Relationship of Erythrocyte Transfusion with Short- and Long-term Mortality in a Population-based Surgical Cohort

Keyvan Karkouti, M.D., M.Sc.,* Thérèse A. Stukel, Ph.D.,† W. Scott Beattie, M.D., Ph.D.,‡ Susie Elsaadany, Ph.D.,§ Ping Li, Ph.D.,‖ Rachel Berger, A.R.T.-I.H. (C.S.M.L.S.),# Duminda N. Wijeysundera, M.D., Ph.D.**

ABSTRACT

Background: When comparing transfused *versus* nontransfused patients, erythrocyte transfusion is consistently associated with increased mortality. Nonetheless, unmeasured confounding may unduly influence this comparison. This unmeasured risk may have less influence on comparisons of patients undergoing surgery at hospitals with differing transfusion rates.

Methods: Administrative databases were used to conduct a population-based cohort study of patients who underwent elective hip- or knee-replacement surgery from 1999 to 2008 in Ontario, Canada. The authors used Cox proportional-hazards models to determine the adjusted association of hospital-specific erythrocyte transfusion rates (*i.e.*, comparing hospitals with differing transfusion rates) with postoperative mortality. For comparison, they also determined the adjusted association of patient receipt of transfusion (*i.e.*, comparing transfused *vs.* nontransfused patients) with mortality.

Results: Of 162,190 patients, 23% (n = 37,015) were transfused. Hospital-specific transfusion rates at the 66 included hospitals ranged from 10.3 to 57.9%. Compared with nontransfused patients, transfused patients experienced increased adjusted 30-day (hazard ratio 2.32; 95% CI, 1.91–2.83) and 1-yr mortality (hazard ratio 1.75; 95% CI, 1.60–1.91). However, when hospitals were categorized into quartiles based on hospital-specific transfusion rates, mortality rates were similar (highest transfusion quartile *vs.* lowest transfusion quartile: 30-day mortality, hazard ratio 1.11, 95% CI 0.82–1.50; 1-yr mortality, hazard ratio 1.02, 95% CI 0.82–1.26).

Conclusions: The association of transfusion with postoperative mortality differed significantly when comparing transfused *versus* nontransfused patients, as opposed to comparing hospitals with differing transfusion rates. This discrepancy raises questions about the true relationship between transfusion and mortality.

What We Already Know about This Topic

- Although an association between erythrocyte transfusion and increased perioperative mortality is usually observed, unmeasured confounding may have unduly influenced this association

What This Article Tells Us That Is New

- In a large administrative database (162,190 patients in 66 hospitals), the impact of erythrocyte transfusion on mortality differed substantially when comparing outcomes at hospitals with differing transfusion rates, as opposed to comparing patients who were or were not transfused, raising question about the true relationship between transfusion and mortality

* Associate Professor, Department of Anesthesia, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada; and Toronto General Hospital Research Institute, Toronto, Ontario, Canada; † Professor, Institute of Health Policy, Management, and Evaluation, University of Toronto, and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, and ‡ Professor Department of Anesthesia, Toronto General Hospital, University Health Network. § Professor, # Transfusion Medicine Advisor, Statistics and Risk Assessment Section, Blood Safety Surveillance and Health Care Acquired Infection Division, Public Health Agency of Canada, Ottawa, Ontario, Canada. ‖ Analyst, Institute for Clinical Evaluative Sciences. ** Assistant Professor, Department of Anesthesia, Toronto General Hospital, University Health Network, University of Toronto; Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada; Institute of Health Policy Management and Evaluation, University of Toronto; Institute for Clinical Evaluative Sciences.

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Address correspondence to Dr. Karkouti: Department of Anesthesia and Pain Management, Toronto General Hospital, 200 Elizabeth Street, EN 3–402, Toronto, Ontario, Canada M5G 2C4. keyvan.karkouti@uhn.ca. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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ERYTHROCYTE transfusion is a common medical intervention, with more than 14 million units transfused annually in the United States.[1] There is, however, ongoing concern that transfusions may worsen outcomes. This concern stems primarily from observational studies showing that transfused patients consistently have higher risk-adjusted morbidity and mortality rates than nontransfused patients.[2] In a recent systematic review, 17 of 18 observational studies found that transfusion was associated with death (pooled odds ratio 1.7; 95% CI, 1.4–1.9).[2]

To the extent that these studies reflect the true risk of transfusion, they highlight an important public health problem. Nonetheless, observational studies comparing patients who did or did not receive transfusions may yield biased results if there are prognostically important unmeasured differences between treated and untreated patients, because multivariable regression and propensity score methods that are generally used to risk-adjust for between-group differences cannot account for unmeasured confounders.[3,4] The decision to transfuse is influenced by numerous unmeasured confounders. For example, the severity of preexisting comorbidity and the extent of intraoperative bleeding are both highly likely to influence the likelihood of a patient being transfused,[5] yet these factors are difficult to measure accurately for research purposes. Consequently, observational studies may overestimate risks attributable to transfusions.[2]

The ideal means for assessing any medical intervention is through random allocation of exposure. However, randomization to transfusion *versus* no transfusion is not feasible because anemia can become severe enough to necessitate transfusions. As a result, existing trials instead randomized patients to different transfusion triggers,[6–8] which addresses the question of anemia tolerance as much as it does transfusion risks.

In the absence of randomized trials, observational studies provide the main means for assessing the risks of transfusion, although limited by unmeasured confounding. Rather than comparing patients who did or did not receive transfusions, an approach that may reduce residual unmeasured confounding is comparing patients who underwent surgery at hospitals with low- *versus* high-transfusion rates. Specifically, the magnitude of unmeasured confounding is likely smaller when comparing patients who underwent surgery at hospitals with differing transfusion rates, as opposed to comparing patients who did or did not receive transfusions. Thus, if important prognostic factors are comparably distributed across hospitals that have widely different transfusion rates,[4] then hospital variations in transfusion rates become analogous to a "natural experiment" where patients are assigned to hospitals that differ in the likelihoods of administering transfusions. Thus, if transfusion is harmful, high-transfusion rate hospitals will be expected to have worse outcomes than low-transfusion rate hospitals.[4]

Notably, there is a wide interhospital variability in transfusion rates that is largely unexplained by patient- or hospital-related factors.[9–12] This variation offers the opportunity to compare the outcomes of patients who undergo surgery at hospitals with low- *versus* high-transfusion rates. We therefore conducted a population-based cohort study of hip- or knee-replacement surgery to measure the association between the hospital-specific erythrocyte transfusion rate and mortality. Our hypothesis was that risk-adjusted postoperative 30-day mortality rates would be higher at hospitals with higher transfusion rates.

Material and Methods

Data Sources and Assembly of Study Cohort

After research ethics board approval at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada), the following linked population-based administrative healthcare databases (housed at the Institute for Clinical Evaluative Sciences in Toronto, Ontario) were used to undertake this retrospective cohort study in Ontario, Canada: Discharge Abstract Database (DAD) of the Canadian Institute for Health Information (hospital admissions), Ontario Health Insurance Plan database (physician service claims), Registered Persons Database (vital statistics), and Canadian census. Although these databases lack physiologic and laboratory measures (*e.g.*, blood pressure, hemoglobin), they have been validated for many procedures, outcomes, exposures, and comorbidities.[13–16] The approximately 13 million residents of Ontario have universal access to physician and hospital services through a publicly funded healthcare program.

By using established DAD procedure codes,[17] all Ontario residents who were older than 40 yr and underwent a single elective total hip or knee replacement surgery between April 1, 1999, and March 31, 2008, were identified. If a patient had more than one eligible surgery during the study period, only the first admission was included. Because we planned to evaluate the association of hospital-specific transfusion rates with outcomes, hospitals that performed less than 100 eligible procedures during the entire study period were excluded to avoid excessive variability caused by low case volumes.

Principal Exposure, Outcomes, and Covariates

The DAD was used to ascertain the principal exposure, namely in-hospital erythrocyte transfusion (coded as present *vs.* absent). Hospitals were ranked according to their overall erythrocyte transfusion rate and then categorized into quartiles with approximately equal number of patients.[18]

The DAD was also used to determine whether patients had received other types of blood products (autologous erythrocytes, platelets, and fresh frozen plasma). Previous validation studies have shown that blood product transfusion is accurately described in the DAD (error rate less than 1%).†† During the study period, all nonautologous

†† Richards J, Brown A, Homan C: The data quality study of the Canadian discharge abstract database. Proceedings of Statistics Canada Symposium 2001. Achieving Data Quality in a Statistical Agency: A Methodological Perspective. Available at: http://www5.statcan.gc.ca/access_acces/alternative_alternatif.action?l=eng&loc=2001001/session16/6282-eng.pdf. Accessed August 9, 2012.

erythrocytes were leukoreduced by the Canadian Blood Services.

The outcome of interest was mortality at 30 days and 1 yr after surgery, as determined from the DAD (in-hospital events) and Registered Persons Database (out-of-hospital events). Because we were principally interested in the effects of erythrocyte transfusion on immediate postoperative mortality, 30-day mortality was designated as the primary outcome.

Demographic information was obtained from the Registered Persons Database. Using the DAD, the following comorbidities were identified based on *International Classification of Diseases* codes (9th or 10th Revisions) from hospitalizations within 3 yr preceding the index surgery: ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation, peripheral vascular disease, pulmonary disease, chronic renal insufficiency, previous venous thromboembolism, malignancy, liver disease, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, and dementia.[19–21] Validated algorithms were used to identify diabetes and hypertension.[13,15] The Ontario Health Insurance Plan database was used to identify patients who required dialysis before surgery. Patients' socioeconomic status was estimated based on their neighborhood median income in the Canadian census, and their residence (rural *vs.* urban) was determined using Statistics Canada definitions.[22]

Previous research has shown that demographics, procedures, blood product transfusion, and mortality are accurately described in these databases.[14,16*] Comorbidities are generally captured with high specificity, but variable sensitivity.[23] Conditions that are captured with generally better sensitivity include ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes, hypertension, atrial fibrillation, pulmonary disease, and malignancy.[13–15,23]

Statistical Analysis

Descriptive statistics were used to compare differences in characteristics between transfused and nontransfused patients, as well across quartiles based on hospital-specific erythrocyte transfusion rates. Continuous variables were described using means and standard deviations, whereas categorical variables were described using counts and percentages. We also determined predicted 30-day mortality rates within these categories. These predicted mortality rates were calculated using a logistic regression model that included surgical procedure, age, sex, socioeconomic status, comorbid disease, surgical procedure, and clinically sensible interaction terms (interaction terms with $P < 0.2$ were retained) as predictors (model c-statistic was 0.79). The purpose of calculating predicted 30-day mortality rates was to provide overall estimates of individuals' perioperative risk as a function of their measured baseline characteristics.

Multivariable Cox proportional-hazards models were then used to determine the adjusted association of the hospital-specific transfusion rate quartile with 30-day and 1-yr mortality. The other covariates in these models were year of surgery, surgical procedure, age, sex, income quintile, rural residence, comorbidities, other hospital-level characteristics (teaching status and procedure volume quartile), and clinically sensible interaction terms (interaction terms with P value less than 0.2 were retained). The included comorbidities were ischemic heart disease, congestive heart failure, cerebrovascular disease, atrial fibrillation, hypertension, diabetes, peripheral vascular disease, pulmonary disease, chronic renal insufficiency, previous venous thromboembolism, malignancy, liver disease, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, and dementia. We used the methods of Lin[24] to account for clustering of observations within hospitals and verified the proportional hazards assumption by visual inspection of estimated logarithm–logarithm survival curves.

For comparison, we used Cox proportional-hazards models to determine the adjusted associations of patient receipt of erythrocyte transfusion (as opposed to the hospital-specific transfusion rate quartile) with 30-day and 1-yr mortality. These models included year, operative procedure, sex, age, income quintile, rural residence, comorbidities, hospital teaching status, hospital procedure volume, and clinically sensible interaction terms as covariates and accounted for clustering of observations within hospitals.

We performed two sensitivity analyses to assess whether our results were influenced by model estimation methods or transfusion of other blood products. First, the main survival analyses were repeated after excluding any patient who received nonerythrocyte or autologous erythrocyte transfusions. Second, we used bootstrap resampling (1,000 samples) to reestimate the point estimates and CI for the survival analyses. Survival analyses were conducted using STATA 9.0 (StataCorp, College Station, TX), whereas all other analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). A two-sided P value less than 0.05 was used to define statistical significance.

Results

The cohort consisted of 162,190 patients who underwent surgery at 66 hospitals. Of these individuals, 23% (n = 37,015) received erythrocyte transfusions. Characteristics and outcomes of patients, according to their transfusion status, are reported in table 1. Transfused patients had a higher risk profile than nontransfused patients: they were older, included more females, underwent more hip replacement surgeries, and had more comorbid diseases. In addition, they had higher predicted 30-day mortality rates and higher observed 30-day and 1-yr mortality rates.

The 66 included hospitals had widely varying erythrocyte transfusion rates, ranging from 10.3 to 57.9%. Although there were small differences in patient risk factors across quartiles of hospital-specific transfusion rates, the mean predicted 30-day mortality was similar across the quartiles (table 2). Hospital quartiles did differ in procedure volume and rate of transfusion of nonerythrocyte blood products (high-transfusion centers were lower-volume hospitals and had greater

Table 1. Characteristics of Patients Who Did or Did Not Receive Erythrocyte Transfusions

	Transfused Patients (n = 37,015)	Nontransfused Patients (n = 125,175)
Predicted 30-day mortality*	187 (0.51%)	368 (0.29%)
Demographics		
Age in yr (mean ± SD)	71 ± 10	67 ± 10
Female	25,292 (68.3%)	70,960 (56.7%)
Rural residence	5,584 (15.1%)	22,050 (17.6%)
Income quintile		
1 (lowest)	6,795 (18.4%)	22,090 (17.6%)
2	7,577 (20.5%)	25,375 (20.3%)
3	7,524 (20.3%)	24,899 (19.9%)
4	7,244 (19.6%)	25,130 (20.1%)
5 (highest)	7,780 (21.0%)	35,097 (21.6%)
Missing	95 (0.3%)	459 (0.3%)
Comorbid diseases		
Ischemic heart disease	4,312 (11.6%)	9,659 (7.7%)
Congestive heart failure	999 (2.7%)	1,645 (1.3%)
Atrial fibrillation	1,193 (3.2%)	2,476 (2.0%)
Hypertension	25,505 (68.9%)	82,195 (65.7%)
Cerebrovascular disease	865 (2.3%)	1,690 (1.4%)
Peripheral vascular disease	650 (1.8%)	1,164 (0.9%)
Diabetes mellitus	6,898 (18.6%)	23,727 (19.0%)
Renal insufficiency or dialysis	937 (2.5%)	1,073 (0.9%)
Pulmonary disease	2,647 (7.2%)	6,798 (5.4%)
Prior venous thromboembolism	277 (0.7%)	491 (0.4%)
Liver disease	270 (0.7%)	511 (0.4%)
Rheumatologic disease	1,650 (4.5%)	3,014 (2.4%)
Hemiplegia or paraplegia	161 (0.4%)	293 (0.2%)
Dementia	413 (1.1%)	447 (0.4%)
Malignancy		
Primary disease	1,021 (2.8%)	2,534 (2.0%)
Metastatic disease	312 (0.8%)	368 (0.3%)
Surgical procedure		
Total hip replacement	18,629 (50.3%)	45,686 (36.5%)
Total knee replacement	18,386 (49.7%)	79,489 (63.5%)
Year of surgery		
1999	4,130 (11.2%)	11,387 (9.1%)
2000	4,243 (11.5%)	10,398 (8.3%)
2001	4,529 (12.2%)	10,897 (8.7%)
2002	4,123 (11.1%)	11,401 (9.1%)
2003	3,650 (9.9%)	12,311 (9.8%)
2004	3,952 (10.7%)	14,348 (11.5%)
2005	4,235 (11.4%)	17,357 (13.9%)
2006	4,208 (11.4%)	18,394 (14.7%)
2007	3,945 (10.7%)	18,682 (14.9%)
Hospital characteristics		
Teaching hospital	11,870 (32.1%)	36,818 (29.4%)
High volume†	15,757 (42.5%)	65,177 (52.1%)
Concomitant transfusions		
Autologous erythrocytes	7,907 (21.4%)	2,841 (2.3%)
Platelets	314 (0.8%)	49 (0.04%)
Plasma	769 (2.1%)	138 (0.1%)

(*continued*)

Table 1. (Continued)

	Transfused Patients (n = 37,015)	Nontransfused Patients (n = 125,175)
Outcomes		
30-day mortality	279 (0.75%)	276 (0.22%)
1-yr mortality	1,065 (2.88%)	1,392 (1.11%)

Data are numbers (percentages) unless otherwise indicated.

* Expected 30-day mortality was calculated using a multivariable logistic regression model with a c-index of 0.79 and $P = 0.94$ for its Hosmer-Lemeshow statistic. † Rank in total number of eligible procedures performed during the study period > 50th percentile.

autologous erythrocyte, plasma, and platelet transfusions) but had similar observed 30-day and 1-yr mortality rates.

Multivariable risk-adjustment using Cox proportional-hazards models found no association between the hospital-specific transfusion rate quartile with either 30-day or 1-yr mortality (table 3). Despite large associated differences in erythrocyte transfusion rates, point estimates for the adjusted hazards ratios were similar across all quartiles. Conversely, when these analyses were repeated using the patient receipt of erythrocyte transfusion as the exposure (*i.e.*, directly comparing transfused *vs.* nontransfused patients), patient receipt of transfusion had a strong association with both 30-day mortality (hazard ratio 2.32; 95% CI, 1.91–2.83; *P* value less than 0.001) and 1-yr mortality (hazard ratio 1.75; 95% CI, 1.60–1.91; *P* value less than 0.001).

The association of quartiles of hospital-specific transfusion rates with mortality was qualitatively unchanged after excluding patients who received platelet, plasma, or autologous erythrocyte transfusions (see Supplemental Digital Content 1, http://links.lww.com/ALN/A882, which is a table showing the results of this sensitivity analysis). It also remained unchanged when the Cox proportional-hazards model was estimated using bootstrap resampling (see Supplemental Digital Content 1, http://links.lww.com/ALN/A882).

Given the relatively wide range of hospital-specific rates within the highest transfusion rate quartile (*i.e.*, Quartile 4), a *post hoc* analysis was performed where we divided this quartile into two groups of approximately equal size and then reestimated the adjusted association of transfusion rate categories with postoperative mortality. The subdivision of Quartile 4 resulted in groups with a smaller within-category range of transfusion rates (see Supplemental Digital Content 2, http://links.lww.com/ALN/A883, which is a table reporting the characteristics of the categories in this *post hoc* analysis). Nonetheless, hospital-specific transfusion rate categories were not associated with increased postoperative mortality in this *post hoc* analysis (see Supplemental Digital Content 3, http://links.lww.com/ALN/A884, which is a table reporting the association of these categories with postoperative mortality).

Discussion

The objective of this population-based cohort study of patients who underwent elective total hip- or knee-replacement surgery at 66 hospitals with widely different erythrocyte transfusion rates was to explore the effects of erythrocyte transfusion on short-term and long-term mortality. When we compared the adjusted mortality rates of patients who did or did not receive erythrocyte transfusions, we found a strong relationship between transfusions and increased short- and long-term mortality. Conversely, when we compared the risk-adjusted outcomes of high-transfusion rate hospitals with low-transfusion rate hospitals, we found that the hospital transfusion rate had no influence on short- or long-term mortality.

Our comparison of transfused *versus* nontransfused patients is consistent with numerous existing observational studies that also found patient receipt of transfusion to be associated with higher risk-adjusted mortality rates. However, traditional risk-adjustment methods cannot control for bias from unmeasured confounders,[3,4] which generally place transfused patients at higher risk for adverse events than nontransfused patients. Consequently, the harms attributable to transfusions were likely overestimated by these previous studies, as well as our comparison of transfused *versus* nontransfused patients.

Our finding that hospital variations in transfusion rates were not associated with differences in mortality rates is consistent with this argument. We confirmed that the hospital-specific transfusion rate was reasonably analogous to a "natural experiment" or "instrumental variable,"[4,25] in that it was associated with wide differences in the probability that a patient would receive transfusions, but not with measured attributes that might affect mortality. Indeed, the range of mean predicted 30-day mortality rates (0.32–0.36%) across transfusion quartiles was relatively small (table 2) compared with the substantial difference in the predicted 30-day mortality rates between transfused (0.51%) and nontransfused (0.29%) individuals (table 1). It was therefore likely that the magnitude of unmeasured confounding was also smaller when comparing hospitals with widely differing transfusion rates, as opposed to comparing two patients who did or did not receive erythrocyte transfusions. Consequently, the risk estimates obtained from our comparison across hospital transfusion rate quartiles may be less prone to residual unmeasured confounding than those obtained from comparing transfused *versus* nontransfused patients.

Table 2. Characteristics across Quartiles of Hospital-specific Erythrocyte Transfusion Rate

	Quartile of Hospital-specific Erythrocyte Transfusion Rate			
	Quartile 1 (15 Hospitals; 39,859 Patients)	Quartile 2 (15 Hospitals; 41,678 Patients)	Quartile 3 (16 Hospital; 39,033 Patients)	Quartile 4 (20 Hospitals; 41,620 Patients)
Erythrocyte transfusions				
Number	5,069 (12.7%)	7,289 (17.5%)	9,247 (23.7%)	15,410 (37.0%)
Range of hospital-specific rates	10.3% to 14.6%	14.7% to 19.5%	19.6% to 26.7%	26.8% to 57.9%
Predicted 30-day mortality*	131 (0.32%)	142 (0.34%)	131 (0.34%)	151 (0.36%)
Demographics				
Female	23,905 (60.0%)	24,253 (58.2%)	23,047 (59.0%)	25,047 (60.2%)
Age in yr (mean ± SD)	68 ± 10	68 ± 10	68 ± 10	69 ± 10
Rural residence	5,065 (12.7%)	9,186 (22.0%)	9,011 (23.1%)	4,372 (10.5%)
Income quintile				
1 (lowest)	6,983 (17.5%)	8,061 (19.3%)	6,936 (17.8%)	6,905 (16.6%)
2	8,329 (20.9%)	8,331 (20.0%)	7,816 (20.0%)	8,476 (20.4%)
3	7,812 (19.6%)	7,885 (18.9%)	8,065 (20.7%)	8,661 (20.8%)
4	7,752 (19.4%)	8,059 (19.3%)	8,054 (20.6%)	8,509 (20.4%)
5 (highest)	8,882 (22.3%)	9,216 (22.1%)	8,012 (20.5%)	8,987 (21.6%)
Missing	101 (0.3%)	126 (0.3%)	150 (0.4%)	82 (0.2%)
Comorbid diseases				
Ischemic heart disease	3,459 (8.7%)	3,383 (8.1%)	3,166 (8.1%)	3,963 (9.5%)
Congestive heart failure	571 (1.4%)	725 (1.7%)	684 (1.8%)	664 (1.6%)
Atrial fibrillation	850 (2.1%)	957 (2.3%)	876 (2.2%)	986 (2.4%)
Hypertension	26,246 (65.8%)	27,338 (65.6%)	26,014 (66.6%)	28,102 (67.5%)
Cerebrovascular disease	578 (1.5%)	706 (1.7%)	625 (1.6%)	646 (1.6%)
Peripheral vascular disease	360 (0.9%)	486 (1.2%)	433 (1.1%)	535 (1.3%)
Diabetes mellitus	7,310 (18.3%)	7,912 (19.0%)	7,524 (19.3%)	7,879 (18.9%)
Renal insufficiency or dialysis	405 (1.0%)	540 (1.3%)	474 (1.2%)	591 (1.4%)
Pulmonary disease	2,392 (6.0%)	2,492 (6.0%)	1,914 (4.9%)	2,647 (6.4%)
Prior venous thromboembolism	163 (0.4%)	204 (0.5%)	178 (0.5%)	223 (0.5%)
Liver disease	171 (0.4%)	250 (0.6%)	164 (0.4%)	196 (0.5%)
Rheumatologic disease	1,086 (2.7%)	1,393 (3.3%)	986 (2.5%)	1,199 (2.9%)
Hemiplegia or paraplegia	117 (0.3%)	130 (0.3%)	83 (0.2%)	124 (0.3%)
Dementia	211 (0.5%)	209 (0.5%)	206 (0.5%)	234 (0.6%)
Malignancy				
Primary	870 (2.2%)	950 (2.3%)	785 (2.0%)	950 (2.3%)
Metastatic	126 (0.3%)	180 (0.4%)	136 (0.3%)	238 (0.6%)
Hospital characteristics				
Teaching hospital	10,014 (25.1%)	17,668 (42.4%)	6,642 (17.0%)	14 364 (34.5%)
High volume†	22,481 (56.5%)	28,163 (67.6%)	22,474 (57.6%)	7,816 (18.8%)
Surgical procedure				
Total hip replacement	14,861 (37.3%)	17,522 (42.0%)	15,142 (38.8%)	16,790 (40.3%)
Total knee replacement	24,998 (62.7%)	24,156 (58.0%)	23,891 (61.2%)	24,830 (59.7%)
Year of surgery				
1999	3,625 (9.1%)	3,834 (9.2%)	3,931 (10.1%)	4,127 (9.9%)
2000	3,205 (8.0%)	3,894 (9.3%)	3,716 (9.5%)	3,826 (9.2%)
2001	3,694 (9.3%)	3,915 (9.4%)	3,759 (9.6%)	4,058 (9.8%)
2002	3,897 (9.8%)	3,926 (9.4%)	3,709 (9.5%)	3,992 (9.6%)
2003	4,234 (10.6%)	3,713 (8.9%)	3,849 (9.9%)	4,165 (10.0%)
2004	4,449 (11.2%)	4,833 (11.6%)	4,405 (11.3%)	4,613 (11.1%)

(*continued*)

Table 2. (Continued)

	Quartile of Hospital-specific Erythrocyte Transfusion Rate			
	Quartile 1 (15 Hospitals; 39,859 Patients)	Quartile 2 (15 Hospitals; 41,678 Patients)	Quartile 3 (16 Hospital; 39,033 Patients)	Quartile 4 (20 Hospitals; 41,620 Patients)
2005	5,274 (13.2%)	5,919 (14.2%)	5,115 (13.1%)	5,284 (12.7%)
2006	5,728 (14.4%)	5,879 (14.1%)	5,253 (13.5%)	5,742 (13.8%)
2007	5,753 (14.4%)	5,765 (13.8%)	5,296 (13.6%)	5,813 (14.0%)
Concomitant transfusions				
Autologous erythrocytes	2,210 (5.5%)	1,131 (2.7%)	2,682 (6.9%)	4,725 (11.4%)
Platelets	40 (0.1%)	53 (0.1%)	53 (0.1%)	217 (0.5%)
Plasma	124 (0.3%)	187 (0.4%)	173 (0.4%)	423 (1.0%)
Outcomes				
30-day mortality	117 (0.29%)	145 (0.35%)	132 (0.34%)	161 (0.39%)
1-yr mortality	553 (1.39%)	665 (1.60%)	560 (1.43%)	679 (1.63%)

Data are numbers (percentages) unless otherwise indicated.

* Predicted 30-day mortality was calculated using a multivariable logistic regression model with a c-index of 0.79 and $P = 0.94$ for its Hosmer-Lemeshow statistic. † Rank in total number of eligible procedures performed during the study period > 50th percentile.

The discrepancy between our comparison of transfused *versus* nontransfused patients and comparison of hospitals with widely differing transfusion rates raises important questions about the true nature of the relationship between erythrocyte transfusion and mortality. Notably, our findings are consistent with a recently published multicenter cohort study of 102,470 patients who underwent primary coronary artery bypass graft surgery in the United States.[9] Although transfusion rates varied from 7.8 to 92.8% at the 798 included hospitals, the investigators found no association between hospital-specific transfusion rates and postoperative mortality.

Our findings, however, must be interpreted within the context of the study's design and limitations. First, the results of our comparison of outcomes at hospitals with differing transfusion rates only apply to those patients in whom the transfusion decision was influenced by the hospital-specific transfusion rate. These patients, referred to as "marginal" patients in the econometric literature,[26] are individuals who would have not been transfused if they had surgery at a low-transfusion rate hospital, but would have been transfused if they had surgery at a high-transfusion rate hospital. Thus, this group excludes individuals for whom erythrocyte transfusion is likely always indicated (*e.g.*, anemia in the setting of acute coronary syndrome),[27,28] as well as individuals for whom transfusion is likely always not indicated (*e.g.*, hemoglobin concentration greater than 10 g/dl).[29] Thus, the hospital-level results are only applicable in the aggregate and should not be used for deciding whether an individual patient should or should not receive a transfusion.

Second, our administrative data sources did not capture some important patient-level clinical information and in-hospital processes-of-care. We therefore cannot be certain that hospital transfusion rate quartiles did not differ significantly in some prognostically important patient-level characteristics such as surgical complexity, preoperative hemoglobin concentration, and perioperative use of anticoagulants. Notably, the absence of this information would have also affected the comparison of transfused *versus* nontransfused patients. In addition, it is possible that unmeasured hospital-level characteristics confounded our comparison of transfusion quartiles.[4] For example, hospitals in different transfusion quartiles may have differed with respect to some characteristics not captured by our data sources, such as the staffing models for critical care units and the overall experience of perioperative physicians. Thus, it is possible that, by shifting the comparison from patients who did or did not receive transfusion to hospitals with differing transfusion rates, we

Table 3. Adjusted Association of Hospital-specific Erythrocyte Transfusion Rate Quartile with 30-day and 1-yr Mortality

Hospital-specific Transfusion Quartile	30-day Mortality	1-yr Mortality
Quartile 1 (lowest)	Reference	Reference
Quartile 2	HR 1.06 (95% CI, 0.83–1.35; $P = 0.66$)	HR 1.05 (95% CI, 0.91–1.22; $P = 0.50$)
Quartile 3	HR 1.07 (95% CI, 0.81–1.40; $P = 0.65$)	HR 0.99 (95% CI, 0.87 –1.13; $P = 0.88$)
Quartile 4 (highest)	HR 1.11 (95% CI, 0.82–1.50; $P = 0.50$)	HR 1.02 (95% CI, 0.82–1.26; $P = 0.88$)

HR = hazard ratio.

may have substituted one set of unmeasured confounders for another.[30] It is important to note, however, that mean predicted and observed mortality rates were similar across the hospitals, and we accounted for variations in important processes-of-care, such as hospital size and type, through exclusion or risk adjustment. In addition, some characteristics of hospitals in the highest transfusion rate quartile (table 2), such as a higher proportion of low-volume hospitals,[18] suggest that our comparison, if anything, would have been biased against hospitals with high transfusion rates.

Third, we cannot be certain that the results of our comparison of hospitals with differing transfusion rates are more accurate than our comparison of transfused *versus* nontransfused patients. Our most definitive conclusion is that the two analytic approaches result in markedly different results, thereby raising important questions about the true nature of the relationship between erythrocyte transfusion and mortality. However, the magnitude of residual unmeasured confounding is likely smaller when comparing patients at hospitals with differing transfusion rates than when directly comparing transfused *versus* nontransfused patients. Thus, the comparison across hospitals is more likely to involve comparing individuals with otherwise similar prognostic characteristics—an important prerequisite for attributing any causal links, in what is termed the "counterfactual framework,"[31] between transfusion and adverse outcomes.

Fourth, we only analyzed the effects of transfusion on mortality in a population with relatively low rates of perioperative blood loss and postoperative mortality. Erythrocyte transfusion has many side effects, ranging from mild (*e.g.*, febrile reactions) to serious (*e.g.*, transfusion-related acute lung or kidney injury).[32–34] Moreover, erythrocytes undergo important changes during storage that may contribute to organ injury in susceptible patients, but the clinical significance of these changes is unclear.[35–37] Because administrative databases generally do not accurately capture these other postoperative complications,[38] our current analysis does not provide a comprehensive assessment of the potential harms of erythrocyte transfusion. Fifth, as with any observational study, our single study does not prove, or disprove, the presence of a causal link between erythrocyte transfusion and postoperative mortality. Our research therefore warrants confirmation in other multicenter studies across different settings and data sources, especially with respect to our finding that risk-adjusted mortality rates were similar at hospitals with widely differing transfusion rates.

Conclusions

In summary, the estimated impact of erythrocyte transfusion on postoperative mortality differed substantially when comparing outcomes at hospitals with widely differing transfusion rates, as opposed to comparing outcomes of patients who were or were not transfused. This discrepancy raises important questions about the nature of the relationship between erythrocyte transfusion and postoperative mortality.

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