



## Packed red blood cell donor age affects overall survival in transfused patients undergoing hepatectomy for non-hepatocellular malignancy

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### ABSTRACT

**Background:** Patients undergoing hepatectomy often require packed red blood cell (PRBC) transfusion, which has been associated with worse oncologic outcomes. However, limited data exist regarding the impact of PRBC donor factors. We hypothesized that PRBC donor age impacts survival after hepatectomy for non-hepatocellular malignancies.

**Methods:** Patients who underwent hepatectomy for non-hepatocellular malignancy from 2005 to 2014 were retrospectively evaluated. Impact of clinicopathologic and PRBC factors on oncologic outcomes were assessed.

**Results:** Of 149 identified patients, 76 received a perioperative PRBC transfusion (median 2 units). Transfusion was associated with increased median length of stay (8 vs. 6 days;  $p < 0.01$ ) and median operative blood loss (700 vs. 350 mL;  $p < 0.01$ ) versus non-transfused, respectively. In transfused patients, receipt of PRBC from older donors compared to younger resulted in decreased RFS (0.94 vs. 2.63 years, respectively;  $p = 0.02$ ) and OS (1.94 vs. 3.44 years, respectively;  $p = 0.6$ ). The PRBC donor age was an independent predictor of decreased recurrence free survival on multivariate analysis (HR 2.5,  $p = 0.04$ ).

**Conclusions:** In patients undergoing hepatectomy for non-hepatocellular malignancies and receiving perioperative transfusion, PRBC donor age may impact survival and warrants further investigation.

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### Introduction

Evidence for the deleterious effects of allogenic blood products in patients with a variety of disease states has accumulated over the past decade.<sup>1–4</sup> Specifically, blood product administration among patients with malignancy has been associated with worse oncologic outcomes, including cancer recurrence and shorter recurrence-free survival.<sup>5–7</sup> The immunomodulatory effects of

allogenic blood product transfusion, in particular packed red blood cells (PRBC), appear to contribute to these phenomena.<sup>8–10</sup> Recognition that PRBC transfusion impacts cancer-specific survival has led to the development of scoring systems to identify patients at increased risk of transfusion during and after hepatectomy in order to potentially curtail deleterious transfusion effects.<sup>11,12</sup> Although surgical techniques and perioperative management of patients undergoing hepatectomy for malignancy have improved in recent decades,<sup>13</sup> perioperative PRBC transfusion is often still necessary.<sup>14–16</sup> The incidence of transfusion increases for large tumors,<sup>17</sup> administration of neoadjuvant chemotherapy with resultant hepatotoxicity,<sup>18</sup> and underlying liver disease.<sup>19</sup> While evidence exists to demonstrate a deleterious effect of PRBC transfusion in patients undergoing hepatectomy for stage I and II

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hepatocellular carcinoma (HCC), these results are not reproducible in cases of stage III and IV HCC, and are confounded by the disproportionate number of patients affected by cirrhosis, portal hypertension, and tumor heterogeneity.<sup>20</sup>

To better characterize the deleterious effects of PRBC transfusion in hepatic surgery without the potential confounding medical comorbidities seen in cirrhotic patients undergoing hepatectomy, several authors have described associations between perioperative transfusion and adverse outcomes among patients undergoing liver resection for colorectal cancer metastases. Postlewait et al.<sup>21</sup> reported that perioperative PRBC transfusion was an independent predictor of major complications [OR 2.61 (95% CI 1.53–4.44)], Kooby et al.<sup>22</sup> reported that perioperative transfusion was associated with increased mortality within 60 days [HR 4.2 (95% CI 2.0–9.0)], and Rosen et al.<sup>23</sup> reported that patients who received a perioperative PRBC transfusion had lower 5-year survival than patients with no transfusion (21% vs. 32%,  $p = 0.03$ ). While associations between PRBC transfusion and outcomes among non-hepatocellular hepatectomy patients have been well described, more research is needed to determine specific characteristics of the transfused PRBCs that contribute to transfusion-related morbidity and mortality. Although PRBC storage duration has been one such subject of investigation, human studies have not identified an association between storage duration, tumor recurrence, and survival in a variety of malignancies.<sup>24,25</sup>

Preclinical studies have demonstrated that transfusion of aged mice with blood from young mouse donors has significant vascular, muscular, and neurologic effects, supporting the hypothesis that the biologic activity of PRBC transfusion may be affected by age-related changes in donated blood.<sup>26–28</sup> While multicenter clinical studies investigating the relationship between donor age and mortality for diffuse patient populations have reported conflicting results, the impact of blood donor age on patients with non-hepatocellular malignancies are unknown.<sup>29,30</sup> Given these data and the potential for immunosenescence in older PRBC donors,<sup>31–33</sup> we hypothesized that PRBC donated from older subjects would have a beneficial impact on survival among patients undergoing hepatic surgery for non-hepatocellular malignancies.

## Methods

The University of Florida Institutional Review Board approved all portions of this study. Patients with primary or secondary liver tumors, of non-hepatocellular origin, who underwent hepatic resection from April 2005–June 2014 were identified by Current Procedural Terminology and International Classification of Diseases-9 codes through the Integrated Data Repository at the University of Florida. Patients with hepatocellular carcinoma were excluded to avoid the confounding influences of cirrhosis, portal hypertension, and concomitant thrombocytopenia. A retrospective database was created to collect demographic and clinicopathologic parameters from the electronic medical record. We additionally collected all PRBC donation records directly from the local blood bank (LifeSouth Community Blood Centers; Gainesville, FL) for each patient to encompass  $\pm 72$  h perioperatively. The  $\pm 72$  h period was chosen to maintain consistency with recently published literature regarding perioperative transfusion for patients undergoing abdominal surgery for malignant tumors.<sup>34</sup> Major hepatectomy was defined as resection of 3 or more Couinaud liver segments; minor hepatectomy was defined as resection of less than three segments.<sup>35</sup>

For each PRBC unit, pre-storage leukoreduction (PLR) status, storage duration, and donor age were recorded. Pre-storage leukoreduction became universal at our institution in September 2010, during the middle portion of the study period. Survival outcomes

were reported as recurrence-free survival (RFS), defined as the time interval from surgery to tumor recurrence or metastatic disease as diagnosed on surveillance computed tomography scan, and overall survival (OS), defined as the time interval from surgery to death or last follow-up, at which point the data were censored. Mortality was assessed by medical record documentation, telephone calls, and obituaries for patients who were lost to clinical follow-up.

Statistical analysis was performed in StataSE (v13; StataCorp; College Station, TX). Test of normality was performed via the Shapiro-Wilk test. Continuous variables and categorical variables between cohorts were compared with Student's t-test, the Kruskal-Wallis test, and Chi-squared test, where appropriate. Mean and median values were reported with standard deviation (SD) and interquartile range (IQR), respectively. Kaplan-Meier log rank test was used to compare recurrence-free and overall survival differences between cohorts. All RFS and OS data are presented as median values unless otherwise specified. Cox logistic regression analysis was used to assess predictors of RFS and OS among patients who received a transfusion by univariate analysis. Variables with  $p \leq 0.1$  on univariate analysis were subsequently analyzed in a multivariate model. Continuous variables were dichotomized at the median for purposes of univariate analysis. In order to determine the appropriate PRBC donor age for use in univariate and multivariate analysis, Receiver Operating Characteristic (ROC) analysis was performed. From the derived Area Under the Curve (AUC), Youden's index was calculated to determine the appropriate PRBC donor age cutoff.<sup>36</sup> Significance was set at  $\alpha = 0.05$  with 95% confidence intervals (CI) for all analyses.

## Results

### *Patient demographics and the effect of packed red blood cell transfusion*

A total of 149 patients were identified, of which, 76 received a median of 2 units of PRBCs in the  $\pm 72$  h perioperative period. Compared to the 2005–2009 era, the majority of transfusions occurred during the 2010–2014 time period (46.1% vs. 53.9%, respectively). However, PRBC administration occurred more often in the earlier perioperative hepatectomy period in the 2005–2009 era ( $n = 35$ ; 92.1%) vs. 2010–2014 ( $n = 41$ ; 36.9%). Demographic and clinical characteristics for all patients are listed in [Table 1](#), stratified by receipt of perioperative PRBC transfusion. The two cohorts were similar in all parameters evaluated except for sex, preoperative hematocrit, post-operative length of stay, and operative blood loss (OBL). Patients who received a PRBC transfusion had greater median OBL (700 vs. 350 mL,  $p = 0.002$ ), median post-operative length of stay (8 vs. 6 days,  $p = 0.0001$ ), and higher overall mortality (52.6% vs. 16.4%,  $p < 0.01$ ) compared to the non-transfused cohort, during the evaluable period of 2005–2018, respectively.

### *Survival impact of packed red blood cell transfusion and donor age*

Given the association between receipt of PRBC transfusion and operative blood loss, we first sought to determine the impact of these two variables on RFS and OS among all 149 patients. Kaplan-Meier logistic regression analysis demonstrated a decreased median RFS (0.9 vs. 1.4 years,  $p = 0.12$ ) and median OS (3.2 vs. 4.7 years,  $p = 0.7$ ), in patients who had an OBL of  $> 500$  ml versus those who did not, respectively ([Fig. 1A–B](#)), but neither reached statistical significance. Compared with patients who did not receive a PRBC transfusion, the receipt of any perioperative PRBC transfusion in the entire cohort was not associated with a difference in RFS (1.64 vs. 1.54 years,  $p = 0.96$ , respectively; [Fig. 1C](#)) but was associated with

**Table 1**

Clinical parameters for patients undergoing surgical treatment of non-hepatocellular malignancy stratified by receipt of perioperative PRBC transfusion.

Patient characteristics	No Transfusion n = 73	Transfusion n = 76	p
Sex			<b>0.03</b>
Male	47 (64.4%)	35 (46.1%)	
Female	26 (35.6%)	41 (53.9%)	
Age (years)			0.31
Mean (SD)	58.4 (10.8)	60.3 (11.0)	
Median (IQR)	57.4 (16.9)	59 (15)	
Diagnosis			0.42
Colorectal	55 (75.3%)	55 (72.4%)	
Neuroendocrine	2 (2.7%)	6 (7.9%)	
Cholangiocarcinoma	3 (4.1%)	5 (6.6%)	
Other	13 (31.5%)	10 (13.2%)	
Transfusion Era			<b>&lt;0.01</b>
2005–2009	3 (4.1%)	35 (46.1%)	
2010–2014	70 (95.9%)	41 (53.9%)	
Preoperative Chemotherapy			0.15
No	13 (17.8%)	21 (27.6%)	
Yes	60 (82.2%)	55 (72.4%)	
Type of Resection			0.86
Major	48 (65.8%)	51 (67.1%)	
Minor	25 (34.2%)	25 (32.9%)	
Preoperative Hematocrit			<b>&lt;0.01</b>
Mean (SD)	40.8 (3.6)	36.9 (4.6)	
Median (IQR)	41.4 (4.7)	37.3 (5.6)	
Operative Blood Loss (mL)			<b>&lt;0.01</b>
Mean (SD)	522 (434)	939 (1101)	
Median (IQR)	350 (500)	700 (600)	
Duration of Operation (minutes)			0.97
Mean (SD)	279 (107)	278 (76)	
Median (IQR)	275 (112)	294 (100)	
PRBC Units Transfused			n/a
Mean (SD)	–	4 (6.5)	
Median (IQR)	–	2 (2)	
PRBC Donor Age (years)			n/a
Mean (SD)	–	41.4 (18.7)	
Median (IQR)	–	40.5 (33.5)	
PRBC Storage Duration (days)			n/a
Mean (SD)	–	18.9 (10.1)	
Median (IQR)	–	17 (19)	
Received Leukocyte Reduced PRBCs	–	40 (52.6%)	n/a
Post-Operative Length of Stay (days)			<b>&lt;0.01</b>
Mean (SD)	6.5 (3.5)	13.2 (16.7)	
Median (IQR)	6 (3)	8 (5.5)	
Surgical Site Infection	1 (1.4%)	6 (7.9%)	0.06
30-day Readmission	10 (13.7%)	11 (14.5%)	0.89

decreased OS (median not reached vs. 2.8 years,  $p = 0.0002$ ; Fig. 1D) in patients who received a PRBC transfusion.

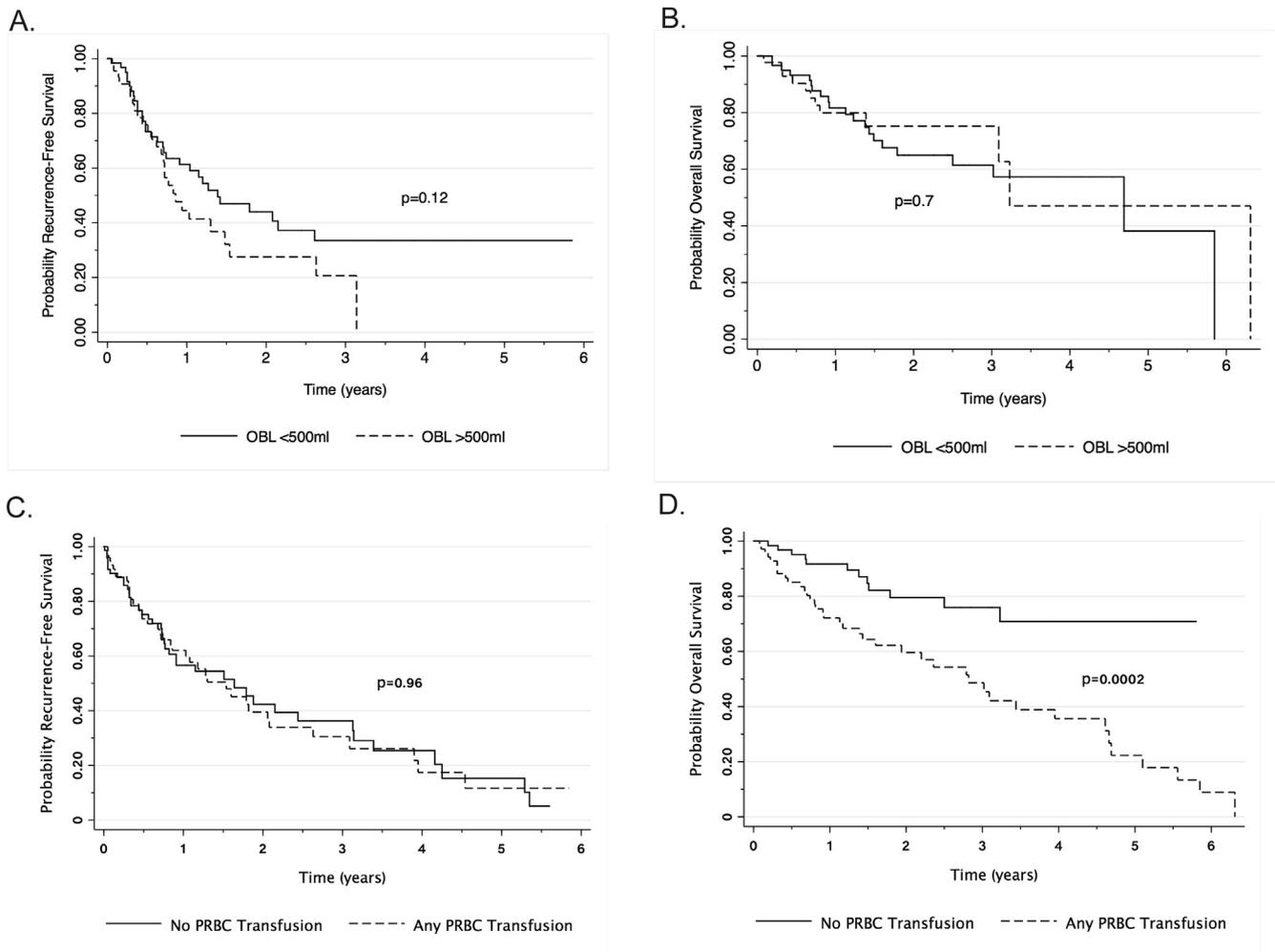
To further evaluate potentially contributory factors of PRBC units themselves, we next analyzed survival data for the 76 patients who received a PRBC transfusion in the perioperative period. Again, the median RFS was shorter in patients who had an OBL >500 ml (0.9 years) compared with those who did not (2.1 years;  $p = 0.05$ ) in this cohort but no statistically significant difference was observed regarding median OS (1.4 vs. 3.1 years, respectively;  $p = 0.14$ ; Fig. 2A–B). We next evaluated survival stratified by PRBC donor age. As patients may have received multiple units of PRBC, the age of the youngest PRBC donor for each individual patient was used to perform ROC analysis. Youden's index was performed and demonstrated an AUC of 0.62 with an age cutpoint of 24.5 years (data not shown), for which the transfusion cohort was dichotomized. There was no difference in patient characteristics between the two patient cohorts (data not shown). The median RFS for patients who received PRBC from a older (>24.5 years) donor compared to younger PRBC donor (<24.5 years) was 0.94 years vs. 2.63 years, respectively ( $p = 0.02$ ; Fig. 2C). Furthermore, there was a decreased OS in patients who received PRBC from older versus younger donors (1.94 years vs. 3.44 years, respectively) but this did

not reach statistical significance ( $p = 0.64$ ; Fig. 2D).

Because greater OBL may be an indicator of a more difficult operation, advanced tumor stage, or comorbidities that predispose to PRBC transfusion, we next evaluated the cohort based on the median OBL <500 ml, which represents the median OBL of the entire cohort. In this cohort with limited blood loss, PRBC transfusion was not associated with RFS ( $p = 0.3$ ; Fig. 3A) but a decreased median OS for patients who received a PRBC transfusion (1.43 years) compared with no transfusion (median not reached,  $p = 0.0008$ ; Fig. 3B) was noted.

Predictors of survival in patients undergoing hepatectomy for non-hepatocellular malignancy after perioperative packed red blood cell transfusion.

Acknowledging the heterogenous nature of the cohort in regard to disease type, comparison of RFS and OS for the entire cohort demonstrated no significant difference between groups ( $p = 0.46$  and 0.99, respectively). Additionally, there was no difference in RFS or OS between disease subtypes in those patients who received a PRBC transfusion ( $p = 0.07$  and 0.14, respectively). Therefore, we assessed predictors of recurrence-free and overall survival among patients who received a perioperative PRBC transfusion by univariate and multivariate analysis (Table 2). In this cohort, when the



**Fig. 1.** Kaplan-Meier analysis of the entire cohort of patients undergoing hepatectomy for non-hepatocellular cancer demonstrated no statistical difference in recurrence-free survival (RFS) in patients with >500 ml operative blood loss (OBL; A;  $p=0.12$ ) or overall survival (B;  $p=0.7$ ). With the receipt of any packed red blood cell transfusion, there was no difference in RFS (C;  $p=0.96$ ) but a statistically significant reduction in overall survival (D;  $p=0.0002$ ).

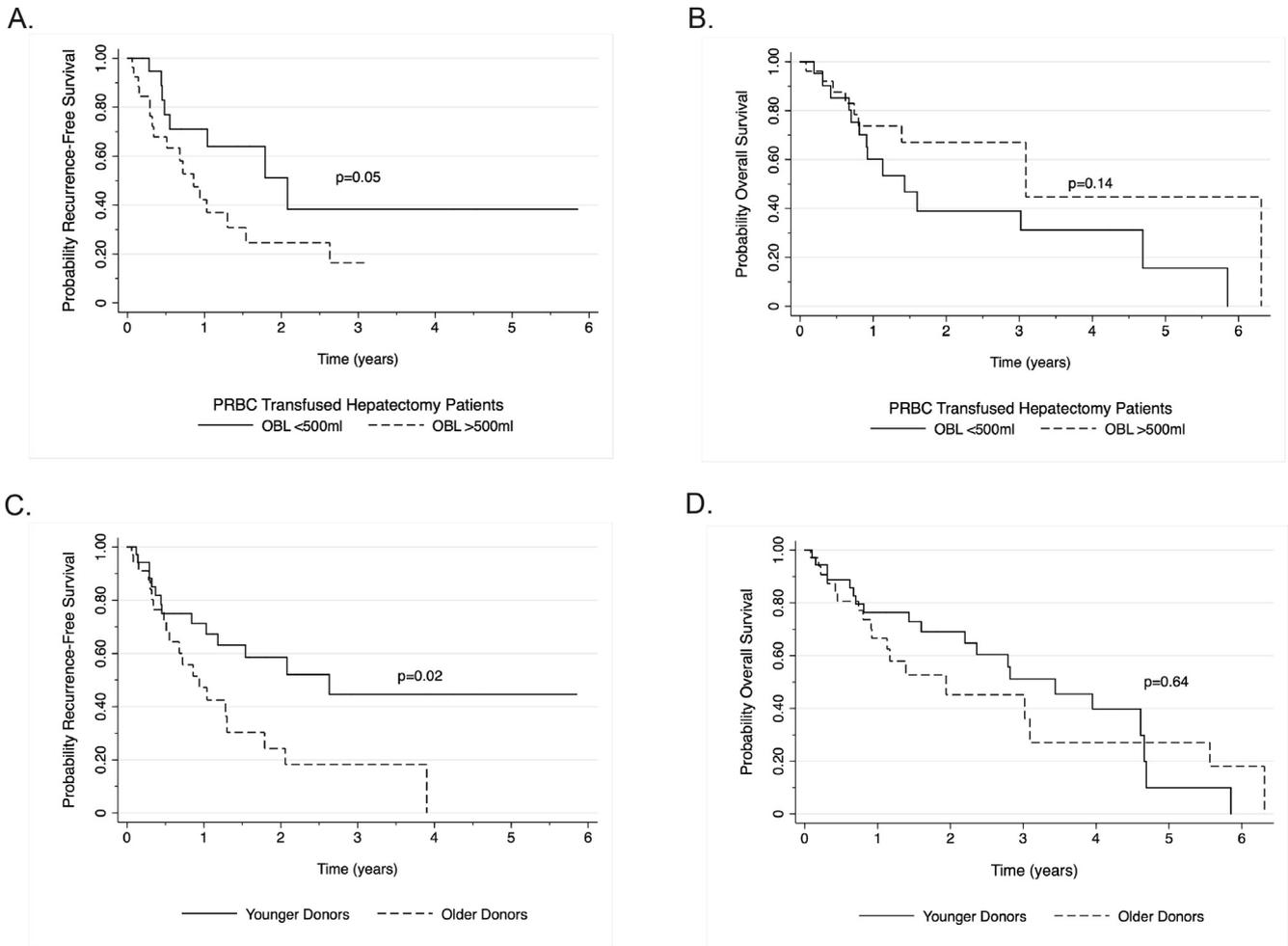
median OBL of the entire cohort (500 ml) was utilized in the univariate analysis, it was associated with a decreased RFS (HR 2.2, 95% CI 0.96–5.2;  $p=0.06$ ) but did not reach statistical significance. Likewise, OBL >500 ml in the transfused cohort was associated with decreased RFS on multivariate analysis (HR 2.2 95% CI 0.93–5.1;  $p=0.07$ ) but did not reach statistical significance (Table 3). Regarding age factors, patient age >59 years (HR 2.03, 95% CI 1.03–4;  $p=0.04$ ) was a predictor of OS on univariate analysis (Table 2). Recipients of PRBC from an older (age >24.5 years) donor was associated with a decreased RFS (HR 2.25 95% CI 1.12–4.5;  $p=0.022$ ) but not OS (HR 1.17 95% CI 0.6–2.3;  $p=0.64$ ) on univariate analysis (Table 2). Finally, on multivariate analysis with the variables of major liver resection, OBL >500 ml, and PRBC donor age >24.5 years entered into the model, only receipt of blood from an older PRBC donor was independently associated with a worse RFS (Table 3).

## Discussion

With growing cognizance of the deleterious effects of PRBC transfusion, this study presents additional data regarding the potential harm of blood transfusion for cancer patients and also investigates the source of the blood transfusion, specifically the age of the donor. In congruence with recent literature and management,

the overall utilization of PRBC transfusion in our cohort has decreased with 36.9% of hepatectomy patients undergoing a perioperative PRBC transfusion in the  $\pm 72$  h perioperative timeframe during the 2010–2014 period compared to 92.1% in the older era from 2005 to 2009. Contrary to our hypothesis that age-related immunosenescence may provide a protective effect for patients receiving PRBC from older donors compared with younger, more immunocompetent donors, our data demonstrate the deleterious effects of PRBC transfused from older donors which is in line with our recent publication in critically ill patients.<sup>4</sup> Specifically, in our study cohort, PRBC transfusion from younger donors was independently associated with improved RFS on multivariate analysis. Although PRBC transfusions are necessary under certain clinical scenarios, these data suggest the potential utility of protocols for age-stratification of PRBC units such that the most vulnerable populations (e.g. cancer patients) receive transfusions from younger donors.

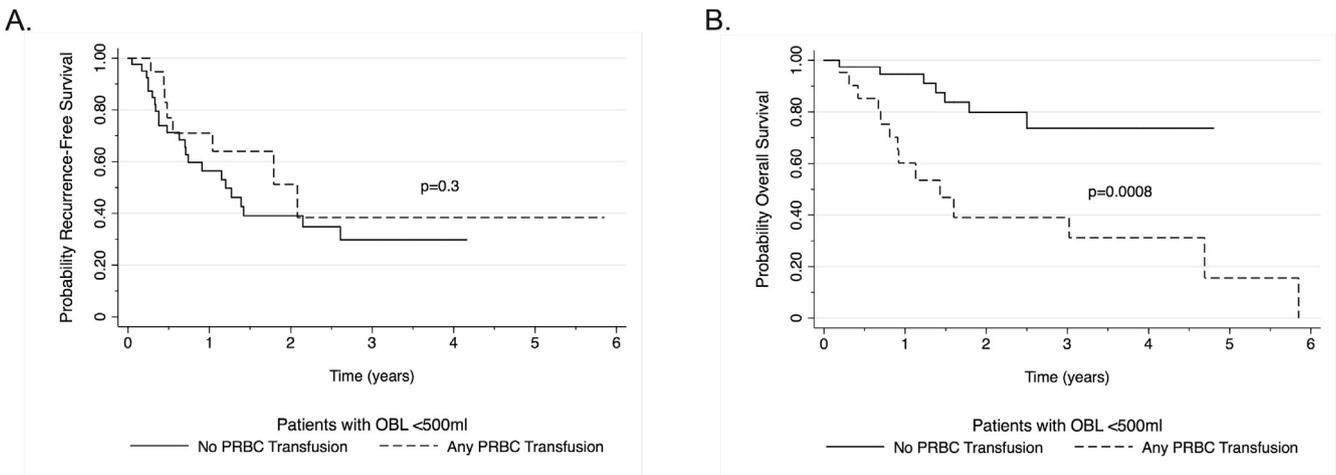
Using ROC and Youden's index it was determined that the optimal PRBC donor age cutoff in our cohort was 24.5 years. Admittedly, from a clinical and physiologic standpoint it is difficult to determine what truly represents “younger” from “older” blood donors. Using this dichotomy, however, there was a stark difference in RFS between matched patients based on the receipt of a particular donor age of blood. Granted, when patients receive multiple



**Fig. 2.** In patients undergoing hepatectomy for non-hepatocellular cancer who received a packed red blood cell transfusion, Kaplan-Meier analysis demonstrated a reduced RFS in patients with an OBL >500 ml (A;  $p = 0.05$ ) but no difference in overall survival (B;  $p = 0.14$ ). Transfusion from older donors (>24.5 years) was associated with a decreased RFS compared to younger (C;  $p = 0.02$ ) but no statistical difference in OS was noted (D;  $p = 0.64$ ).

units of blood from donors of various ages, it is difficult to determine which of those units is potentially most impactful on cancer survival. Based on our initial hypothesis we chose to stratify

patients based on the age of the *youngest* PRBC donor; originally hypothesizing that it is the more immunogenic PRBCs from younger donors that would impact survival. Contrary to our



**Fig. 3.** Kaplan-Meier analysis of patients with limited operative blood loss (OBL <500 ml) demonstrated no impact of PRBC transfusion on RFS (A;  $p = 0.3$ ). However, despite limited blood loss in this cohort, OS was significantly reduced in patients who received PRBC transfusion (B,  $p = 0.0008$ ).

**Table 2**  
Univariate predictors of survival for patients who underwent hepatectomy for non-hepatocellular malignancy and received a perioperative PRBC transfusion.

Factor	Recurrence-Free Survival		Overall Survival	
	Hazard ratio (CI)	p	Hazard ratio (CI)	p
Female	0.93 (0.49–1.8)	0.84	0.76 (0.4–1.46)	0.41
Patient Age >59 years	1.1 (0.6–2.1)	0.7	2.03 (1.03–4)	0.04
Metastatic Colorectal Cancer	1.1 (0.52–2.3)	0.81	1.15 (0.5–2.63)	0.75
Major Resection	1.93 (0.93–4)	0.08	1.76 (0.83–3.74)	0.14
Operative Blood Loss >500 mL	2.2 (0.96–5.2)	0.06	0.52 (0.22–1.25)	0.14
Duration of Operation >294 min	0.62 (0.2–1.91)	0.41	0.53 (0.1–2.75)	0.45
Received >2 Units PRBC	0.74 (0.39–1.4)	0.38	1.14 (0.6–2.16)	0.69
Blood Donor Age (>24.5 years)	2.25 (1.12–4.5)	0.02	1.17 (0.6–2.3)	0.64
PRBC Storage Duration (days)				
>10	0.88 (0.4–1.93)	0.74	0.9 (0.42–1.92)	0.78
>20	1 (0.53–1.91)	0.98	1.49 (0.77–2.87)	0.23
>30	1.22 (0.56–2.67)	0.62	1.81 (0.83–3.93)	0.13
Received Leukocyte Reduced PRBC	1.14 (0.61–2.15)	0.68	0.87 (0.46–1.67)	0.69

hypothesis, it did impact survival but in the beneficial sense. Mechanistically this is feasible as it has been shown in multiple malignancies that increased myeloid-derived suppression cells (MDSC) results in an immunotolerant phenotype and facilitate cancer progression.<sup>37–39</sup> Transfusion of leukocyte reduced PRBC may still inadvertently result in transfer of MDSCs and their immunosuppressive, pro-tumorigenic, properties with reduction in cancer survival parameters.<sup>40</sup> Future studies would need to stringently control PRBC donor age in a prospective fashion to further characterize our findings. Correlation with immune or cytokine profiling would potentially delineate specific mediators that impact survival. Such data would advance knowledge of immune-mediated cancer recurrence and provide a framework by which PRBC transfusions to cancer patients are based on PRBC donor age or immune profiling.

This study is limited by its retrospective design, heterogeneity of the patient population in terms of cancer diagnosis, and relatively small cohort numbers. We sought to test our hypothesis in non-HCC patients because of the myriad of medical and surgical confounders often present in HCC patients. While survival differences may be due to disease subtype, there was no RFS or OS difference between disease types for the entire cohort or those who received a transfusion. Thus, we believe that including non-HCC malignancies as a single cohort is warranted for the purposes of this study to increase study power. Larger patient cohorts would likely rectify this potential confounder but based on our cohort, the study would be underpowered investigating any one disease individually. Additionally, many patients received more than one unit of PRBC and thus the transfusions themselves are heterogeneous regarding donor age. Therefore, we established a PRBC donor age cutoff by ROC analysis based on the age of the youngest donor for each patient who underwent hepatectomy and observed that PRBC donor age impacted survival. To our knowledge, this study is the first to interrogate the effect of PRBC donor age on cancer outcomes in patients undergoing hepatectomy. While we were unable to discern triggers for transfusion or control for provider propensity to

**Table 3**  
Multivariate analysis of recurrence-free survival for patients who underwent hepatectomy for non-hepatocellular malignancy and received a perioperative PRBC transfusion.

Factor	Recurrence-Free Survival	
	HR (CI)	p
Major Resection	1.2 (0.5–2.8)	0.71
Operative Blood Loss >500 mL	1.8 (0.7–4.3)	0.2
Blood Donor Age ≥24.5 years	2.5 (1.1–6)	0.04

transfuse patients, a phase 3 multi-center trial is actively recruiting which may add clarity ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03229941), NCT03229941). These findings have the potential to be practice-changing in that PRBC units may be allocated to certain individuals based on donor age and recipient risk for transfusion-related morbidity and mortality.

In conclusion, the impact of PRBC transfusion in the peri-hepatectomy period for non-HCC malignancies on recurrence-free and overall survival is likely multifactorial. Our data support the role for PRBC donor age in this process as it was an independent predictor of decreased RFS when patients received PRBC from older donors. Future studies should investigate the clinical relevance of biologic differences in blood from young versus aged donors and the impact of blood donor age on patients with and without malignancies. If our findings are externally validated, and if there are identifiable groups of patients who are disproportionately affected by PRBC from younger donors, blood transfusion allocation could be targeted to optimize outcomes.

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## Sentence summary

In patients undergoing hepatectomy for non-hepatocellular malignancies and receiving perioperative packed red blood cell transfusion, age of blood donor may impact survival and warrants further investigation.

## Conflicts of interest

The authors have no conflict of interests to declare.

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