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TRANSFUSION MEDICINE

TRANSFUSION

Oncological impact of perioperative blood transfusion in bladder cancer patients undergoing radical cystectomy: Do we need to consider storage time of blood units, donor age, or gender matching?

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Abstract

Background: The oncological impact of perioperative blood transfusions (PBTs) of patients undergoing radical cystectomy (RC) because of bladder cancer (BCa) has been a controversial topic discussed in recent years. The main cause for the contradictory findings of existing studies might be the missing consideration of the storage time of red blood cell units (BUs), donor age, and gender matching.

Study Design and Methods: We retrospectively analyzed BCa patients who underwent RC in our department between 2004 and 2021. We excluded patients receiving BUs before RC, >10 BUs, or RC in a palliative setting. We assessed the effect of blood donor characteristics and storage time on overall survival (OS) and cancer-specific survival (CSS) through univariate and multivariable Cox regression analysis. We also performed a propensity score matching with patients who received BUs and patients who did not on a 1:1 ratio.

Results: We screened 1692 patients and included 676 patients for the propensity score matching. In the multivariable analysis, PBT was independently associated with worse OS and CSS ($p < .001$). Postoperative transfusions were associated with better OS ($p = .004$) and CSS ($p = .008$) compared to intraoperative or mixed transfusions. However, there was no influence of blood donor age, storage time, or gender matching on prognosis.

Discussion: In our study of BCa patients undergoing RC, we demonstrate that PBT, especially if administered intraoperatively, is an independent risk factor for a worse prognosis.
However, storage time, donor age, or gender matching did not negatively affect oncological outcomes. Therefore, the specific selection of blood products does not promise any benefits.

1 | INTRODUCTION

For patients with muscle-invasive or very high-risk non-muscle-invasive bladder cancer (BCa), radical cystectomy (RC) in combination with perioperative chemotherapy is a curative therapeutic option.[1] RC is often performed in multimorbid patients and is associated with significant perioperative morbidity.[2] About 9 to 75% of all patients undergoing RC for BCa require allogenic perioperative blood transfusion (PBT).[3–5] Allogenic PBT can cause transient, yet profound immunosuppressive effects in the recipient also referred to as transfusion-related immune modulation (TRIM).[6] Numerous responsible mediators have been identified, including cytokines, eicosanoids, and growth factors like TGF-β, VEGF, or PDGF-D.[6,7] Surgical manipulation can lead to hematogenic tumor cell circulation.[8,9] Therefore, any kind of perioperative immunosuppression might facilitate distal seeding of circulating tumor cells during surgical resection.[10,11] Accordingly, several studies proposed that TRIM might promote tumor growth in cancer patients.[6,7] However, the available literature is inconclusive about the role of PBT and the impact of intra- versus postoperative PBT[12] on oncological outcomes in patients undergoing surgery due to different types of cancer, including BCa.[5,11,13–17] In the most recent meta-analysis of 15 studies including 21,915 BCa patients undergoing RC, PBT was associated with an increased risk of all-cause and cancer-specific mortality.[5] The main cause for these contradictory findings in existing retrospective studies might be an incomplete consideration of blood-donor and transfusion-specific variables including storage time of red blood cell units (BUs),[18] donor age,[19,20] and gender matching.[21] For BUs stored for more than 14 days, increased markers of RBC storage lesions were reported.[18] A preclinical study suggested that transfusion of erythrocytes with a storage duration of ≥9 days might stimulate stronger tumor growth compared to transfusion of erythrocytes with shorter storage.[22] Two large cohort studies including 30,503 and 97,886 patients investigated the impact of blood donor age on overall survival (OS) of patients receiving BUs for various reasons.[19,20] The authors reported that receiving a BU from a younger donor compared to an older donor was associated with higher in-hospital mortality.[19,20] In a meta-analysis including 86,737 patients undergoing PBT for multiple indications, gender mismatch between donor and recipient was associated with an increased risk of mortality.[21] Of note, the oncological impact of blood donor-specific variables has not been assessed in BCa yet. Therefore, we present the first study investigating the influence of storage time of BUs, donor's age, and gender matching between donor and recipient on oncologic outcomes of BCa patients undergoing RC.

2 | MATERIALS AND METHODS

2.1 | Study design and selection criteria

This retrospective cohort study was conducted at the Department of Urology, University Hospital, LMU Munich, Germany. Findings were reported based on the STROBE statement for cohort studies.[23] We reviewed the prospectively collected RC database of our department and included all BCa patients who underwent RC with any urinary diversion between January 2004 and March 2021. We excluded patients who received BUs preoperatively, or more than 10 BUs perioperatively, as well as patients undergoing RC for palliative or non-oncological indications. Ethnicity distribution of included patients was not available, since this kind of information is not documented in our department. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institutional ethical committee.

2.2 | Data collection and follow-up

Follow-up was performed by annual written questionnaires and perioperative data was assessed from the medical records. The indication for PBT was based on the discretion of the treating physicians. For patients who underwent allogenic PBT, we obtained the corresponding transfusion data from the Division of Transfusion

Medicine of our hospital. These data included ABO blood group and Rhesus type from both donor and recipient, as well as the exact storage time of the respective BUs before transfusion. Information on blood donor age and gender was obtained through the Eurocode International Blood Labelling System (IBLS).

2.3 | Outcomes

The co-primary outcomes of the present study were the impact of BU storage time, donor age, and gender matching between donor and recipient on OS of BCa patients receiving RC and PBT. Secondary outcomes included: (i) the role of these factors on cancer-specific survival (CSS), (ii) the effect of transfusion on OS and CSS, and (iii) the impact of the timing of PBT on OS and CSS.

2.4 | Propensity score matching and statistical analysis

All patients undergoing PBT were matched with those who did not undergo PBT on a 1:1 ratio through an optimal pair propensity score matching. The two groups were adjusted for sex, age, body mass index, T-stage, and positive lymph nodes after RC. Covariate balance was evaluated with Love plots, and an absolute standardized mean difference below 0.1 indicated adequate matching balance.

Continuous variables were summarized as mean with standard deviation (SD) or median with interquartile range (IQR) and categorical variables as proportions. The assessment of normality and the comparisons between groups were performed with the corresponding statistical tests. The Kaplan–Meier curves with the log-rank test were used to compare OS and CSS in patients undergoing PBT versus no PBT, as well as in patients who received BUs solely intraoperatively versus solely postoperatively (in-hospital) versus both intra- and postoperatively.

In patients undergoing PBT, a univariate Cox regression analysis was performed to assess the effect of gender match between blood donor and recipient, donor age and the storage time on OS and CSS. The effect of these predictors on OS and CSS was also evaluated through a multivariable Cox regression analysis adjusted for preoperative Hb, number of BUs transfused, recipient's sex, age, and body mass index, as well as T-stage and positive lymph nodes after RC. Included independent variables were chosen based on clinical relevance. The proportional hazards assumption was evaluated both statistically with the goodness of fit test and graphically with Kaplan–Meier curves. We resolved any discrepancies with the two tests through construction of observed versus predicted curves and log-minus-log plots. For all survival outcomes, we estimated hazard ratios (HRs) with 95% confidence intervals (CIs) and a two-sided p-value $<.05$ was considered statistically significant. All analyses were undertaken with the R statistical software (version 3.6.3).

3 | RESULTS

3.1 | Baseline characteristics

A total of 676 patients were matched in a 1:1 ratio (PBT/no PBT). Of them, 149 (44%) received BUs intraoperatively, 111 (33%) postoperatively, and 78 (23%) both intra- and postoperatively. Of note, only eight patients (2.4%) received BUs with a compatible, but not identical blood group. Eight Rhesus-positive patients (2.4%) received Rhesus negative BUs, and four patients (1.2%) received gamma-irradiated BUs with an energy dose from 25 to 50 Gy. At a median follow-up of 23 months (IQR: 8–50), 307 (45%) patients died. Of them, 183 deaths occurred in the PBT group and 124 in the no-PBT group. The patient selection process is illustrated in Figure 1. Overall, the mean patient age was 71 ± 10 years, and 477 (71%) patients were male. A total of 43 (6.4%) patients displayed variant histology, 180 (27%) positive lymph nodes (pN+), and 351 (52%) locally advanced BCa (pT≥3) at the time of RC. The mean preoperative Hb was 12.1 ± 2.1 g/dL in patients requiring PBT and 13.7 ± 1.6 g/dL in patients without PBT ($p < .001$) (Table 1). In sum, propensity matching led to evenly distributed groups regarding key prognostic parameters.

3.2 | Effect of blood donor characteristics and storage duration of blood units on survival

Patients requiring PBT received a mean of 2.8 ± 2.1 BUs. A complete sex match between donor and recipient was achieved in 94 (28%) cases and a complete sex mismatch in 82 (24%) cases, while 162 (48%) patients received BUs from both males and females. In the univariate Cox regression analysis, the gender match between donor and recipient did not influence OS (Table 2) or CSS (Table 3). More specifically, patients with complete sex mismatch displayed similar OS (HR: 0.87, 95% CI: 0.58 to 1.30, $p = .5$) and CSS (HR: 0.87, 95% CI: 0.52 to 1.47, $p = .8$) compared to complete sex match. Patients who received BUs from both males and females also displayed similar OS (HR: 0.95, 95% CI: 0.67 to 1.34, $p = .8$) and CSS (HR: 1.04, 95% CI: 0.67 to 1.61, $p = .9$) compared to those with complete sex match. Cox regression analysis also

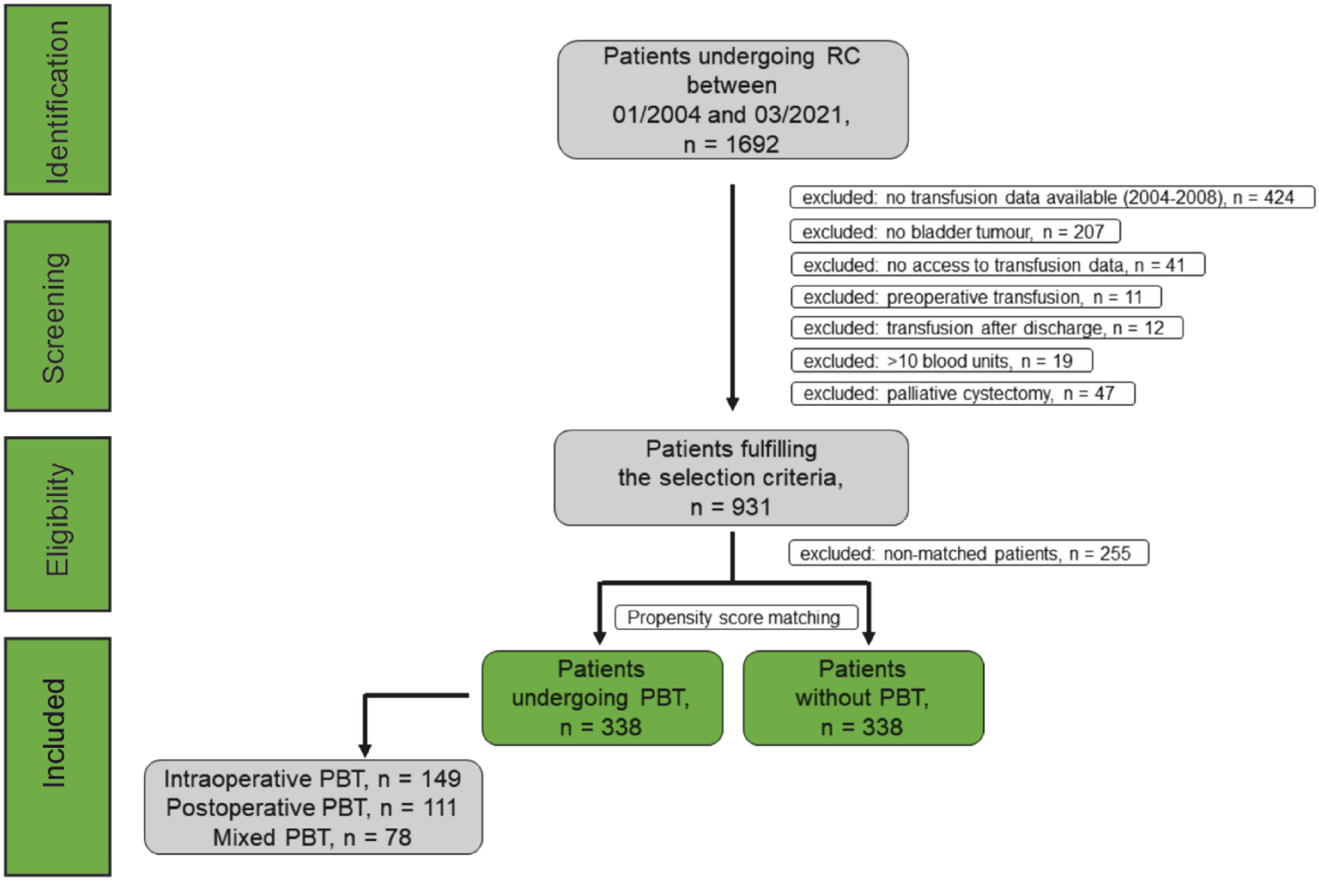

FIGURE 1 Patient selection process. PBT: perioperative blood transfusion; RC: radical cystectomy. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics of patients receiving perioperative blood transfusion versus no blood transfusion.

Characteristic	Overall, $n = 676$	No transfusion, $n = 338$	Transfusion, $n = 338$	p-value
Male	477 (70.6%)	244 (72.2%)	233 (68.9%)	.4
Age (years)	71.4 ± 9.9	71.3 ± 9.7	71.5 ± 10.1	.8
BMI (kg/m^2)	26.4 ± 4.3	26.3 ± 4.0	26.5 ± 4.5	.6
Histology				.8
Urothelial cancer	633 (93.6%)	315 (93.2%)	318 (94.1%)	
Variant histology	43 (6.4%)	23 (6.8%)	20 (5.9%)	
T after cystectomy				.4
Non-muscle invasive	192 (28.4%)	97 (28.7%)	95 (28.1%)	
T2	133 (19.7%)	70 (20.7%)	63 (18.6%)	
T3	256 (37.9%)	131 (38.8%)	125 (37.0%)	
T4	95 (14.1%)	40 (11.8%)	55 (16.3%)	
Positive lymph nodes	180 (26.6%)	89 (26.3%)	91 (26.9%)	>.9
Preoperative Hb (g/dL)	12.9 ± 2.0	13.7 ± 1.6	12.1 ± 2.1	**<.001**
Operation time (minutes)	233.3 ± 62.6	236.2 ± 63.6	230.4 ± 61.6	.2

Note: Values presented as mean ± standard deviation or *n* (%). The t test was performed for comparisons between continuous variables and the chi-squared test between categorical variables.
Abbreviation: BMI, body mass index.

TABLE 2 Univariate and multivariate Cox regression models for overall survival in patients receiving perioperative blood transfusion.

	Univariate			Multivariable		
Characteristic	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex of donor versus recipient						
Gender match	—	—		—	—	
Mixed	0.95	0.67, 1.34	.8	0.80	0.53, 1.21	.3
Gender mismatch	0.87	0.58, 1.30	.5	0.89	0.58, 1.36	.6
Age of donor	1.01	1.00, 1.03	.059	1.01	0.99, 1.03	.2
Storage time	1.02	1.00, 1.04	**.022**	1.01	0.99, 1.04	.2
Sex of recipient				0.97	0.70, 1.33	.8
Age of recipient				1.03	1.01, 1.05	**.001**
BMI of recipient				0.99	0.95, 1.03	.6
T after cystectomy						
2				0.90	0.54, 1.51	.7
3				1.44	0.92, 2.25	.11
4				2.80	1.71, 4.59	**<.001**
Number of units transfused				1.15	1.06, 1.25	**<.001**
Positive lymph nodes				1.90	1.35, 2.68	**<.001**
Preoperative Hb				0.89	0.83, 0.96	**.002**

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

TABLE 3 Univariate and multivariate Cox regression models for cancer specific survival in patients receiving perioperative blood transfusion.

	Univariate			Multivariable		
Characteristic	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex of donor versus recipient						
Gender match	—	—		—	—	
Mixed	1.04	0.67, 1.61	.9	1.12	0.66, 1.91	.7
Gender mismatch	0.87	0.52, 1.47	.6	0.93	0.54, 1.61	.8
Age of donor	1.02	1.00, 1.04	**.038**	1.01	0.99, 1.03	.2
Storage time	1.02	0.99, 1.04	.2	1.01	0.98, 1.03	.6
Sex of recipient				1.08	0.73, 1.61	.7
Age of recipient				1.02	1.00, 1.04	.11
BMI of recipient				0.96	0.92, 1.01	.14
T after cystectomy						
2				0.87	0.42, 1.82	.7
3				1.87	1.02, 3.43	**.041**
4				4.50	2.41, 8.42	**<.001**
Number of units transfused				1.04	0.93, 1.18	.5
Positive lymph nodes				2.52	1.65, 3.86	**<.001**
Preoperative Hb				0.95	0.86, 1.04	.2

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

suggested no association of donor/recipient gender mismatch with OS (Table 2) or CSS (Table 3).

Mean blood donor age was 43 ± 10 years. In univariate analysis, donor age did not significantly affect OS, but did affect CSS (HR: 1.01, 95% CI: 1.00 to 1.03, $p = .059$ and HR: 1.02, 95% CI: 1.00 to 1.04, $p = .038$ for OS and CSS, respectively). In multivariate analysis, survival was not affected by donor age (HR: 1.01, 95% CI: 0.99 to 1.03,

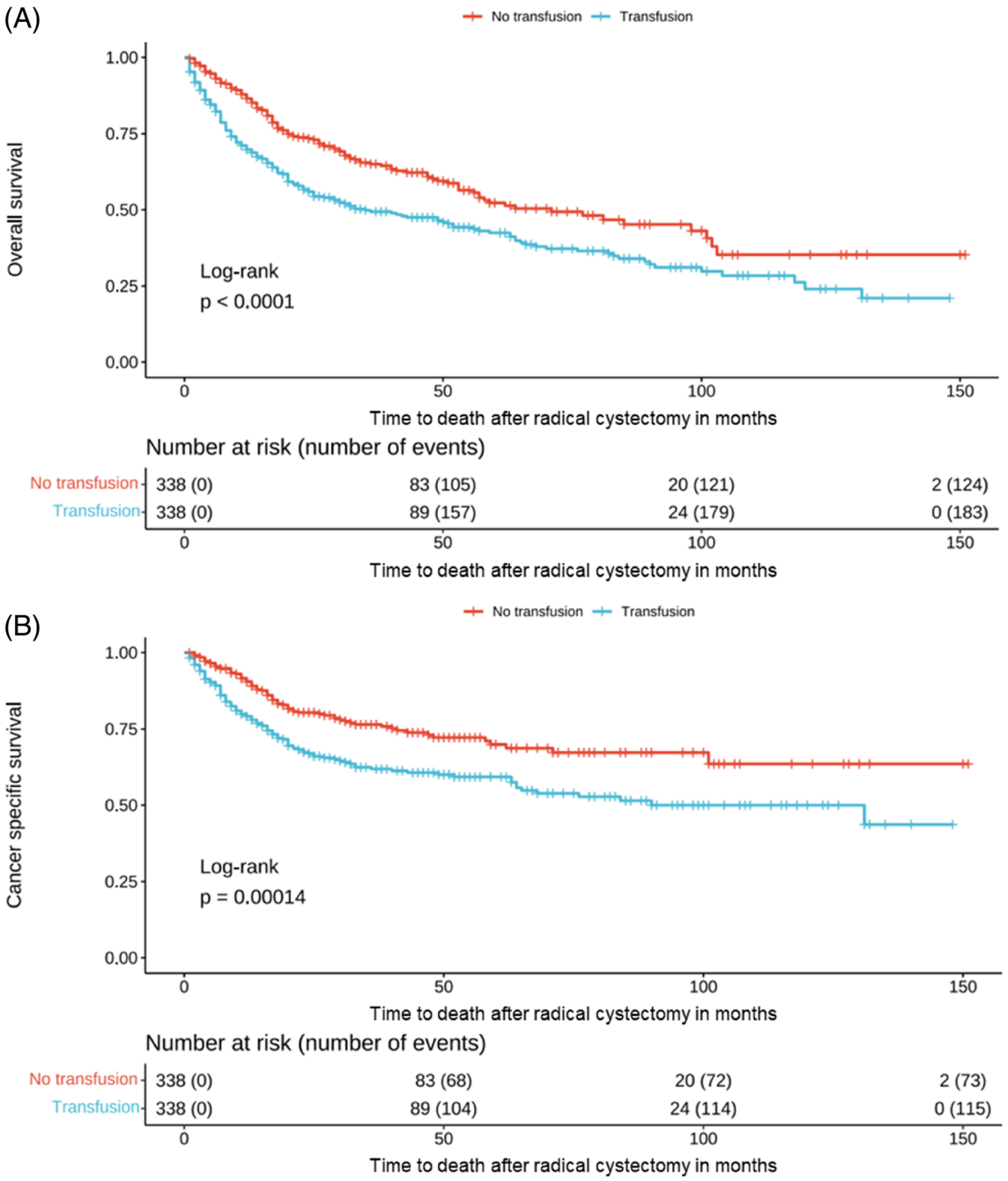

FIGURE 2 Prognostic impact of blood transfusions. Kaplan–Maier curve for overall survival (A) and cancer specific survival (B) in patients undergoing perioperative blood transfusion versus no transfusion. [Color figure can be viewed at wileyonlinelibrary.com]

$p = .2$ and HR: 1.01, 95% CI: 0.99 to 1.03, $p = .2$ for OS and CSS, respectively).

Patients received PBT after a mean of 26 ± 8 days from blood donation. Storage time significantly affected OS (Table 2) in univariate analysis, but not CSS (Table 3) (HR: 1.02, 95% CI: 1.00 to 1.04, $p = .022$ and HR: 1.02, 95% CI: 0.99 to 1.04, $p = .2$ for OS and CSS, respectively). In the multivariate analysis, storage time was not correlated with prognosis.

Factors that were associated with worse outcomes included age ($p < .001$ for OS), lower preoperative Hb (<0.002 for OS), pT4 histological tumor ($p < .001$ for both OS and CSS), and positive lymph nodes ($p < .001$ for both OS and CSS) (see Tables 2 and 3).

3.3 | Effect of transfusion and timing of blood transfusion on survival

The median follow-up in patients without PBT was 27 months (IQR: 12–49) and 20 months (IQR: 6–51) in patients with PBT. Based on the log-rank test, PBT was

independently associated with worse OS ($p < .001$) and CSS ($p < .001$) (Figure 2A, B). Of note, postoperative blood transfusion was associated with better OS ($p = .004$) and CSS ($p = .008$) compared to intraoperative or mixed blood transfusion (Figure 3A, B).

4 | DISCUSSION

4.1 | Influence of storage time of blood units

In our multivariable analysis, storage time of blood units did not influence OSS or CSS for BCa patients undergoing RC. A study including 200 patients demonstrated increased RBC storage lesions markers for BUs stored for over 14 days.[18] In the preclinical setting, longer storage duration of erythrocytes facilitated tumor progression.[22] These observations might be explained by alterations of helper T-cell subpopulations and changes in cytokine levels for BUs with longer storage time, which then might facilitate the development of TRIM.[24] A randomized, controlled, multi-national study including 31,497 patients in a general hospital population reported no significant influence of BU storage time on in-hospital mortality.[25] BU storage time had no significant influence on the oncological outcome of patients undergoing surgery for colorectal[26] or prostate cancer.[27] We conclude that it is not necessary to reserve BUs with shorter storage duration for oncological patients.

4.2 | Influence of donor age

In our study, donor age was no prognostic factor. Of note, the effect of donor age on survival exclusively in oncologic patients has not been addressed in the literature before. Three large cohort studies investigated the impact of blood donor age on overall survival in patients receiving BUs for various reasons. In the first study with 30,503 patients who received a total of 187,960 BUs from 80,755 unique donors,[19] the authors suggested that receiving a BU from a younger versus older donor was associated with worse in-hospital OS.[19] The second study with 25,219 patients who received a total of 97,886 BUs proposed PBT from donors ≤45 years to be associated with higher in-hospital mortality compared to BU transfusions from older donors.[20] In this study, diagnoses included cardiovascular (29%), neoplastic (16%), traumatic (15%), or gastrointestinal (11%) diseases.[20] The authors linked their results to the healthy donor effect, such that young donors may not be aware of ongoing diseases that may affect recipients, whereas the development of medical health issues with increasing age may lead to an exclusion of certain donors, leaving a more healthy older donor pool.[20,28] The largest available study including all patients from Sweden and Denmark who received at least one BU from 2003 to 2012 ($n = 968, 264$) reported no impact of donor age on survival.[29] To our knowledge, we present the first study confirming the oncological safety of blood products of both older and younger donors.

4.3 | Influence of gender

The effect of donor gender on the prognosis of cancer patients is also uncaptured in the literature. In a meta-analysis of five studies with 86,737 patients undergoing PBT for various reasons, gender mismatch between donor and recipient was associated with an increased risk of mortality.[21] It should be highlighted that the majority of patients were undergoing non-oncological surgeries.[21] Based on our analysis, it seems that gender mismatch between donor and recipient does not negatively affect OS and CSS of BCa patients undergoing RC. To our knowledge, this is the first study to assess the influence of BU gender matching on survival in a cohort of cancer patients.

4.4 | Influence of blood transfusion and transfusion time point

In our study, PBT was independently associated with worse OS and CSS. Intraoperative blood transfusion was associated with a worse prognosis compared to postoperative transfusion. These results are in line with a recently published meta-analysis of 15 studies including 21,915 patients with BCa undergoing RC. The authors correlated PBT with an increased risk of disease-specific mortality. The authors reported significantly worse oncological outcomes for intraoperative or combined compared to postoperative transfusions.[5]

TRIM can cause profound immunosuppressive effects.[6] Identified mediators for TRIM include cytokines, eicosanoids, and growth factors like TGF-β, VEGF, or PDGF-D.[6,7] In exosomes isolated from the supernatant of BUs, multiple miRNAs could be found, which could also serve various functions in TRIM.[30] The observation of worse oncological outcomes for intraoperative compared to postoperative transfusions supports the hypothesis of tumor growth mediated through TRIM.[6,7] Intraoperative transfusions might help distal seeding of circulating tumor cells during surgical resection.[10,11] A potential confounder of the impact of intraoperative blood transfusion on oncological outcomes might be the implication of

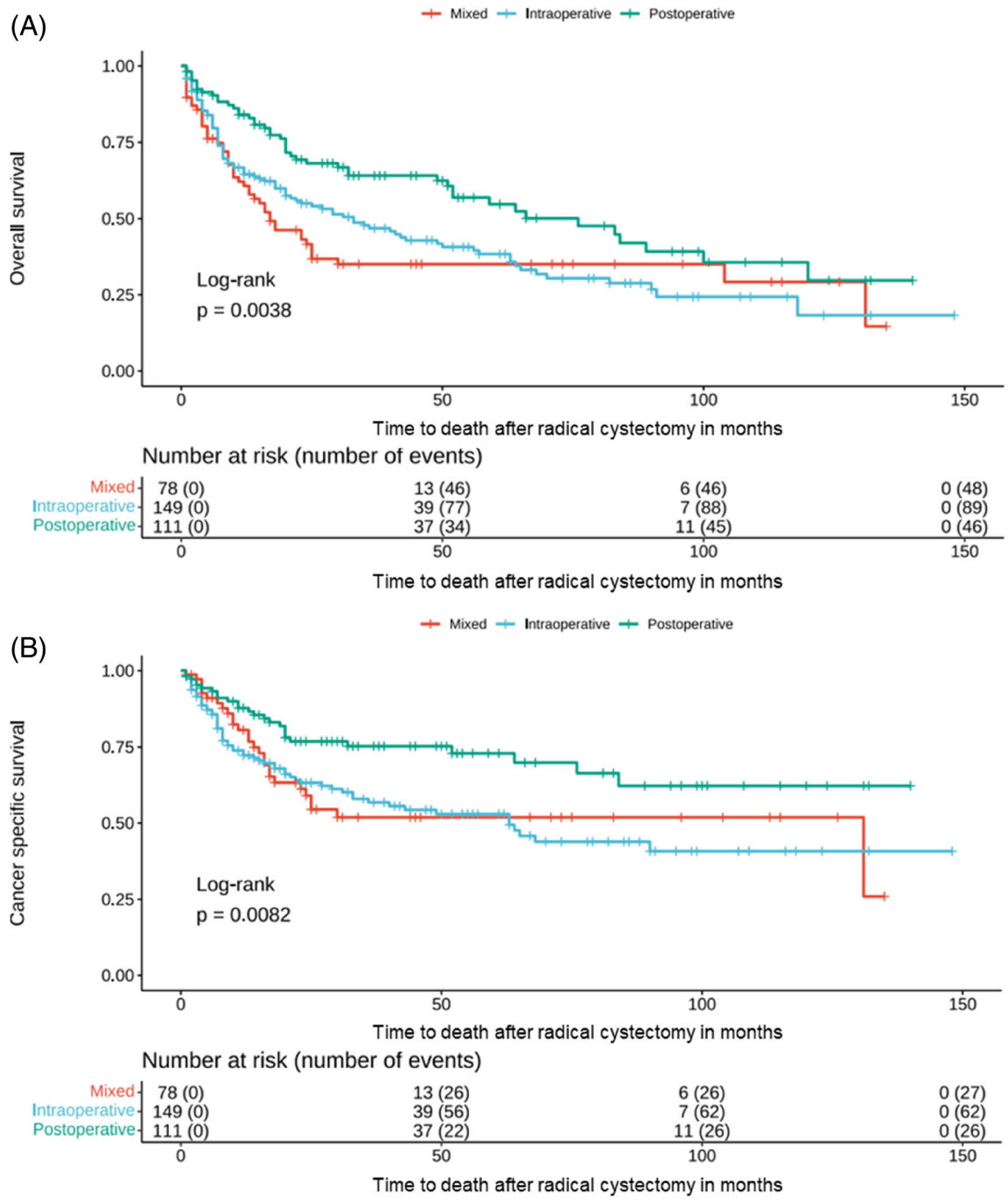

FIGURE 3 Timing of perioperative blood transfusions. Kaplan–Maier curve for overall survival (A) and cancer specific survival (B) in patients undergoing blood transfusion solely intraoperatively versus solely postoperatively versus both intra- and postoperatively. [Color figure can be viewed at wileyonlinelibrary.com]

stronger intraoperative bleeding on surgical precision through restricted visibility of the surgical area. This might lead to an increased risk of residual tumor or tumor cell spillage by unintended cutting into the tumor. Another confounder might be greater blood loss itself, by facilitating hematogenous seeding of tumor cells. However, if these results are validated, postoperative blood transfusions should be preferred over intraoperative transfusions, if this is feasible in the clinical situation. Apart from blood loss during cystectomy, surgical skill level has a great impact on oncological prognosis.[31] Longer operation time might be a surrogate for less experienced surgeons or locally advanced tumor growth. In our study, there was no significant difference between patients without PBT and those receiving PBT regarding operation time. There was also no significant difference

between both groups regarding locally advanced tumor growth (T stage ≥3 or positive lymph nodes).

4.5 | Limitations

The retrospective and single-center design are important limitations of this study. Due to the small number of evaluable patients, weak effects can be missed. Furthermore, the limitation in the number of patients did not permit us to adjust for further baseline characteristics in the propensity score matching. Additionally, there were no standardized criteria for the indication of PBT during or after RC.

5 | CONCLUSION

Blood donor characteristics and storage time of BUs should not be considered detrimental factors for OS and CSS in patients with BCa undergoing RC. Furthermore, our findings demonstrate that PBT, especially if applicated intraoperatively, is an independent risk factor for a worse prognosis. Continued efforts should be made to both understand the immunological effects of blood transfusions and to reduce the rate of PBT in RC patients.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

ETHICS STATEMENT

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institutional ethical committee.

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