99-3.59)
Adjusted for age and CCI	2.66 (1.98-3.57)
Adjusted for surgical volume	2.80 (2.09-3.75)
Adjusted for surgical approach	2.80 (2.08-3.78)
Adjusted for academic hospital status	2.80 (2.08-3.76)
Adjusted for surgical volume, approach and academic hospital status	2.80 (2.09-3.74)
Adjusted for patient age, CCI, surgical volume, approach and academic hospital status	2.64 (1.98-3.53)

Table 3: Unadjusted and adjusted odds ratio for classification of 90-day complications and delayed transfusion compared to early transfusion.

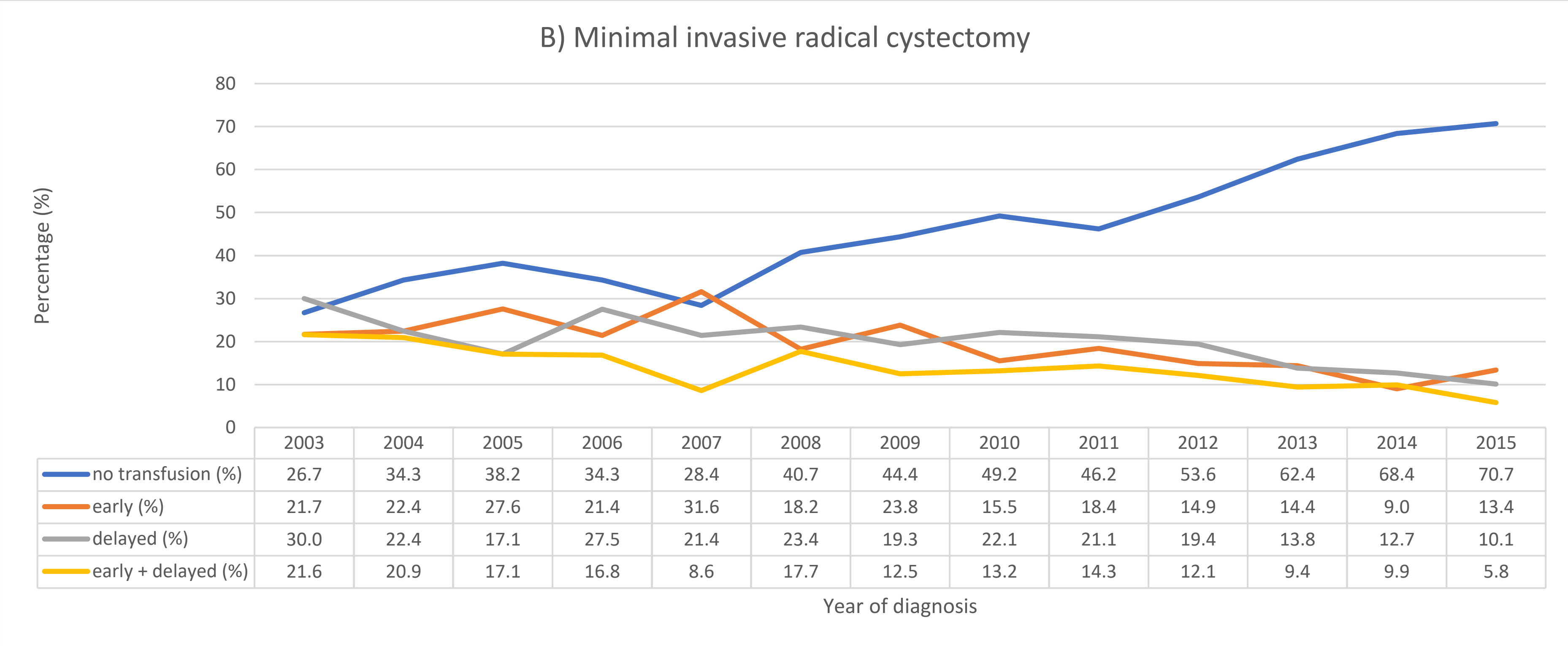
Type of complication	Delayed transfusion (Unadjusted model)	Delayed transfusion (*Adjusted model)
Cardiovascular	1.70 (1.46-1.97), p<0.001	1.62 (1.40-1.87), p<0.001
Infection	2.88 (2.41-3.44), p<0.001	2.82 (2.40-3.31), p<0.001
Renal	1.94 (1.68-2.25), p<0.001	1.89 (1.65-2.16), p<0.001
VTE	2.58 (1.88-3.54), p<0.001	2.51 (1.82-3.45), p<0.001
Wound/ soft tissue	2.70 (2.08-3.50), p<0.001	2.59 (2.00-3.36), p<0.001
Transfusion related adverse reaction	0.95 (0.59-15.27), p=0.97	0.84 (0.03-21.40), p=0.92

*Adjusted for patient age, CCI, surgical approach, surgical volume and academic hospital status

Figure 1: Trends of early and delayed transfusion for A) over and B) minimal invasive radical cystectomy over time

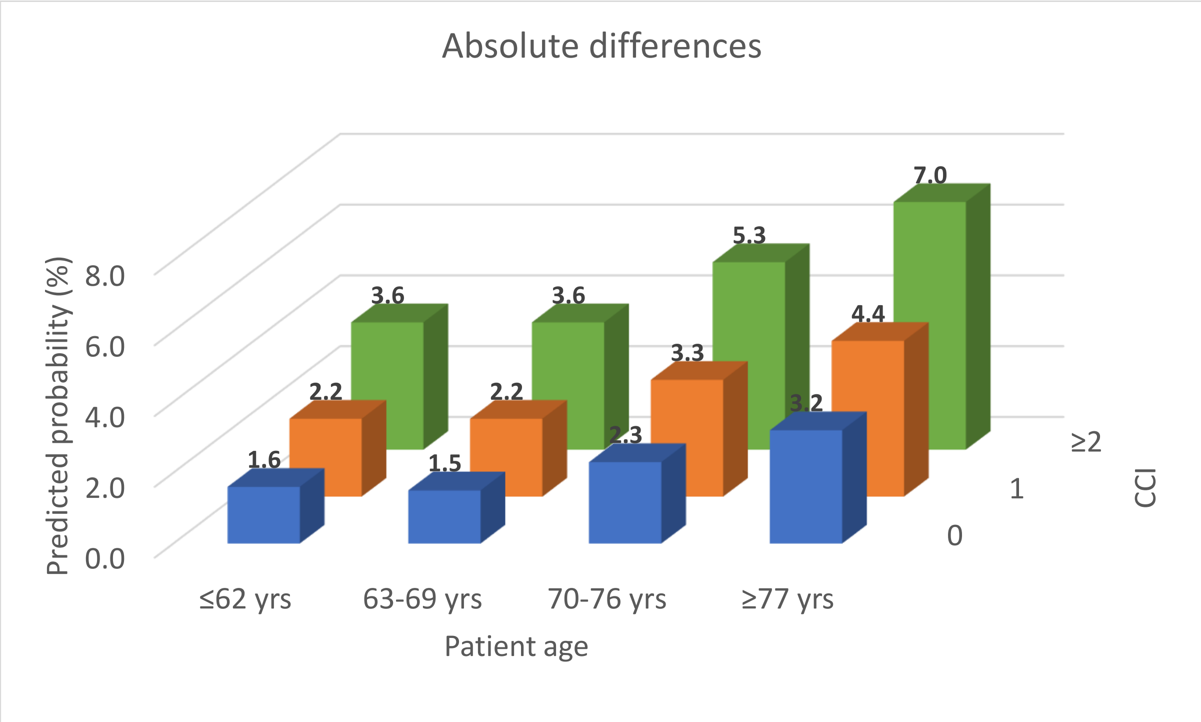


	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
no transfusion (%)	31.0	32.1	30.7	32.2	32.0	31.6	30.8	30.6	37.1	44.3	44.4	50.8	51.3
early (%)	24.9	22.3	23.3	25.7	24.8	23.3	25.5	27.3	20.8	19.8	20.0	19.4	21.9
delayed (%)	28.1	27.5	28.2	25.4	28.5	28.7	26.3	24.2	24.4	20.8	20.2	16.6	14.6
early + delayed (%)	16.0	18.1	17.8	16.7	14.7	16.4	17.4	17.9	17.7	15.1	15.4	13.2	12.2



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
no transfusion (%)	26.7	34.3	38.2	34.3	28.4	40.7	44.4	49.2	46.2	53.6	62.4	68.4	70.7
early (%)	21.7	22.4	27.6	21.4	31.6	18.2	23.8	15.5	18.4	14.9	14.4	9.0	13.4
delayed (%)	30.0	22.4	17.1	27.5	21.4	23.4	19.3	22.1	21.1	19.4	13.8	12.7	10.1
early + delayed (%)	21.6	20.9	17.1	16.8	8.6	17.7	12.5	13.2	14.3	12.1	9.4	9.9	5.8

Figure 2. Predicted probability of mortality for patients with absolute differences based on fitting interactions effects of CCI and patient age in adjusted logistic regression model in patients receiving a delayed transfusion.



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Supplementary Table 1: Unadjusted and adjusted odds ratio of mortality and patients with early and delayed transfusion compared to early transfusion only.

Complication	**Early & delayed transfusion (OR, 95% CI)**
Unadjusted	3.22 (2.35-4.43)
Adjusted for patient age	3.21 (2.34-4.40)
Adjusted for CCI	2.95 (2.13-4.08)
Adjusted for age and CCI	2.96 (2.14-4.09)
Adjusted for surgical volume	3.18 (2.31-4.37)
Adjusted for surgical approach	3.22 (2.35-4.43)
Adjusted for academic hospital status	3.16 (2.30-4.36)
Adjusted for surgical volume, approach and academic hospital status	3.15 (2.29-4.34)
Adjusted for patient age, CCI, surgical volume, approach and academic hospital status	2.88 (2.08-3.99)

Supplementary Table 2: Unadjusted and adjusted odds ratio for classification of 90-day complication and early and late transfusion with early transfusion as a reference.

Type of complication	Late transfusion (Unadjusted model)	Late transfusion (*Adjusted model)
Cardiovascular	1.98 (1.71-2.28), p<0.001	1.77 (1.52-2.07), p<0.001
Infection	3.44 (2.95-4.02), p<0.001	3.25 (2.78-3.81), p<0.001
Renal	2.67 (2.32-3.07), p<0.001	2.44 (2.10-2.84), p<0.001
VTE	2.83 (2.04-3.91), p<0.001	2.80 (2.01-3.90), p<0.001
Wound/ soft tissue	3.54 (2.65-4.74), p<0.001	3.27 (2.43-4.39), p<0.001
Transfusion related adverse reaction	5.71 (0.64-50.64), p=0.12	5.30 (0.58-48.03), p=0.14

*Adjusted for patient age, CCI, surgical approach, surgical volume and academic hospital status