Cardiovascular Surgery

Increased Mortality, Postoperative Morbidity, and Cost After Red Blood Cell Transfusion in Patients Having Cardiac Surgery

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Background—Red blood cell transfusion can both benefit and harm. To inform decisions about transfusion, we aimed to quantify associations of transfusion with clinical outcomes and cost in patients having cardiac surgery.

Methods and Results—Clinical, hematology, and blood transfusion databases were linked with the UK population register. Additional hematocrit information was obtained from intensive care unit charts. Composite infection (respiratory or wound infection or septicemia) and ischemic outcomes (myocardial infarction, stroke, renal impairment, or failure) were prespecified as coprimary end points. Secondary outcomes were resource use, cost, and survival. Associations were estimated by regression modeling with adjustment for potential confounding. All adult patients having cardiac surgery between April 1, 1996, and December 31, 2003, with key exposure and outcome data were included (98%). Adjusted odds ratios for composite infection (737 of 8516) and ischemic outcomes (832 of 8518) for transfused versus nontransfused patients were 3.38 (95% confidence interval [CI], 2.60 to 4.40) and 3.35 (95% CI, 2.68 to 4.35), respectively. Transfusion was associated with increased relative cost of admission (any transfusion, 1.42 times [95% CI, 1.37 to 1.46], varying from 1.11 for 1 U to 3.35 for >9 U). At any time after their operations, transfused patients were less likely to have been discharged from hospital (hazard ratio [HR], 0.63; 95% CI, 0.60 to 0.67) and were more likely to have died (0 to 30 days: HR, 6.69; 95% CI, 3.66 to 15.1; 31 days to 1 year: HR, 2.59; 95% CI, 1.68 to 4.17; >1 year: HR, 1.32; 95% CI, 1.08 to 1.64).

Conclusions—Red blood cell transfusion in patients having cardiac surgery is strongly associated with both infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs. (***Circulation*. 2007;116:2544-2552.)**

Key Words: infection ■ myocardial infarction ■ stroke ■ surgery ■ blood transfusions

Transfusion of allogenic red blood cells (RBCs) is increasingly recognized as a risk factor for adverse outcome after cardiac surgery.[1,2] Unnecessary transfusions are likely to be associated with unnecessary morbidity and additional indirect hospitalization costs. Direct costs also are considerable; adult cardiac surgery accounts for a significant proportion of all RBC transfusions in the United Kingdom and the United States.[3,4]

The evidence base on which RBCs are transfused is poor. A low hematocrit in the absence of hemorrhagic shock remains the most common indication in the critically ill.[5–7] However, the hematocrit level at which the benefits of transfusion outweigh the risks in anemic cardiac surgery patients is unclear. Consequently, the hematocrit threshold at which patients are transfused varies widely both within and between institutions, with 25% to 95% of cardiac surgery patients receiving RBC transfusions in surveys.[4,8]

We analyzed the association between RBC transfusion, nadir hematocrit, clinical outcomes, and hospital costs in a large cohort of patients having cardiac surgery to inform the design of a subsequent randomized controlled trial and potentially to promote collective equipoise among surgeons and cardiac intensivists.

Methods

Study Design

This retrospective cohort study linked data from several routinely collected data sources. The research objectives and the analyses

to address them were planned before the analyses were carried out, and the protocol was approved by a UK National Health Service (NHS) Research Ethics Committee (06/Q2002/50). Because of the dangers of selective outcome reporting[9] and other biases that can arise in the analysis of observational data, we distinguish aspects of the study that were prespecified from those that were not.

Study Population

The Bristol Royal Infirmary established a database of adult cardiac surgery patients in April 1996 (Patient Analysis and Tracking Systems [PATS], Dendrite Clinical Systems, London, UK). A standard set of perioperative and postoperative data are collected prospectively by the anesthetist, surgeon, and intensive care unit (ICU), high-dependency unit (HDU), and ward nurses. All adult patients ($\geq$16 years) in this database up to December 31, 2003, whose data could be linked (see below) were included.

Data Sources

Three databases were linked: (1) the PATS database, (2) the hematology database of blood test results processed through the main laboratory of the hospital (providing longitudinal hematocrits during a patient's hospital stay), and (3) the blood bank database of blood products issued and used. The PATS database also is linked with the UK population register through the NHS Strategic Tracing Service to audit long-term survival.

Because hematocrit is the most important indicator for transfusion,[5–7] we aimed to stratify analyses by the nadir hematocrit during a patient's postoperative course. Hematocrit is measured hourly by ICU staff, not in the main laboratory. Therefore, all available ICU charts for the study period were checked manually to obtain the nadir hematocrit during the first 12 postoperative hours.

Definitions of Exposures of Interest and Potential Confounding Factors

Units of RBC transfused were documented from the blood bank database. Any RBC transfusion versus none was a priori exposure of interest. Because of studies published after writing the protocol that showed a dose-response relationship between outcome and the number of RBCs transfused,[1] we also created an ordered categorical variable for exposure to RBCs: 0, 1, 2, 3 to 4, 5 to 9, and >10 U.

Nadir hematocrit was defined as the lowest hematocrit recorded for a patient on the ICU chart or in the hematology database. Intraoperative hematocrit was not considered when this variable was derived for 3 reasons. First, the effect of low hematocrit on tissue oxygenation is different during cardiopulmonary bypass and during the immediate postoperative period.[10,11] Second, variables correlated with low intraoperative hematocrit (preoperative hematocrit, body mass index, age, operation type, and sex)[12] were included in the propensity model (see below). Third, we carried out a further analysis (not prespecified) stratified by intraoperative RBC transfusion or not.

Specific high-risk subgroups were identified in the analysis plan, namely older age, female gender, valve or other operations, preoperative creatinine >150 mmol/L, presence of lung disease (chronic obstructive airways disease or asthma), diabetes mellitus, and incompleteness of revascularization. We did not anticipate effect modification but specified testing of interactions with these factors because of evidence and opinion suggesting that high risk and elderly patients warrant transfusion at more liberal hematocrit thresholds,[13] as well as the tendency for these patients to be transfused more frequently.[14,15] An additional prespecified subgroup analysis investigated whether the effect of transfusion changed after November 30, 1999, because the UK National Blood Service carried out universal leukodepletion after this date.

Comorbidities were predefined by information collected in the PATS database. Nadir hematocrit was stratified into 4 groups as per protocol: <21, $\geq$21 and <24, $\geq$24 and <27, and $\geq$27. Other clinical characteristics potentially prognostic of outcome were taken into account by calculating a propensity score (see Statistical Analysis).

Definitions of Outcomes of Interest

Two coprimary outcomes were prespecified. A composite infection outcome was defined as respiratory infection or wound infection or septicemia. This outcome was intended to reflect the potential harm from unnecessary RBC transfusion resulting from immunosuppression. A composite ischemic outcome was prespecified as myocardial infarction, permanent or transient stroke, or renal complication (creatinine >200 mmol/L or requirement for hemodialysis, excluding patients on dialysis before their operations). This outcome was intended to reflect the potential harm from not giving an RBC transfusion when transfusion would have been beneficial. We hypothesized that the risk of experiencing the ischemic outcome would outweigh the risk of an infection when the nadir hematocrit was very low.

We used NHS reference costs for 2005 for ICU, HDU, and postoperative stay[16] and the costs of blood products (in October 2006, provided by the UK National Blood Service) to estimate the relative increase in hospital costs for patients who were transfused compared with those who were not.

Finally, we investigated the effect of transfusion on ICU/HDU and hospital stay (time to discharge) and survival after surgery using the NHS Strategic Tracing Service. These outcomes were not prespecified. No other outcomes were analyzed.

Statistical Analysis

Prognostic factors and outcome frequencies were tabulated for patients who were and were not transfused. Propensity scores for RBC transfusion were calculated using prognostic factors available in the PATS database (see Table 1), year of operation, and interactions of these factors that improved the goodness of fit of the final model (ie, a specified model, not fitted by stepwise methods or other statistical criteria to select variables for inclusion). Infrequently missing prognostic factors ($\approx$1%) were recoded to the median or most common category; more frequently missing data were assigned a "missing" category and included in models. The C statistic for the propensity model was 0.84. Nadir hematocrit stratum was always explicitly included in models, not in the propensity score, because we aimed to estimate how it modified the effects of RBC transfusion. Specifically, we predicted effect modification for the ischemic outcome but not for the infection outcome.

Multivariable logistic regression models (infection and ischemic outcome) were fitted, including nadir hematocrit stratum and deciles of propensity score as covariates. Cox regression models were fitted for ICU/HDU and postoperative hospital stay and survival. Models were adjusted by including hematocrit stratum as a covariate, stratifying by decile of propensity score to satisfy the proportional-hazards assumption. Patients who died or had missing ICU/HDU or ward discharge information were censored. Interactions of RBC transfusion with hematocrit stratum, prespecified risk groups (see above), and leukodepletion were investigated. Additional analyses that were not prespecified investigated units of RBCs transfused as an ordered categorical variable, hematocrit fitted as a continuous variable, and prognostic factors fitted as covariates in addition to propensity deciles.

Results are reported as odds or hazard ratios describing the relative risk of the outcome for patients who had RBC transfusions compared with those who did not. All confidence intervals (CIs) were estimated by bootstrapping. Analyses were carried out in STATA 9.2 (Stata Corp, College Station, Tex). We also calculated the proportion of composite infection and ischemic outcomes apparently attributable to RBC transfusion in the whole study population.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population

A total of 8724 patients were recorded in the PATS database during the study period; 63 who had only thoracic or vascular

procedures were excluded. Forty patients had missing hematocrit data, and another 23 patients could not be linked with the blood bank database. The remaining 8598 were all successfully linked with the NHS Strategic Tracing Service. Infection and ischemic outcomes could not be derived for 82 and 80 (neither for 53) of these patients, leaving 8516 and 8518 patients in analyses of the respective outcomes (Appendix A, flow diagram, in the online-only Data Supplement). All 8598 patients were included in analyses of length of ICU/HDU and postoperative hospital stay and survival. Table 1 shows the patients' characteristics.

Some patients (221 of 8598, 2.6%) died in hospital; most had data that allowed the infection (79%), ischemic (86%), and survival outcomes (100%) to be derived, and they were included. (About half of the patients with missing information on infection and ischemic outcomes died in hospital; 53% of patients who died in hospital and who had missing information about infection and ischemic outcomes died on the day of operation or the following day.) Patients who died in hospital were more likely to have been transfused than those who survived to discharge (96% versus 56%). Similar percentages of patients who died in hospital and who had missing infection or ischemic outcomes were transfused (44 of 48 [92%] and 28 of 32 [88%], respectively).

Infections and Ischemic Events

Frequencies of infection and ischemic outcomes were higher for patients who were transfused than for those who were not (Table 2). Interactions of hematocrit stratum and RBC transfusion, adjusted for propensity score, were not significant for either outcome (Appendix B in the online-only Data Supplement). Adjusted odds ratio estimates were 3.38 (95% CI, 2.60 to 4.40) and 3.35 (95% CI, 2.68 to 4.35; Figure 1) for the associations of transfusion with infection and ischemic outcomes, respectively.

In prespecified subgroup analyses, interactions of any RBC transfusion with prognostic factors were not statistically significant except for type of operation (infection and ischemic outcomes) and age (infection only; Figure 1). No interaction was present of transfusion and operation date after November 30, 1999, when all blood in the United Kingdom was leukodepleted. Additional analyses of high-risk subgroups that were not prespecified, by previous cardiac surgery and ejection fraction (<30%, ≥30%, and <50%), also were not significant.

Further analyses (not prespecified) investigated nadir hematocrit, units of RBCs transfused, and the interaction of RBC units with nadir hematocrit and took into account units of platelets transfused, intraoperative transfusion, postoperative mediastinal blood loss at 12 hours >1000 mL, and use of an intra-aortic balloon pump, as well as deciles of propensity score. For both infection and ischemic outcomes, the odds ratio increased steadily with increasing units transfused (Table 3), and modest interactions with hematocrit stratum were present ($P=0.07$ and $P=0.01$, respectively). No clear pattern to the interactions could be discerned, although odds ratios for increasing

Table 1. Characteristics of Patients

Prognostic Factor	Not Transfused (N=3689), n (%)	Transfused (N=4909), n (%)	P
Operation			
Isolated on-pump CABG	1506 (40.8)	2454 (50.0)	<0.0001
Isolated off-pump CABG	1436 (38.9)	655 (13.3)	…
Valve replacement	430 (11.6)	865 (17.6)	…
Valve replacement+CABG	89 (2.4)	535 (10.9)	…
Other*	228 (6.2)	400 (8.2)	…
Age, y			
≥16 and <50	460 (12.5)	370 (7.5)	<0.0001
≥50 and <60	1036 (28.1)	782 (15.9)	…
≥60 and <70	1418 (38.4)	1,825 (37.2)	…
≥70	775 (21.0)	1932 (39.4)	…
Male gender	3186 (86.4)	3232 (65.8)	<0.0001
CCS class >2	1777 (48.2)	2454 (50.0)	0.09
NYHA class >3	159 (4.3)	500 (10.2)	<0.0001
Ejection fraction <30%	149 (4.0)	335 (6.8)	<0.0001
MI in the last month	146 (4.0)	275 (5.6)	0.0009
Congestive cardiac failure	127 (3.4)	534 (10.8)	<0.0001
Previous stroke	95 (2.6)	171 (3.5)	0.02
Creatinine >150 μmol/L	98 (2.7)	525 (10.7)	<0.0001
Asthma/COAD	325 (8.8)	543 (11.1)	0.001
Peripheral vascular disease/DVT	229 (6.2)	385 (7.8)	0.004
Previous cardiac surgery	138 (3.7)	304 (6.2)	<0.0001
Left main stem stenosis >50%	391 (10.6)	555 (11.3)	0.30
Preoperative intravenous nitrates/heparin	245 (6.6)	399 (8.1)	0.01
Hypertension	1992 (54.0)	2623 (53.4)	0.60
Diabetes mellitus	520 (14.1)	731 (14.9)	0.30
Triple vessel disease	1819 (49.3)	2680 (54.6)	<0.0001
Smoking history			
Nonsmoker	1043 (28.3)	1748 (35.6)	<0.0001
Ex-smoker	2121 (57.5)	2653 (54.0)	…
Current smoker	525 (14.2)	508 (10.4)	…
Operative priority			
Elective	1918 (52.0)	2018 (41.1)	<0.0001
Urgent	1738 (47.1)	2635 (53.7)	…
Emergency/salvage	33 (0.9)	256 (5.2)	…
Parsonnet score			
0–9	2680 (72.7)	2372 (48.3)	<0.0001
10–19	873 (23.7)	1691 (34.5)	…
≥20	136 (3.7)	846 (17.2)	…

CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; MI, myocardial infarction; COAD, chronic obstructive airways disease; and DVT, deep vein thrombosis.

*Other operations included repair of congenital anomalies and cardiac operations combined with vascular or thoracic procedures but excluded isolated thoracic or vascular procedures (eg, aorta or carotid endarterectomy).

Table 2.   Frequencies of Composite Infection and Ischemic Outcomes

Outcome	Not Transfused			Transfused		
	N	n	%	N	n	%
Infection*	3674	...	...	4842	...	...
Nadir hematocrit <21	52	1	1.9	982	120	12.2
Nadir hematocrit ≥21 and <24	390	16	4.1	2164	243	11.2
Nadir hematocrit ≥24 and <27	1176	42	3.6	1385	200	14.4
Nadir hematocrit ≥27	2056	82	4.0	311	33	10.6
Ischemia†	3670	...	...	4848	...	...
Nadir hematocrit <21	52	1	1.9	982	132	13.4
Nadir hematocrit ≥21 and <24	390	13	3.3	2167	307	14.2
Nadir hematocrit ≥24 and <27	1175	40	3.4	1389	231	16.6
Nadir hematocrit ≥27	2053	72	3.5	310	36	11.6

N indicates denominator hematocrit stratum/total; n, number experiencing the outcome.

*737 of 8516 (8.7%) had this outcome (missing for 82): 381 (4.5%) had a respiratory infection; 220 (2.6%) had a wound infection; 136 (1.6%) had both. Eight of 14 patients with septicemia also had a respiratory infection.

†832 of 8518 (9.8%) had this outcome (missing for 80): 543 (6.4%) had renal impairment (142 required dialysis); 77 (0.9%) had a stroke; 134 (1.6%) had a myocardial infarction; 39 (0.5%) had renal impairment and stroke (11 required dialysis); 30 (0.4%) had renal impairment and a myocardial infarction (11 required dialysis); 5 (0.06%) had a stroke and a myocardial infarction; and 4 (0.05%) had renal impairment, stroke, and a myocardial infarction (2 required dialysis).

units appeared to be lower for the highest stratum (Appendix C in the online-only Data Supplement).

Proportions of infections and ischemic outcomes in the study population attributable to transfusion (assuming that the observed associations are causal) were 80% and 81%, respectively. The corresponding proportions were 64% and 66% when patients with a nadir hematocrit <21 were excluded

(assuming that transfusions below this criterion were clinically necessary).

Effect of RBC Transfusion on the Cost of Admission

Costs of admission in UK pounds were calculated for each patient using the following unit costs: £1172, £914, and
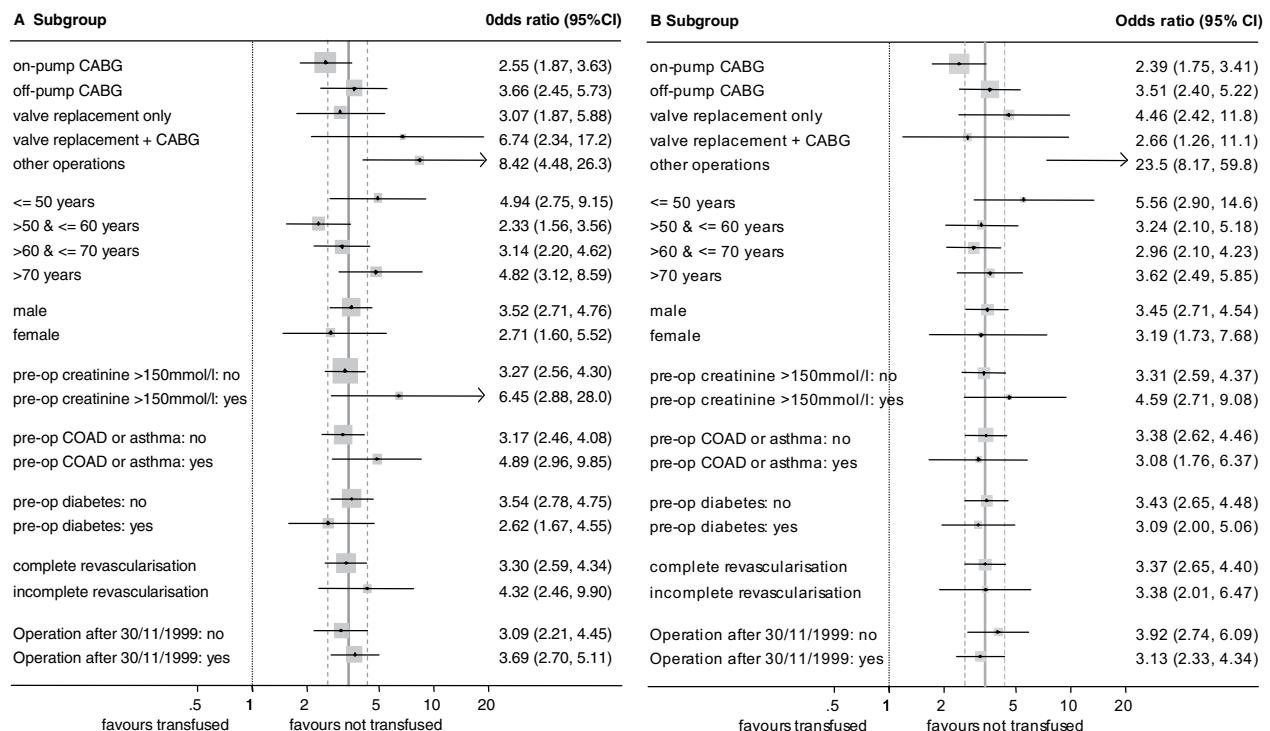

Figure 1. Adjusted odds ratios in prespecified subgroups for RBC-transfused versus nontransfused patients for (A) composite infection and (B) composite ischemic outcomes. Gray vertical lines represent the overall adjusted odds ratio (solid line) and CI (dashed lines) (ie, adjusted for hematocrit group and propensity score). CABG indicates coronary artery bypass grafting; COAD, chronic obstructive airway disease.

Table 3.   Estimates of the Increase in Effects of Transfusion With Increasing Number of Units of RBCs

| RBCs Transfused, U | Infection Outcome | | Ischemic Outcome | | Relative Increase in Cost* | | Portion of Study Population, % |
	Odds Ratio	95% CI	Odds Ratio	95% CI	Mean	95% CI	
Any	3.73	2.32–5.07	4.05	2.63–5.70	1.42	1.37–1.46	57.1
0	1.00	...	1.00	...	1.00	...	42.9
1	1.46	0.92–2.11	1.63	1.02–2.48	1.11	1.08–1.14	13.6
2	2.36	1.42–3.30	2.30	1.32–3.50	1.21	1.18–1.25	14.5
3 or 4	3.82	2.22–5.47	4.49	2.78–6.22	1.41	1.36–1.46	15.2
5–9	10.75	5.83–15.9	11.79	6.80–16.7	1.81	1.71–1.90	10.0
>9	45.44	22.6–73.6	46.39	24.5–75.4	3.35	3.03–3.70	3.8

*Effect estimates were estimated from adjusted models, including the interaction of units of RBCs and hematocrit stratum as described in the text, and pooled over hematocrit strata using stratum-specific coefficients weighted by the number of patients (see Appendix D in the online-only Data Supplement). This method of estimation explains the apparent contradiction between odds ratios reported in the Table for any transfusion vs none, compared with the estimates from the prespecified analysis reported earlier.

£376 per day of ICU, HDU, and ward stay, respectively, and £130.50, £214, and £31.50 per unit of RBCs, platelets, and fresh frozen plasma. Costs were transformed into natural logarithms to normalize their distribution. The effect of RBC transfusion was estimated from a linear regression model that included RBC units, hematocrit stratum, the interaction of these 2 exposures, propensity score, and the factors added in further models described above. Figure 2 shows how the relative increase in cost varied with RBC units transfused and nadir hematocrit stratum. Table 3 shows the increase in relative cost overall and for increasing units of RBCs transfused.

Length of ICU and Postoperative Hospital Stay

Figure 3 shows Kaplan-Meier curves for the cumulative probability of discharge from ICU/HDU and hospital with increasing postoperative time. After adjustment, transfused patients were ≈30% less likely to have been discharged from ICU/HDU (hazard ratio, 0.69; 95% CI, 0.65 to 0.72; $P<0.0001$) and ≈35% less likely to have been discharged from hospital (hazard ratio, 0.63; 95% CI, 0.60 to 0.67; $P<0.0001$) at any postoperative time. The proportional-hazards assumption was satisfied in both analyses.

All-Cause Mortality

Figure 4 shows Kaplan-Meier curves for all-cause mortality up to 7 years after surgery (median duration of follow-up, 4.25 years). The proportional-hazards assumption was violated because most deaths within 30 days after surgery occurred among transfused patients. The analysis was rerun with follow-up time divided into 3 epochs: 0 to 30 days (≈20% of deaths), 31 days to 1 year (≈20% of deaths), and >1 year (≈60% of deaths); each epoch considered only participants under observation during that epoch. For each epoch, survivors were censored at the end of follow-up or the end of the epoch, whichever occurred first. This improved the model fit (χ^2, 29.4; *df*, 2; $P<0.0001$). Adjusted hazard ratios for the 3 epochs were 6.69 (95% CI, 3.66 to 15.1; $P<0.0001$), 2.59 (95% CI, 1.68 to 4.18; $P<0.0001$), and 1.32 (95% CI, 1.08 to 1.64; $P=0.003$), respectively.

Discussion

The study has 5 main findings. First, RBC transfusion was strongly associated with infection, and a strong dose-response relationship was present. We did not find any evidence that
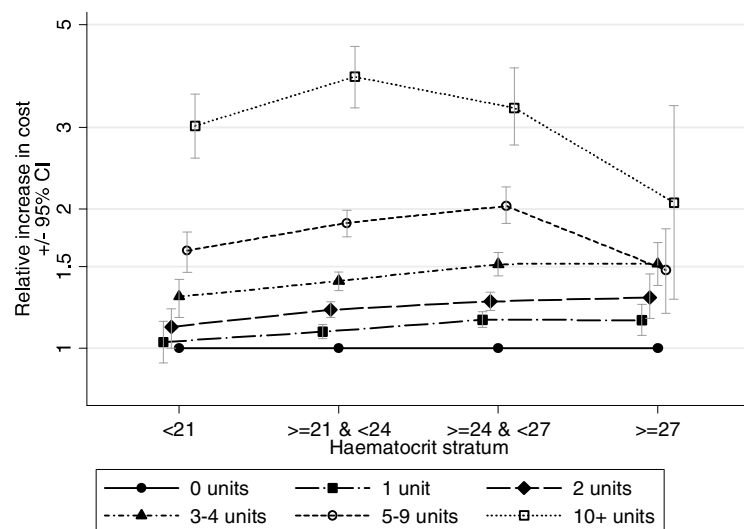

Figure 2. Relative increase in cost of admission by number of RBC units transfused and by hematocrit stratum vs patients who were not transfused.
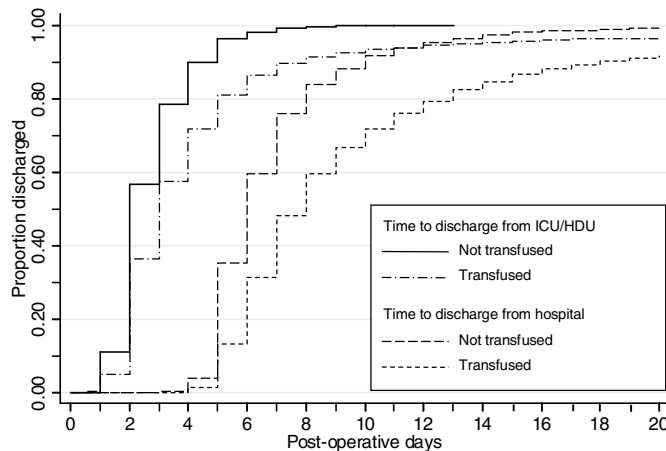
Figure 3. Kaplan–Meier "survival" curve showing the cumulative proportion of patients discharged from ICU/HDU and from hospital over time according to whether patients had had an RBC transfusion. Patients who died in hospital were censored at death.

Number at risk (discharge from ICU/HDU):

Not transfused:	3689	3274	795	136	26	10	4	2	2	2	2
Transfused:	4909	4362	2034	887	477	331	250	204	171	145	128

Number at risk (discharge from hospital):

Not transfused:	3689	3686	3675	2376	889	443	229	134	73	52	34
Transfused:	4909	4873	4826	4161	2446	1579	1123	824	617	488	400

the likelihood of infection was reduced by leukodepletion of red cells.

Second, RBC transfusion also was strongly associated with the composite ischemic outcome. Again, a strong dose-response relationship was present. This finding is counter to our original conception in which we reasoned that ischemia-related morbidity would be more likely to occur in patients who would have benefited from transfusion but who did not receive one.

Third, these associations of transfusion with early complications were highly consistent. When comparing any with no transfusion, no effect modification by nadir hematocrit could be discerned, and the associations were apparent in all prespecified "high-risk" subgroups.

Fourth, the increased morbidity associated with transfusion translated into longer ICU/HDU and total postoperative hospital stays and increased admission costs. The impact of these associations could be considerable; if

causal, avoiding transfusion would have prevented well over 50% of all infections and ischemic events in our hospital and would have reduced the nonoperative costs of an admission by ≈40%.

Fifth, transfusion affects mortality. The hazard of death in the first 30 days was almost 6 times higher for transfused patients than for those who were not transfused. Transfused patients continued to have a substantially increased hazard of death through the first postoperative year and possibly thereafter.

Study Limitations and Strengths

It is important to consider whether these observational findings could have arisen because of confounding. Transfused patients were sicker before their operations and may have had poorer outcomes for this reason rather than because they were transfused. Four observations argue against this. First, prognostic factors were well balanced
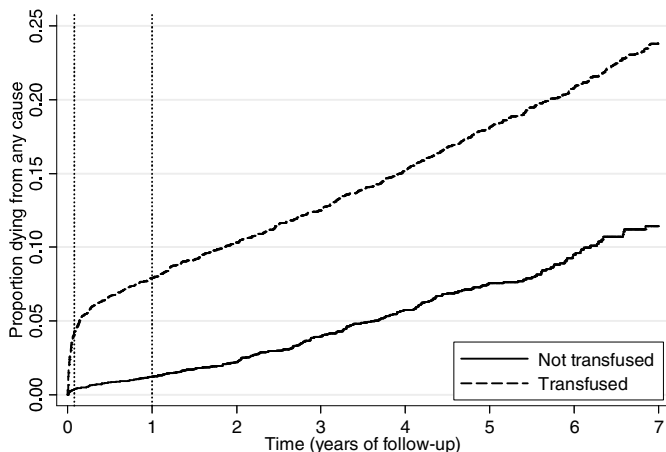

Figure 4. Kaplan–Meier survival curve showing the cumulative proportion of patients who died over time according to whether patients had had an RBC transfusion. Vertical dotted lines separate the epochs of follow-up time for which hazard ratios were estimated (ie, 0 to 30 days, 31 days to 1 year, and after 1 year).

Number at risk:

Not transfused:	3689	3529	2925	2383	1842	1261	772	391
Transfused:	4909	4449	3913	3340	2773	2213	1713	1073

across transfused and nontransfused groups within propensity deciles, implying that the propensity analysis achieved a reasonably unbiased comparison. Second, the mean nadir hematocrit was very similar across transfused and nontransfused groups within hematocrit strata, and the results did not change when nadir hematocrit was modeled as a continuous variable. Third, adjustment did not substantially alter the effects observed (Appendix B in the online-only Data Supplement). Fourth, the effects were observed within strata of patients with and without important risk factors. Therefore, we believe that the harmful effects of RBC transfusion are real. Residual confounding may mean that the adjusted estimates are slightly too extreme but could not plausibly account for the effects observed. Residual confounding also may mean that the CIs are slightly too narrow,[17] but not to the extent that the main findings would become nonsignificant.

Some data were missing but no evidence existed that patients with missing hematocrit data differed from those with data. Many patients with missing outcomes died in hospital, but their transfusion rate was no different from that of included patients who died in hospital. Moreover, if additional patients who died in hospital (who had a high probability of transfusion and of experiencing one or another outcome before dying) had been included, it is difficult to see how their inclusion would have reduced the effects of transfusion. The survival analysis was not limited by missing data and suggested a 6-fold increase in the risk of death within 30 days.

Exposures and outcomes may have been misclassified for some patients (a potential problem with routine data sets), but no reason exists to suspect that misclassification would be differential for patients who were transfused and not transfused. Using routine databases minimizes susceptibility to information bias because data were collected independently of the researchers and before potentially adverse effects of transfusion were widely publicized. Nondifferential misclassification would cause observed associations to be underestimated.

Several strengths of the study offset these potential limitations. The study included an entire cohort of cardiac surgery patients. We were able to link the necessary databases and to obtain ICU data for almost all patients in the cohort. The transfusion data came from an entirely independent source, which is widely regarded as having extremely high quality.

Findings in the Context of the Literature
Our findings with respect to the effect of RBC transfusion on the composite infection outcome and use of hospital resources are consistent with previous research, and we do not consider these further.[18] However, the effects of RBC transfusion on the composite ischemic outcome merit discussion.

RBC transfusion is intended primarily to maintain or restore tissue oxygenation. Cardiac surgery can be associated with severe bleeding, with some patients at risk of hemorrhagic shock. In such cases, transfusion is life-saving. The majority of patients in the cohort were transfused, but most were clearly not in hemorrhagic shock. The finding that transfusion is associated with an increased likelihood of the composite ischemic outcome suggests that many transfusions are at best ineffective because causality between transfusion and ischemia is not demonstrated. At worst, RBC transfusion may cause tissue ischemia and organ dysfunction.

Some previous studies support a causal association between RBC transfusion and tissue ischemia, counter to our original conception. RBC transfusion in critically ill septic patients has been observed to reduce intragastric pH, an index of mesenteric ischemia.[19] Transfusion of stored RBCs also has been shown to induce tissue hypoxia in rodents.[20,21] Increased red cell aggregability[22] and rigidity,[23] the diminished microvascular autoregulatory abilities of stored red cells,[20,24] and the accumulation of potentially toxic microparticles,[25] lipophosphatidylcholines,[26] or proinflammatory cytokines[27] in the storage supernatant may all contribute to tissue hypoxia and organ dysfunction in transfused patients. Alternatively, systemic inflammation, a feature of the response to transfusion of nonleukodepleted red cells,[27] is implicated in atherosclerotic plaque rupture, stroke, and acute coronary syndromes.[28,29] It has been proposed that leukodepletion reduces the deleterious effects of transfusion. However, we did not observe this, in keeping with some previous randomized trials in which the benefits of leukodepletion were found to be small or nonexistent.[30,31] Whether transfusion of leukodepleted red cells results in systemic inflammation has not been investigated. However, many of the pathological cellular changes and accumulation of toxic species in the supernatant seen during storage occur in both leukodepleted and nonleukodepleted cells.

Setting a hematocrit level as the trigger for RBC transfusion, with more liberal thresholds for elderly and high-risk patients,[13] is not supported by this study. The reason is that hematocrit levels in isolation, unless very low, are poor indicators of tissue hypoxia.[32] Tissue hypoxia occurs in healthy adults at hemoglobins as low as 5 to 6 g/dL (hematocrits of 15 to 18).[33,34] This level of anemia is considerably lower than commonly tolerated by physicians when managing their cardiac surgery patients (typically hematocrits of 24 to 26). More restrictive transfusion thresholds (eg, hematocrit of 21) have been shown to be beneficial in critically ill noncardiac surgical patients in a randomized trial.[35] In the present study, no apparent benefit was derived from RBC transfusion at hematocrits as low as 21. Therefore, this may represent a practical "restrictive" threshold for a randomized trial.

Low cardiac output is a key determinant of tissue oxygenation after cardiac surgery.[36,37] In such cases, more objective measures of tissue oxygenation are required. Using clinical organ dysfunction or evidence of global tissue hypoxia as indicators for transfusion is neither practical nor desirable. Noninvasive measurement of regional tissue oxygenation is possible using near-infrared spectroscopy, and future refinement of this technology has the potential to guide transfusion therapy.

Conclusions

RBC transfusion appears to be harmful for almost all cardiac surgery patients and wastes a scarce commodity and other health service resources. It is difficult to identify patients in whom transfusion is truly necessary on the basis of hematocrit, age, or comorbidity. This study reinforces the need for prospective evaluation of restrictive transfusion triggers and objective clinical indicators for RBC transfusion in cardiac surgical patients.

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None.

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CLINICAL PERSPECTIVE

This single-center, observational retrospective study investigated associations between red blood cell transfusion and infectious and ischemic adverse outcomes in >8500 cardiac surgery patients who had operations over an 8-year period. As reported previously, transfusion was strongly associated with infection. More important, however, were 3 new findings. First, transfusion was strongly associated (both large in magnitude and dose-related) with a composite ischemic outcome (stroke, myocardial infarction, and renal failure); this finding is inconsistent with the widely held belief that red cell transfusion improves tissue oxygenation. Second, this effect was constant across diverse risk groups and perioperative nadir hemoglobin levels. Third, transfusion (blood products and associated morbidity) increased overall hospitalization costs by >40% on average. These findings highlight the need for additional research on potential pathophysiological mechanisms of transfusion. Despite many reports of the potential harms of red blood cell transfusion, we know little about how transfusion affects immune function or tissue oxygenation or how to make stored allogeneic blood products safer. The study also demonstrates our poor understanding of the indications for red blood cell transfusion. Conventionally, decisions to transfuse are based on hemoglobin thresholds tailored to the patient's age and comorbidity. However, in our study, these factors did not influence the observed risks from transfusion. Finally, we hope that demonstrating the impact of red blood cell transfusion on hospitalization costs will provide the impetus for governments to fund research to address these gaps in knowledge.

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