The impact of red blood cell transfusions on perioperative outcomes in the contemporary era of liver resection

Julie Hallet, MD, MSc(c),[a,b] Iryna Kulyk, MD,[a] Eva S. W. Cheng, BHSc,[c] Jessica Truong, BHSc,[c] Sherif S. Hanna, MD, MSc,[a,b] Calvin H. L. Law, MD, MPH,[a,b] Natalie G. Coburn, MD, MPH,[a,b] Jordan Tarshis, MD,[d] Yulia Lin, MD,[e,f] *and* Paul J. Karanicolas, MD, PhD,[a,b] *Toronto, Ontario, Canada*

Background. *Perioperative red blood cell transfusions (RBCTs) are common in patients undergoing partial hepatectomy. We sought to explore the relationship between RBCTs and posthepatectomy perioperative outcomes in the contemporary surgical era.*
Methods. *We reviewed all patients undergoing partial hepatectomy from 2003 to 2012. Primary outcome was 30-day major morbidity (MM). We compared patients who did and received perioperative RBCT (defined as from time of operation until 30 days postoperatively. Multivariate analysis was performed to identify factors associated with MM and duration of stay, using logistic and negative binomial regression.*
Results. *Among 712 patients, 16.8% experienced MM, of whom 53.3% received RBCT. Patients who received RBCT experienced MM more commonly (30.8% vs 11.1%; P < .001). On multivariate analysis, the only factors associated with MM were age (relative risk [RR], 1.03; 95% CI, 1.00–1.06), greater operative time (RR, 1.29; 95% CI, 1.11–1.50), and RBCT (RR, 3.57; 95% CI, 1.81–7.04). RBCT was associated independently with a greater duration of stay (RR, 1.47; 95% CI, 1.13–1.91).*
Conclusion. *Receipt of RBCT is associated independently with perioperative MM and prolonged hospitalization after partial hepatectomy. These findings further the rationale supporting the need for a strategy of blood management to decrease the use of RBCT after hepatectomy. (Surgery 2016;159:1591-9.)*

From the Division of General Surgery,[a] Sunnybrook Health Sciences Centre – Odette Cancer Centre; Department of Surgery,[b] and Faculty of Medicine,[c] University of Toronto; Department of Anesthesiology,[d] and Division of Clinical Pathology,[e] Sunnybrook Health Sciences Centre; and Department of Laboratory Medicine and Pathobiology,[f] University of Toronto, Toronto, Ontario, Canada

Advances in the perioperative and intraoperative management of patients undergoing partial hepatectomy have led to decreased postoperative morbidity and mortality.[1] Bleeding remains a substantial concern during liver resection. Despite the report of several anesthetic and surgical techniques to decrease blood loss during liver transection, including technical devices for parenchymal transection, hepatic inflow inclusion, pharmacologic interventions, and management of low central venous pressure,[2-6] ≤40% of patients undergoing partial hepatectomy still are given perioperative red blood cell transfusions (RBCTs).[7,8]

In addition to adverse transfusion reactions, such as transmission of infections, hemolytic reactions, acute lung injury, and volume overload, RBCTs have been associated with impaired postoperative recovery and even increased cancer recurrence from colorectal cancer surgery.[9-12] Transfusion-related immunomodulation is thought to be responsible for such negative impacts on postoperative outcomes.[13,14] In hepatic surgery, where RBCTs are common, the literature focuses mostly on

Funding: No external funding was received to conduct this project.

Part of this study was presented as a poster presentation at the 2014 Canadian Surgery Forum of the Canadian Association of General Surgeons, in Vancouver, BC.

Accepted for publication December 17, 2015.

Reprint requests: Dr Paul J. Karanicolas, MD, PhD, Sunnybrook Health Sciences Centre, Odette Cancer Centre 2075, Bayview Avenue, Toronto, ON, Canada M4N 3M5. E-mail: paul.karanicolas@sunnybrook.ca.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.12.015

identifying factors associated with the need for transfusion.[8,15] Studies examining the impact of RBCTs on postoperative outcomes are limited by either small sample sizes or noncontemporary cohorts.[16-18]

In this study, we sought to define the association between perioperative RBCTs and perioperative outcomes in a large set of patients (n = 712) undergoing liver resection.

METHODS

We conducted a retrospective review of the prospective liver resection database of the Odette Cancer Centre. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Selection of participants. Patients undergoing elective liver resection between 2003 and 2012 at a single tertiary care academic institution (Sunnybrook Health Sciences Centre–Odette Cancer Centre) specializing in hepatopancreatobiliary surgery were identified using the institutional liver resection database. Adult patients (≥18 years old) undergoing liver resection were included regardless of the indication or extent of resection. Patients for which morbidity could not be abstracted or classified were excluded.

Outcomes and data collection. The primary outcome was 30-day postoperative major morbidity (MM), defined as a Clavien-Dindo grade III, IV, or V complication.[19] Secondary outcomes were 30-day mortality, duration of stay, and 30-day readmission (unplanned >24-hour hospital stay). Perioperative RBCT was defined as transfusion of one or more units of allogeneic RBC during or 30 days postoperatively. The World Health Organization definition was used for anemia (hemoglobin ≤ 130 g/L), using the most recent hemoglobin value in the 30 days before hepatectomy.[20] The presence of underlying liver cirrhosis was captured from the description on the pathology report. Major liver resection was defined as resection of >3 liver segments. Intraoperative complications were captured based on the operative report dictated by the attending surgeon, including major bleeding, injury to surrounding structures, pneumothorax, hypotension, and clinically relevant cardiac events. Clinically relevant posthepatectomy liver failure (PHLF) was determined based as grades B and C of the International Study Group on Liver Surgery PHLF.[21] MM was broken down into system-specific complications, including cardiac events (atrial fibrillation, myocardial infarction, congestive heart failure, cardiac arrest), respiratory events (pulmonary edema, pleural effusion, pneumonia, respiratory failure), and venous thromboembolic events (deep vein thrombosis, pulmonary embolus, portal vein thrombosis).

Liver resections at our institution are performed at a low central venous pressure. Patients are monitored for ≥24 hours in an intensive care unit postoperatively. According to institutional guidelines, RBCTs were administered for a hemoglobin level of <70 g/L, in case of symptoms in the nonbleeding patient, and to maintain hemoglobin between 70 and 80 g/L in the bleeding patient.

Statistical analysis. Categorical data were reported as absolute number (n) and proportion (%), and continuous data as median with interquartile range. Comparisons were first made based on the presence or absence of MM to define specific characteristics of patients experiencing MM. The Pearson Chi-square test, Fisher exact test, or Mann–Whitney *U* test were used as appropriate. Primary and secondary outcomes were then compared based on transfusion status. A first multivariate model was constructed to examine factors associated with MM (logistic regression), and a second one for duration of stay (negative binomial regression). Variables identified as significantly associated with MM on univariate analysis ($P < .05$) were included in the model, in addition to covariates defined a priori as potential confounders (age, diagnosis, preoperative anemia, surgeon, number of liver lesions, size of the largest liver lesion, and major liver resection). In case of collinearity, the variable most relevant to the study question was included in the regression model. Results are reported as relative risks (RR) with 95% CIs. All analyses were conducted with SPSS 21.0 (IBM Corp., Armonk, NY).

RESULTS

During the study period, 712 liver resections were included in this analysis. Overall RBCT was administered to 29.2% of patients (n = 208/712). No difference was identified in the proportion of patients requiring RBCT over time (P = .368; Fig 1). The median number of RBCTs per patient was 3 (2–5), with 46.2% (n = 96/208) of transfused patients receiving ≥4 units. Baseline and clinical characteristics of the included patients based on RBCT status are presented in Table I. Patients receiving RBCT were more likely to be female and have preoperative anemia.

Overall rate of MM was 16.8% (n = 120/712). Patients experiencing MM were older with a median of 68.0 years old (60.5–74.0) compared with 63.0 years old (54.0–72.0; P = .01), and more likely to have underlying cirrhosis (7.5% vs 3.0%;

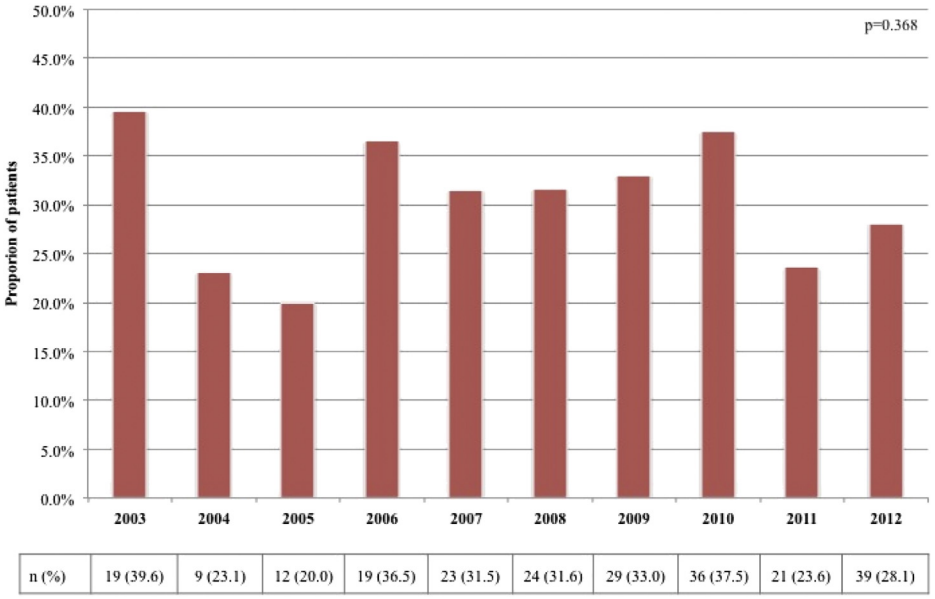

Fig 1. Proportion of patients receiving perioperative red blood cell (RBC) transfusion, according to year of hepatectomy.

Table I. Baseline characteristics of included patients, based on RBC transfusion status

	No RBC transfusion (n = 504)	*RBC transfusion (n = 208)*	P *value*
Age (y)	64.0 (55.0–73.0)	64.0 (54.0–72.0)	.852
Female sex	200 (39.7)	104 (50.0)	.011
Body mass index (kg/m^2)	27.0 (24.3–30.6)	28.6 (24.4–33.0)	.342
Serum albumin (g/L)	43.0 (40.0–45.0)	41.0 (38.0–44.0)	.001
Serum bilirubin (μmol/L)	8.0 (6.0–10.0)	8.0 (5.0–11.0)	.005
Platelets ($\times 10^9$ cells/L)	229.0 (190.0–278.0)	232.0 (186.7–295.2)	.019
INR	0.98 (0.94–1.03)	1.0 (0.95–1.08)	.012
Preoperative anemia*	164 (32.9)	127 (61.7)	<.001
Diagnosis			.010
Cholangiocarcinoma	55 (10.9)	20 (9.6)	
Colorectal liver metastases	244 (68.3)	121 (58.2)	
Hepatocellular carcinoma	29 (5.8)	26 (12.5)	
Neuroendocrine liver metastases	17 (3.4)	9 (4.3)	
Other benign liver disease	22 (4.4)	6 (2.9)	
Other liver metastases	25 (5.0)	17 (8.2)	
Other malignant liver disease	12 (2.4)	9 (4.3)	
≥3 Lesions	127 (28.6)	62 (34.1)	.176
Largest lesion ≥5 cm	122 (29.8)	69 (40.6)	.012
Preoperative chemotherapy	254 (50.4)	104 (50.0)	.923

*Hemoglobin ≤ 130 g/L.
Values are n (%) and median (interquartile range).
INR, International Normalized Ratio; *RBC*, red blood cells.

$P = .02$). They presented with lesser median preoperative albumin levels with median of 41.0 g/L (38.0–44.7) compared with 43.0 g/L (39.0–45.0; $P = .02$) for those without MM.

No difference was observed based on MM status in terms of sex, preoperative anemia, diagnosis, number or size of liver lesions, receipt of preoperative chemotherapy, or major liver resection. Infectious processes (incisional surgical site infection, wound dehiscence, intraabdominal collection or abscess, anastomotic leaks, urinary tract infection, sepsis, and septic shock) accounted for most of the MM events (45.8%), with intraabdominal collections, abscesses, and biloma representing the majority of events (37.5%; Fig 2). PHLF occurred overall in 41 patients (5.7%), including 18

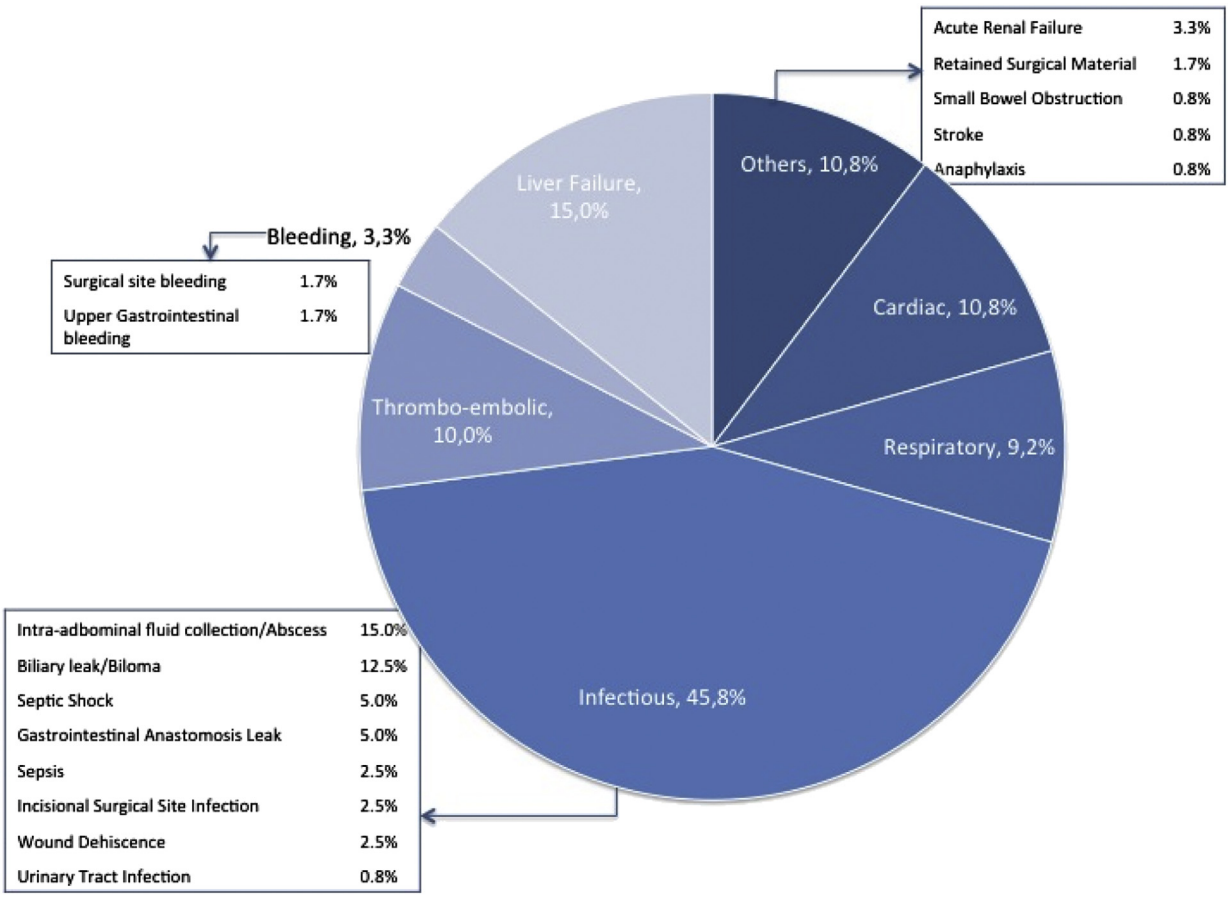

Fig 2. Details of major morbidity events (Clavien-Dindo grades III–V) among the included patients. As per Clavien-Dindo classification, the most significant/highest grade complication is reported per patient.

(2.5%) grade C events corresponding with grades 3–5 Clavien-Dindo complications. Grade C PHLF accounted for 15 of the 25 postoperative deaths within 30 days. The remaining 3 patients with grade C PHLF passed away >30 days after hepatectomy. Other causes of 30-day mortality were infectious in 4 patients (sepsis from colonic anastomosis leak, severe *Clostridium difficile* colitis, aspiration pneumonia, and biliary peritonitis from anastomotic leak), thromboembolic in 1 (massive pulmonary embolism), bleeding in 2 (upper gastrointestinal bleeding, intraabdominal bleeding with abdominal compartment syndrome), and cardiac in 3 (myocardial infarctions in patients with cardiovascular comorbidities, severe ventricular arrhythmia).

The operative characteristics of patients according to RBC transfusion status are presented in Table II. Median operative time was 1.1 hours greater in transfused patients. Median estimated blood loss was 0.7 L greater in the RBCT group.

Patients who received RBCT more commonly experienced MM (30.8% vs 11.1%; $P < .001$) than patients who did not receive transfusions (Fig 3, *A*). No difference was observed in 30-day mortality ($P = .502$) or readmission rate ($P = .37$). PHLF occurred more often in patients receiving RBCT (10.2% vs 4.0%; $P = .002$). When considering system-specific MM, univariate analysis revealed associations between RBCT and infectious events (RR, 1.73; 95% CI, 1.18–2.53), respiratory events (RR, 4.00; 95% CI, 1.55–10.30) and venous thromboembolic events (RR, 2.05; 95% CI, 1.00–4.17), but not cardiac events (RR, 1.61; 95% CI, 0.76–3.44). Median duration of stay was 9 days (5–9) for transfused patients and 6.5 days (6.75–16) for not transfused patients ($P < .001$).

Analysis of postoperative outcomes among transfused patients based on the amount of transfusion received is depicted in Fig 3, *B*. No difference was observed in MM, mortality, or readmission between patients receiving <4 RBCTs or ≥4 RBCTs.

Owing to the high correlation between estimated blood loss and RBCT, only RBCT was included in the regression models. Similar high

Table II. Operative characteristics of included patients, based on RBC transfusion status

	No RBC transfusion (n = 504)	*RBC transfusion (n = 208)*	P *value*
Operative time (h)	4.2 (2.9–5.5)	5.3 (3.7–6.6)	<.001
Estimated blood loss (L)	0.6 (0.4–1.0)	1.3 (0.8–2.2)	<.001
Intraoperative use of tranexamic acid	89 (18.2)	28 (13.9)	.167
Intraoperative complication	21 (4.2)	25 (12.0)	<.001
Major liver resection*	336 (66.7)	156 (75.0)	.029
Extrahepatic resection	126 (25.0)	44 (21.2)	.274
Laparoscopic approach	55 (11.0)	8 (3.9)	.003

*Major liver resection: >3 liver segments.
Values are n (%) and median (interquartile range).
RBC, Red blood cells.

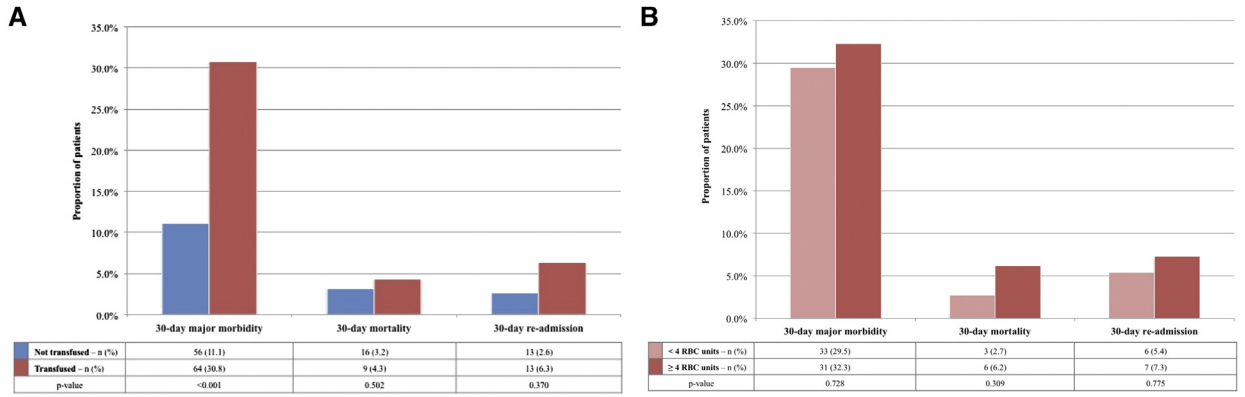

Fig 3. Postoperative outcomes of patients undergoing hepatectomy, according to RBC transfusion status (*A*) and amount of RBC transfusions received (*B*). *RBC*, Red blood cell.

correlation was observed between diagnosis and underlying liver cirrhosis, such that only diagnosis was included in the models. On multivariate analysis, older age (RR, 1.03; 95% CI, 1.00–1.06), greater operative time (RR, 1.29; 95% CI, 1.11–1.50), and RBCT (RR, 3.57; 95% CI, 1.81–7.04) were associated independently with the occurrence of MM (Table III). Female sex (RR, 0.75 [95% CI, 0.56–0.99]; RR, 0.61 [95% CI, 0.41–0.89]) and RBCT (RR, 1.47; 95% CI, 1.13–1.91) were associated independently with greater duration of stay (Table IV). Including underlying liver cirrhosis in the models instead of diagnosis did not alter the direction and significance of the association.

DISCUSSION

This study examined the association between perioperative RBCT and postoperative MM in patients undergoing liver resection, with a view to delineate the need and potential impact of further strategies of blood conservation in liver surgery. Perioperative RBCT was associated with a 3-fold increase in the odds of postoperative MM (P = .001) after adjusting for preoperative and intraoperative variables. We also identified an independent increase in duration of stay in patients receiving RBCT. The lack of difference in MM when considering the amount of RBCT received indicates that the potential detrimental impact of RBCT is observed even for 1 unit transfused.

The repercussions of RBCT on the healing process after different operations have been reported in preclinical models of intestinal anastomoses, indicating potential detrimental effects on morbidity.[22,23] Clinical findings from nonhepatic gastrointestinal surgery demonstrate similar findings. In an analysis of the American College of Surgeons National Surgical Quality Improvement Program examining 6,301 noncardiac surgery patients, RBCT was associated with increased risk of morbidity (odds ratio [OR], 9.28; 95% CI, 5.74–15) and mortality (OR, 2.84; 95% CI, 2.07–3.89), and identified as being independently associated with prolonged duration of stay ($P < .001$). More specifically, a greater number of occurrences of postoperative infections have been reported in patients receiving RBCTs.[11,24,25] Furthermore, this finding seems to translate into increased costs,

Table III. Multivariate regression of factors associated with postoperative major morbidity (logistic regression)

Factor	*Relative risk*	*95% CI*	P *value*
Age (y)	1.03	1.00–1.06	.034
Female sex	0.67	0.33–1.36	.264
Preoperative serum albumin (g/L)	0.99	0.94–1.04	.702
Diagnosis			
Cholangiocarcinoma	0.93	0.32–2.72	.901
Colorectal liver metastases	0.71	0.16–3.12	.707
Hepatocellular carcinoma	1.56	0.21–11.69	.664
Neuroendocrine liver metastases	5.00	0.24–10.37	.298
Other benign liver disease	0.57	0.07–4.47	.595
Other liver metastases	1.64	0.12–21.55	.705
Other malignant liver disease		Reference	
Preoperative anemia*	0.95	0.46–1.96	.900
Surgeon			
1	0.74	0.33–1.70	.483
2	0.88	0.39–1.95	.748
3	2.03	0.53–7.83	.303
4		Reference	
Largest lesion ≥5 cm	0.94	0.46–1.92	.874
Major liver resection†	0.55	0.22–1.37	.200
Operative time (h)	1.29	1.11–1.50	.001
Intraoperative complication	0.79	0.23–2.75	.717
Perioperative RBC transfusion	3.57	1.81–7.04	<.001

*Hemoglobin ≤130 g/L.
†Major liver resection: >3 liver segments.
RBC, Red blood cell.

with each unit of transfused RBC adding 2% to hospital charges after colorectal cancer resection.[9]

The evidence is more limited in liver surgery. The largest report to date came from the Memorial Sloan Kettering Cancer Center and included 1,351 patients who were treated between 1986 and 2001.[18] Although this study observed an increased rate of complications (27% vs 12%), mortality (12% vs 5.8%), and duration of stay (median 10 vs 8 days) with the use of RBCTs, that report involved a cohort patients treated in a different era of liver surgery. Indeed, the transfusion rate was as high as 55%. Since then, operative techniques and anesthetic management of hepatectomies have changed tremendously.[3-5,26] More recently, 2 retrospective studies reported a negative impact of RBCT on morbidity, with the ORs of 1.39 (95% CI, 1.09–3.58) and 3.9 (1.5–10.0); those studies, however, were limited by sample sizes of 127 and 239 patients.[16,17] With our >700 patients from 2003 to 2012, and after adjustments for preoperative and intraoperative characteristics, age, operative time, and perioperative RBCT were the only factors independently associated with MM.

Contrary to other analyses of posthepatectomy morbidity, major liver resection was not associated with MM after adjusting for other variables in the current analysis. Our study population consisted of a majority of major liver resections within a practice favoring the use of parenchymal preserving techniques. We used a traditional definition of extent of liver resection relying on the number of segments resected, although in the contemporary era of parenchymal sparing procedures, this definition may not reflect adequately the technical difficulty and risk of resection. Indeed, multiple wedge resections or limited nonlobar resections such as anterior sectorectomy can be more demanding technically and result in the creation of a greater raw surface than formal anatomic resections including a greater number of segments. Considering operative time as a surrogate for complexity of the type of hepatectomy, this factor was indeed revealed as associated with MM.

Several hypotheses have been proposed to explain the reported associations of RBCT with worse postoperative outcomes. The most common MM related to PRBCT is transfusion-related immunomodulation, identified initially when greater survival was observed for cadaveric kidney grafts in patients who received RBCTs.[14] No clear mechanism has yet been identified behind the

Table IV. Multivariate regression of factors associated with postoperative duration of stay (negative binomial regression)

Factor	*Relative risk*	*95% CI*	P *value*
Age (y)	1.01	0.99–1.02	.092
Female sex	0.75	0.56–0.99	.042
Preoperative serum albumin (g/L)	0.99	0.97–1.01	.494
Diagnosis			
Cholangiocarcinoma	1.50	0.56–3.96	.418
Colorectal liver metastases	1.24	0.50–3.10	.644
Hepatocellular carcinoma	1.35	0.51–3.57	.539
Neuroendocrine liver metastases	1.36	0.44–4.24	.592
Other benign liver disease	2.33	0.53–10.27	.264
Other liver metastases	1.11	0.38–3.24	.843
Other malignant liver disease		Reference	
Preoperative anemia*	1.04	0.78–1.39	.769
Surgeon			
1	0.81	0.59–1.12	.212
2	0.88	0.51–1.52	.658
3	0.97	0.72–1.31	.837
4		Reference	
Largest lesion ≥5 cm	1.02	0.77–1.35	.867
Major liver resection†	1.17	0.88–1.56	.265
Operative time (h)	1.01	0.97–1.06	.661
Intraoperative complication	0.64	0.37–1.11	.110
Perioperative RBC transfusion	1.47	1.13–1.91	.005

*Hemoglobin ≤130 g/L.
†Major liver resection: >3 liver segments.
RBC, Red blood cell.

impairment in immunity created by transfusions. Hypotheses include a decrease in natural killer cell function, decreased T-cell function, increased number of suppressor T cells, and impaired macrophagic and monocytic functions.[13] Furthermore, the duration of storage of the blood has been implicated in adverse effects from transfusions, with a greater number of inflammatory cytokines and other bioactive molecules being generated with prolonged storage.[27,28]

Beyond the detrimental impact on short-term outcomes after surgery, RBCTs have also been associated with worse long-term outcomes, including cancer recurrence and survival. Indeed, RBCTs have been related to decreased overall survival and decreased disease-free survival in gastric, breast, lung, and colorectal cancers.[10,29-31] Ascertaining the effects of RBCTs on oncologic outcomes after liver resection fell beyond the scope of the current study; however, previous work has highlighted how postoperative MM can translate into worse long-term outcomes, such as inferior disease-free survival, disease-specific survival, and overall survival for colorectal liver metastases.[32-35]

Our findings further support the rationale to use comprehensive management strategies aimed at decreasing the rate of RBCT after hepatectomy. By defining the potential for detrimental effects of RBCTs on posthepatectomy morbidity with contemporary management of liver resection, this study highlights an opportunity to improve the care of those patients. Although some RBCT cannot be avoided, a nonnegligible proportion can be deemed unnecessary according to current guidelines. In a recent, retrospective institutional review of transfusion practices in hepatobiliary surgery, up to one-half of transfusions were considered unnecessary.[36] Indeed, variation in transfusion practice regarding both transfusion rates and "triggers" for transfusion suggests the need to standardize these criteria based on available evidence.[36,37] Thus, it is possible that some RBCTs may be avoided safely with the uptake of more restrictive strategies for transfusion.[38-41] The implementation of dedicated blood conservation programs to promote the adoption of this evidence has proven successful in decreasing the use of RBCTs by ≤50% in colorectal, orthopedic, and cardiac operations.[42-44] For cardiac artery bypass, such programs have also resulted in decreased morbidity, mortality, and ensuing costs in a before-and-after study including >40,000 patients in multiple US institutions.[44] Those programs

rely on multidisciplinary transfusion education sessions, transfusion consultation services, and mandated documentation of indications for transfusions. Identifying specific predictors of the need for RBCT during and after hepatectomy fell beyond the scope of this study, but prior works have focused on developing tools to determine which patients are at a greater risk for requiring RBCT and on whom blood management strategies should focus more specifically.[45]

Strengths of this study include the large sample size, contemporary timing, and inclusion of detailed preoperative and intraoperative data in an adjusted analysis of the association between MM and RBCTs. Our work provides a unique assessment of the effects of RBCTs on perioperative outcomes after partial hepatectomy. We acknowledge the limitations implied by the retrospective design of the study, especially the potential information bias and unknown confounders that we cannot account for. In particular, the leap from association to causation is not possible with this retrospective design. Nevertheless, the independent association between RBCT and inferior outcomes should not be overlooked. These data further the rationale to attempt to decrease RBCT use, especially in light of the large proportion of unnecessary transfusions still being administered.

In conclusion, receipt of RBCT is independently associated with perioperative MM and prolonged hospitalization after partial hepatectomy after adjusting for known potential confounders. These findings further the rationale to attempt to decrease the use of RBCT for hepatectomy, which could be accomplished through the development and implementation of more comprehensive strategies for perioperative blood management.

REFERENCES

1. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854-62.
2. Cheang T, Hanna SS, Wright FC, Law CHL. Use of a collagen-sealing device in hepatic resection: a comparative analysis to standard resection technique. HPB 2006; 8:194-9.
3. Gurusamy KS, Li J, Vaughan J, Sharma D, Davidson BR. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection (review). Cochrane Database Syst Rev 2012:CD007338.
4. Gurusamy KS, Li J, Sharma D, Davidson BR. Pharmacological interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database Syst Rev 2009:CD008085.
5. Gurusamy KS, Pamecha V, Sharma D, Davidson BR. Techniques for liver parenchymal transection in liver resection. Cochrane Database Syst Rev 2009:CD006880.
6. Melendez JA, Arslan V, Fischer ME, Wuest D, Jarnagin WR, Fong Y, et al. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. J Am Coll Surg 1998;187:620-5.
7. Lucas DJ, Schexneider KI, Weiss M, Wolfgang CL, Frank SM, Hirose K, et al. Trends and risk factors for transfusion in hepatopancreatobiliary surgery. J Gastrointest Surg 2013;18:719-28.
8. Pulitanò C, Arru M, Bellio L, Rossini S, Ferla G, Aldrighetti L. A risk score for predicting perioperative blood transfusion in liver surgery. Br J Surg 2007;94: 860-5.
9. Vamvakas EC, Carven JH. Allogeneic blood transfusion, hospital charges, and length of hospitalization: a study of 487 consecutive patients undergoing colorectal cancer resection. Arch Pathol Lab Med 1998;122:145-51.
10. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006:CD005033.
11. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. J Trauma 2003;54: 908-14.
12. OBrien SF, Yi QL, Fan W, Scalia V, Fearon MA, Allain JP. Current incidence and residual risk of HIV, HBV and HCV at Canadian Blood Services. Vox Sang 2012;103:83-6.
13. Blumberg N, Heal JM. Effects of transfusion on immune function. Cancer recurrence and infection. Arch Pathol Lab Med 1994;118:371-9.
14. Opelz G. Improved kidney graft survival in nontransfused recipients. Transplant Proc 1987;19:149-52.
15. McNally SJ, Revie EJ, Massie LJ, McKeown DW, Parks RW, Garden OJ, et al. Factors in perioperative care that determine blood loss in liver surgery. HPB 2012;14:236-41.
16. Cannon RM, Brown RE, St Hill CR, Dunki-Jacobs E, Martin RCG, McMasters KM, et al. Negative effects of transfused blood components after hepatectomy for metastatic colorectal cancer. Am Surg 2013;79:35-9.
17. Gruttadauria S, Saint Georges Chaumet M, Pagano D, Marsh JW, Bartoccelli C, Cintorino D, et al. Impact of blood transfusion on early outcome of liver resection for colorectal hepatic metastases. J Surg Oncol 2011;103: 140-7.
18. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, DeMatteo RP, et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg 2003;237:860-9.
19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. Ann Surg 2004;240:205-13.
20. Benoist B, McLean E, Egli I, Cogswell M. Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia. World Health Organization Cataloguing-in-Publication Data; 2008:51.
21. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
22. Tadros T, Wobbes T, Hendriks T. Blood transfusion impairs the healing of experimental intestinal anastomoses. Ann Surg 1992;215:276-81.

23. Tadros T, Wobbes T, Hendriks T. Opposite effects of interleukin-2 on normal and transfusion-suppressed healing of experimental intestinal anastomoses. Ann Surg 1993;218:800-8.
24. Mynster T, Christensen IJ, Moesgaard F, Nielsen HJ. Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer. Danish RANX05 Colorectal Cancer Study Group. Br J Surg 2000;87:1553-62.
25. Bellantone R, Sitges-Serra A, Bossola M, Doglietto GB, Malerba M, Franch G, et al. Transfusion timing and postoperative septic complications after gastric cancer surgery: a retrospective study of 179 consecutive patients. Arch Surg 1998;133:988-92.
26. Bui LL, Smith AJ, Bercovici M, Szalai JP, Hanna SS. Minimising blood loss and transfusion requirements in hepatic resection. HPB 2002;4:5-10.
27. Ho J, Sibbald WJ, Chin-Yee IH. Effects of storage on efficacy of red cell transfusion: when is it not safe? Crit Care Med 2003;31:S687-9.
28. Ghio M, Contini P, Mazzei C, Brenci S, Barberis G, Filaci G, et al. Soluble HLA class I, HLA class II, and Fas ligand in blood components: a possible key to explain the immunomodulatory effects of allogeneic blood transfusions. Blood 1999;93:1770-7.
29. Fong Y, Karpeh M, Mayer K, Brennan MF. Association of perioperative transfusions with poor outcome in resection of gastric adenocarcinoma. Am J Surg 1994;167:256-60.
30. Nowak MM, Ponsky JL. Blood transfusion and disease-free survival in carcinoma of the breast. J Surg Oncol 1984;27:124-30.
31. Little AG, Wu HS, Ferguson MK, Ho CH, Bowers VD, Segalin A, et al. Perioperative blood transfusion adversely affects prognosis of patients with stage I non-small-cell lung cancer. Am J Surg 1990;160:630-2.
32. Correa-Gallego C, Gonen M, Fischer M, Grant F, Kemeny NE, Arslan-Carlon V, et al. Perioperative complications influence recurrence and survival after resection of hepatic colorectal metastases. Ann Surg Oncol 2013;20:2477-84.
33. Farid SG, Aldouri A, Morris-Stiff G, Khan AZ, Toogood GJ, Lodge JPA, et al. Correlation between postoperative infective complications and long-term outcomes after hepatic resection for colorectal liver metastasis. Ann Surg 2010; 251:91-100.
34. Ito H, Are C, Gonen M, D'Angelica M, DeMatteo RP, Kemeny NE, et al. Effect of postoperative morbidity on long-term survival after hepatic resection for metastatic colorectal cancer. Ann Surg 2008;247:994-1002.
35. Hallet J, Tsang M, Cheng ESW, Habashi R, Kulyk I, Hanna SS, et al. The impact of perioperative red blood cell transfusions on long-term outcomes after hepatectomy for colorectal liver metastases. Ann Surg Oncol 2015;22: 4038-45.
36. Ejaz A, Spolverato G, Kim Y, Frank SM, Pawlik TM. Identifying variations in blood use based on hemoglobin transfusion trigger and target among hepatopancreaticobiliary surgeons. J Am Coll Surg 2014;219:217-28.
37. Hutton B, Fergusson DA, Tinmouth A, McIntyre LA, Kmetic A, Hébert PC. Transfusion rates vary significantly amongst Canadian medical centres. Can J Anaesth 2005; 52:581-9.
38. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin J, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340: 409-17.
39. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. FPCUS Investigators. Liberal orrestrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
40. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, McKenzie M, Alcorn KW, et al. Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011;108: 1108-11.
41. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-2.
42. Freedman J, Luke K, Escobar M, Vernich L, Chiavetta JA. Experience of a network of transfusion coordinators for blood conservation (Ontario Transfusion Coordinators [ONTraC]). Transfusion 2008;48:237-50.
43. Froman JP, Mathiason MA, Kallies KJ, Bottner WA, Shapiro SB. The impact of an integrated transfusion reduction initiative in patients undergoing resection for colorectal cancer. Am J Surg 2012;204(6):944-51.
44. Lapar DJ, Crosby IK, Ailawadi G, Ad N, Choi E, Spiess BD, et al. Blood product conservation is associated with improved outcomes and reduced costs after cardiac surgery. J Thorac Cardiovasc Surg 2013;145:796-804.
45. Sima CS, Jarnagin WR, Fong Y, Elkin E, Fishcer M, Wuest D, et al. Predicting the risk of perioperative transfusion for patients undergoing elective hepatectomy. Ann Surg 2009; 250:914-21.