Morbidity and Mortality after High-dose Transfusion

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ABSTRACT

Background: It is well recognized that increased transfusion volumes are associated with increased morbidity and mortality, but dose–response relations between high- and very-high-dose transfusion and clinical outcomes have not been described previously. In this study, the authors assessed (1) the dose–response relation over a wide range of transfusion volumes for morbidity and mortality and (2) other clinical predictors of adverse outcomes.

Methods: The authors retrospectively analyzed electronic medical records for 272,592 medical and surgical patients (excluding those with hematologic malignancies), 3,523 of whom received transfusion (10 or greater erythrocyte units throughout the hospital stay), to create dose–response curves for transfusion volumes and in-hospital morbidity and mortality. Prehospital comorbidities were assessed in a risk-adjusted manner to identify the correlation with clinical outcomes.

Results: For patients receiving high- or very-high-dose transfusion, infections and thrombotic events were four to five times more prevalent than renal, respiratory, and ischemic events. Mortality increased linearly over the entire dose range, with a 10% increase for each 10 units of erythrocytes transfused and 50% mortality after 50 erythrocyte units. Independent predictors of mortality were transfusion dose (odds ratio [OR], 1.037; 95% CI, 1.029 to 1.044), the Charlson comorbidity index (OR, 1.209; 95% CI, 1.141 to 1.276), and a history of congestive heart failure (OR, 1.482; 95% CI, 1.062 to 2.063).

Conclusions: Patients receiving high- or very-high-dose transfusion are at especially high risk for hospital-acquired infections and thrombotic events. Mortality increased linearly over the entire dose range and exceeded 50% after 50 erythrocyte units.
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BLOOD transfusion, the most commonly performed procedure in U.S. hospitals,[1] can be a life-saving measure in hemorrhaging patients or in those with moderate-to-severe anemia. In the past decade, massive transfusion protocols have evolved, based on the studies attempting to identify the ideal ratio of blood components administered,[2–4] which continues to be somewhat controversial. What remains to be determined, however, are the clinical factors that predict outcomes after high- or very-high-dose transfusion, and the relation between transfusion dose and rates of morbidity and mortality.

It is recognized that large transfusion volumes are associated with increased morbidity and mortality.[5–11] However, as more aggressive approaches to transfusion are being adopted, more patients are receiving high- or very-high-volume transfusions. In fact, a massive transfusion is generally regarded as a patient receiving more than 10 units within 24 h,[12] but, to the best of our knowledge, no studies have characterized the effect of incrementally increasing doses greater than 10 units on important clinical outcomes. The purpose of this investigation was to determine the dose–response relation for transfusion volume and mortality as a primary outcome. The secondary outcomes were to determine (1) the dose–response relation for transfusion volume and morbid events, (2) the morbid events that were most common after high-dose transfusion, and (3) the clinical variables associated with adverse outcomes in high-dose transfused patients.

What We Already Know about This Topic

- Massive transfusion is associated with serious complications and mortality; however, the dose dependence remains unclear
- The authors evaluated the records of more than 272,000 patients, of whom 3,523 were given at least 10 units of erythrocytes

What This Article Tells Us That Is New

- Mortality increased linearly with erythrocyte dose, reaching 50% in patients given more than 50 units of blood
- Infection and thrombotic events were the most common complications

Materials and Methods

After receiving approval from the institutional review board at the Johns Hopkins Medical Institutions (Baltimore, Maryland), we acquired electronic medical record data from a Web-based intelligence portal (IMPACT Online; Haemonetics Corp., USA) and from our hospital billing database for 283,025 inpatients discharged from the Johns Hopkins Hospital between January 2009 and October 2014. Our

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use of these databases and our quality control methods have been described previously.[13,14] Collected data included up to 29 prehospital comorbidities for each patient, the Charlson comorbidity index, and the number of erythrocyte units each patient received throughout his/her hospitalization. In addition, in-hospital morbid events were determined by *International Classification of Diseases*, 9th edition (ICD-9) codes upon discharge, as we have described previously.[14]

We excluded 10,433 patients whose final diagnosis-related group description contained the following words: "bone marrow transplant," "leukemia," or "lymphoma," because patients with hematologic malignancies have unique blood transfusion requirements (due to bone marrow aplasia and chemotherapy). The remaining 272,592 patients were further analyzed. Of these patients, 3,523 received high-dose transfusion (10 or greater erythrocyte units during their hospitalization). We analyzed this subset of patients to determine the predictors of clinical outcomes.

On the basis of the total number of allogeneic erythrocyte units transfused over the course of their hospitalization, we stratified patients into the following eight groups: 0, 1 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 75, and greater than 75 units. We also compared the baseline characteristics of these groups. The primary outcomes were composite morbidity (occurrence of any of the five morbid events) and mortality during the hospital stay. Morbid events were defined as (1) infection (*Clostridium difficile*, sepsis, surgical-site infection, or drug-resistant infection), (2) thrombotic event (deep venous thrombosis, pulmonary embolus, or disseminated intravascular coagulation), (3) kidney injury, (4) respiratory event, and (5) ischemic event (myocardial infarction, transient ischemic attack, or cerebrovascular accident). Both individual and composite morbidities are reported. The composite morbidity was defined as having any of the above listed five morbid events during their hospitalization. Data to determine morbid events were obtained through the hospital's billing database by using ICD-9 codes as outlined in detail in the appendix. Conditions that were flagged as present on admission were not considered to be hospital-acquired morbid events. In our institution, as required by the Centers for Medicare and Medicaid Services in the state of Maryland since 2007, these conditions are routinely identified as present on admission in the database, which allowed us to exclude them as hospital-acquired events.

Outcome Assessment and Statistical Analysis

Using the eight groups of total number of allogeneic erythrocyte units transfused (which included all 272,592 patients), dose–response curves were constructed for both morbidity and mortality. Once plotted, a linear and logarithmic model was performed to fit each curve respectively. The model that best predicted the dose–response curve was determined by using the R^2 value. These dose–response curves were repeated for the nonsurgical and surgical patient subsets.

For the subset of patients receiving high-dose transfusion (10 or greater erythrocyte units during their hospitalization), we analyzed the relation between the number of erythrocyte units transfused and clinical outcomes (both morbidity and mortality) in a risk-unadjusted and risk-adjusted manner by using univariable and multivariable logistic regressions, respectively. All 17 of the baseline patient characteristics and comorbidities were included in the multivariable logistic regression model, with the primary aim of determining independent predictors of adverse outcomes in high-dose transfused patients.

Continuous variables that were normally distributed are reported as mean ± SD; those that were not normally distributed as well as ordinal variables are reported as median and interquartile range. Normality of distribution was tested by the Shapiro–Wilk test. *P* value less than 0.05 was used to define significance; however, we applied a Bonferroni correction to adjust for multiple comparisons using an α of 0.0028 (0.05/18), 18 being the number of independent variables tested as potential predictors of outcomes. Odds ratios (ORs) and 95% CIs are reported. Analyses were generated with JMP version 9.0.2 (SAS Institute, Inc., USA).

Results

For each of the groups stratified by erythrocyte dose, we compared patient characteristics and prehospital admission comorbidities (table 1). As expected, patients who were transfused had more comorbidities, as did those receiving more erythrocyte units. A dose–response curve was then created for morbidity according to the total number of erythrocyte units transfused during the hospital stay (fig. 1). The incidence of composite morbidity (having one or more of the five morbid events) increased in a curvilinear manner over the entire range of erythrocyte units administered. Patients who received no transfusion had a morbidity rate of 9.8% (22,919 of 233,460); those who received 1 to 9 units, 28.5% (10,149 of 35,609); 10 to 19 units, 55.7% (1,348 of 2,418); 20 to 29 units, 66.8% (385 of 576); 30 to 39 units, 73.9% (153 of 207); 40 to 49 units, 76.7% (79 of 103); 50 to 75 units, 78.9% (101 of 128); and greater than 75 units, 80.2% (73 of 91). These values resulted in a best-fit curve of percent morbidity = 36.53 ln(erythrocyte units) + 10.4, with an R^2 value of 0.96. A 50% morbidity rate occurred in patients who received 10 or greater erythrocyte units.

The dose–response curve for percent mortality according to the number of erythrocyte units transfused during the hospital stay is shown in figure 1. Mortality increased in a linear manner with increasing transfusion dose. Patients who received no transfusion had a mortality of 0.74% (1,728 of 233,460); those who received 1 to 9 units, 4.7% (1,674 of 35,609); 10 to 19 units, 18.1% (437 of 2,418); 20 to 29 units, 30.2% (174 of 576); 30 to 39 units, 36.7% (76 of 207); 40 to 49 units, 42.7% (44 of 103); 50 to 75 units, 58.6% (75 of 128); and greater than 75 units, 61.5% (56 of 91). These values gave a best-fit line of percent mortality = 9.47(erythrocyte units) – 10.56, with an R^2 value of 0.99. The slope of the mortality line of fit (9.47) indicates that mortality increased by approximately 10% for every 10 erythrocyte units. A 50% mortality rate occurred at a dose of 50 erythrocyte units.

Table 1. Patient Characteristics for Groups Defined by Units of Erythrocytes Transfused

	0 Units, n = 232,460 (85.64%)	1–9 Units, n = 35,609 (13.06%)	10–19 Units, n = 2,418 (0.89%)	20–29 Units, n = 576 (0.21%)	30–39 Units, n = 207 (0.08%)	40–49 Units, n = 103 (0.04%)	50–75 Units, n = 128 (0.05%)	> 75 Units, n = 91 (0.03%)
Age, yr (mean ± SD)	42 ± 24	49 ± 23	49 ± 23	47 ± 24	48 ± 24	44 ± 26	43 ± 23	36 ± 23
Male, n (%)	114,549 (49)	17,058 (48)	1,438 (59)	356 (62)	131 (63)	74 (72)	74 (58)	63 (69)
Charlson score (median [IQR])	1 (0–2)	2 (1–4)	2 (1–4)	2 (1–4)	3 (1–5)	3 (1–5)	3 (1–4)	2 (1–4)
Surgical patient, n (%)	64,492 (27)	15,346 (43)	1,320 (55)	348 (60)	143 (69)	65 (63)	85 (66)	66 (73)
Comorbidities, n (%)								
CHF	15,978 (7)	4,143 (12)	463 (20)	140 (25)	52 (26)	29 (29)	31 (24)	30 (35)
Valvular disease	11,629 (5)	4,023 (12)	363 (15)	96 (17)	32 (16)	21 (21)	23 (18)	13 (15)
PVD	7,856 (3)	2,675 (8)	345 (15)	79 (14)	31 (16)	17 (17)	17 (13)	14 (16)
Hypertension	61,321 (27)	10,590 (30)	681 (29)	130 (24)	49 (25)	24 (24)	19 (15)	14 (16)
Lung	37,730 (16)	5,152 (15)	350 (15)	69 (12)	22 (11)	13 (13)	11 (9)	15 (17)
Diabetes mellitus	29,255 (13)	5,642 (16)	390 (17)	100 (18)	33 (17)	14 (14)	18 (14)	8 (9)
Kidney	18,775 (8)	6,013 (17)	487 (21)	141 (26)	49 (25)	20 (20)	40 (32)	16 (19)
Liver	10,802 (5)	2,809 (8)	281 (12)	97 (18)	41 (21)	17 (17)	33 (26)	13 (15)
HIV	4,417 (2)	896 (3)	71 (2)	4 (1)	2 (1)	2 (1)	2 (1)	2 (1)
Metastatic cancer	11,705 (5)	4,428 (13)	181 (8)	37 (7)	11 (6)	4 (4)	5 (4)	0 (0)
Tumor	24,368 (11)	5,799 (17)	267 (11)	52 (9)	18 (9)	9 (9)	12 (9)	3 (3)
Obesity	22,294 (10)	2,872 (8)	210 (9)	46 (8)	13 (7)	8 (8)	9 (7)	8 (9)
Anemia	26,865 (12)	9,690 (28)	491 (21)	96 (17)	37 (19)	15 (15)	14 (11)	4 (5)

CHF = congestive heart failure; HIV = human immunodeficiency virus; IQR = interquartile range; PVD = peripheral vascular disease.

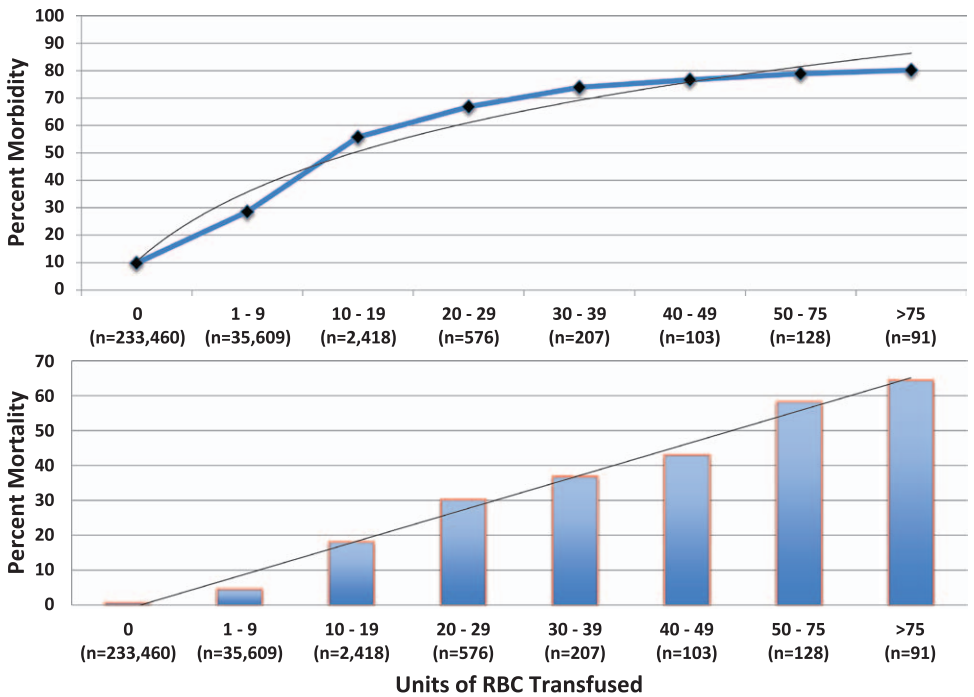

Fig. 1. In-hospital morbidity and mortality rates according to the number of erythrocyte units transfused. In-hospital morbidity (a composite of all five morbid events shown in fig. 2) increased with erythrocyte dose in a curvilinear manner, reaching a 50% rate of morbidity at 10 or greater erythrocyte units. The slope was steepest up to 30 erythrocyte units, with an inflection point and plateau at higher doses. The formula defining the curve is $y = 36.5 \ln(x) + 10.4$ ($R^2 = 0.962$). Mortality increased in a linear manner with a slope close to 10, indicating that for each 10-erythrocyte unit increment, mortality increased approximately 10%. After transfusion of 50 units, mortality exceeded 50%. The formula defining the curve is $y = 9.47 (x) - 10.56$ ($R^2 = 0.99$). RBC = erythrocyte.

The dose–response curves for morbidity and mortality were plotted for the surgical (n = 79,865) and nonsurgical (n = 192,727) patient subsets. To test for interaction between erythrocyte dose and surgical status, two independent variables (erythrocyte dose as a continuous variable and surgical status) were entered into a multiple logistic regression with

either morbidity or mortality as dependent variables. Being a surgical patient was associated with decreased morbidity when adjusted for erythrocyte dose (OR, 0.892; 95% CI, 0.853 to 0.932). Likewise, surgical status was associated with decreased mortality when adjusted for erythrocyte dose (OR, 0.493; 95% CI, 0.449 to 0.541).

For the secondary analysis, we included only patients who were transfused with 10 or greater erythrocyte units (n = 3,523). We performed univariable and multivariable analyses to identify the predictors of morbidity in the high-dose transfused patients (table 2). The comorbidities associated with increased in-hospital morbidity included congestive heart failure, peripheral vascular disease, renal disease, and liver disease in the univariate model. The Charlson comorbidity index and the number of erythrocyte units were associated with increased morbidity in both the risk-adjusted and risk-unadjusted models.

Next, we performed univariable and multivariable analyses to identify the predictors of mortality in the high-dose transfused patients (table 3). The comorbidities associated with increased in-hospital mortality included congestive heart failure and liver disease in the univariate model. The Charlson comorbidity index, number of erythrocyte units, being a nonsurgical patient, and congestive heart failure were associated with increased mortality in both the risk-unadjusted and risk-adjusted models.

Finally, we analyzed the entire cohort of 272,592 patients to identify the relation between erythrocyte transfusion dose and occurrence of the five different morbid events included in the composite morbidity outcome (fig. 2). Hospital-acquired infections increased dramatically up to a rate of 40% at 40 erythrocyte units and then plateaued at higher doses. Thrombotic events increased dramatically up to a rate of 50% at 50 units and then exhibited a similar plateau with higher doses. Renal, respiratory, and ischemic event rates increased gradually up to rates of 5 to 10% at an erythrocyte dose of 20 units but showed very little increase with higher doses. These findings suggest a difference in the dose–response for the various morbidities with respect to transfusion.

Discussion

In this study, we found that for high- and very-high-dose transfused patients, overall morbidity increased in a dose-related curvilinear manner, with a 50% morbid event rate occurring at 10 or greater erythrocyte units. Infections and thrombotic events occurred four to five times more commonly than renal, respiratory, or ischemic events at the higher transfusion doses. Mortality also increased in a dose-related but in a linear manner (10% increase with every 10 erythrocyte units) and exceeded 50% after 50 erythrocyte units. Sicker patients (indicated by the Charlson comorbidity index), those with congestive heart failure, and patients who did not undergo surgery had worse clinical outcomes.

Previous retrospective studies have shown the incremental risk associated with increasing transfusion dose but have focused primarily on lower blood doses compared with those examined in our study. Turan *et al.*[7] showed that 30-day mortality was greater in patients who received 5 or greater units

Table 2. Predictors of Morbidity* in High-dose Transfused Patients†

	Univariable		Multivariable	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (per yr)	1.003 (0.999–1.007)	0.046	0.997 (0.992–1.003)	0.13
Male	0.971 (0.786–1.199)	0.68	0.964 (0.77–1.206)	0.62
Charlson score	1.14 (1.088–1.196)	**< 0.0001**	1.204 (1.113–1.304)	**< 0.0001**
Erythrocyte units‡	1.023 (1.015 1.032)	**< 0.0001**	1.021 (1.013–1.03)	**< 0.0001**
Surgical patient	1.21 (0.983–1.491)	0.0061	1.133 (0.907–1.413)	0.093
CHF	1.711 (1.315–2.241)	**< 0.0001**	1.293 (0.952–1.764)	0.012
Valvular disease	1.269 (0.951–1.704)	0.014	1.03 (0.744–1.43)	0.79
PVD	1.422 (1.051 1.939)	**0.0005**	1.191 (0.856–1.667)	0.11
Hypertension	0.973 (0.77–1.233)	0.73	1.066 (0.81–1.406)	0.49
Pulmonary disease	0.998 (0.74–1.352)	0.99	0.82 (0.594–1.134)	0.067
Diabetes mellitus	1.061 (0.801–1.412)	0.53	0.8 (0.586–1.095)	0.033
Renal disease	1.44 (1.113–1.872)	**< 0.0001**	1.141 (0.839–1.556)	0.2
Liver disease	1.586 (1.161–2.188)	**< 0.0001**	1.053 (0.726–1.534)	0.68
HIV	0.702 (0.351 1.412)	0.13	0.363 (0.168–0.785)	**< 0.0001**
Metastatic cancer	1.103 (0.732–1.682)	0.48	0.654 (0.352–1.218)	0.041
Tumor	0.997 (0.711–1.406)	0.98	0.802 (0.513–1.258)	0.14
Obesity	1.297 (0.889–1.919)	0.041	1.297 (0.868–1.961)	0.054
Anemia	1.24 (0.948–1.628)	0.017	1.146 (0.862–1.53)	0.15

Odds ratios (OR) and CIs are reported after a Bonferroni correction for multiple comparisons ($\alpha = 0.0028$). Bold font indicates statistical significance after Bonferroni correction.

* Morbidity was defined as (1) infection (*Clostridium difficile*, sepsis, surgical-site infection, or drug-resistant infection), (2) thrombotic event (deep venous thrombosis, pulmonary embolus, or disseminated intravascular coagulation), (3) kidney injury, (4) respiratory event, and (5) ischemic event (myocardial infarction, transient ischemic attack, or cerebrovascular accident). † High-dose transfusion was defined as 10 or greater units of erythrocytes during the hospital stay (n = 3,523). ‡ Erythrocyte units as continuous, not categorical, variable.

CHF = congestive heart failure; HIV = human immunodeficiency virus; PVD = peripheral vascular disease.

Table 3. Predictors of Mortality* in High-dose Transfused Patients†

	Univariable		Multivariable	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (per yr)	1.004 (0.999–1.01)	0.0086	1.005 (0.998–1.012)	0.024
Male	1.046 (0.821–1.335)	0.58	0.97 (0.744–1.265)	0.73
Charlson score	1.148 (1.106–1.19)	**< 0.0001**	1.209 (1.141–1.276)	**< 0.0001**
Erythrocyte units‡	1.035 (1.028–1.042)	**< 0.0001**	1.037 (1.029–1.044)	**< 0.0001**
Surgical patient	0.735 (0.579–0.932)	**< 0.0001**	0.572 (0.439–0.743)	**< 0.0001**
CHF	1.806 (1.376–2.362)	**< 0.0001**	1.482 (1.062–2.063)	**0.0004**
Valvular disease	1.218 (0.886–1.656)	0.062	1.056 (0.727–1.519)	0.66
PVD	1.18 (0.847–1.625)	0.13	1.027 (0.705–1.482)	0.83
Hypertension	0.802 (0.606–1.052)	0.015	0.843 (0.604–1.17)	0.12
Pulmonary disease	0.819 (0.569–1.159)	0.089	0.654 (0.437–0.962)	**0.001**
Diabetes mellitus	1.115 (0.81–1.52)	0.3	0.907 (0.633–1.286)	0.41
Renal disease	1.312 (0.992–1.726)	0.0037	0.938 (0.666–1.317)	0.58
Liver disease	1.947 (1.421–2.654)	**< 0.0001**	1.233 (0.827–1.825)	0.12
HIV	1.069 (0.46–2.26)	0.8	0.594 (0.237–1.37)	0.066
Metastatic cancer	0.863 (0.522–1.374)	0.36	0.583 (0.286–1.165)	0.02
Tumor	0.898 (0.598–1.319)	0.41	0.803 (0.474–1.333)	0.2
Obesity	0.908 (0.581–1.381)	0.5	0.916 (0.56–1.456)	0.58
Anemia	0.755 (0.546–1.029)	0.0067	0.736 (0.499–0.993)	**0.0023**

Odds ratios (OR) and CIs are reported after a Bonferroni correction for multiple comparisons ($\alpha = 0.0028$). Bold font indicates statistical significance after Bonferroni correction.

* Mortality was defined as death during hospitalization. † High-dose transfusion was defined as 10 or greater units of erythrocytes during the hospital stay (n = 3,523). ‡ Erythrocyte units as continuous, not categorical, variable.

CHF = congestive heart failure; HIV = human immunodeficiency virus; PVD = peripheral vascular disease.

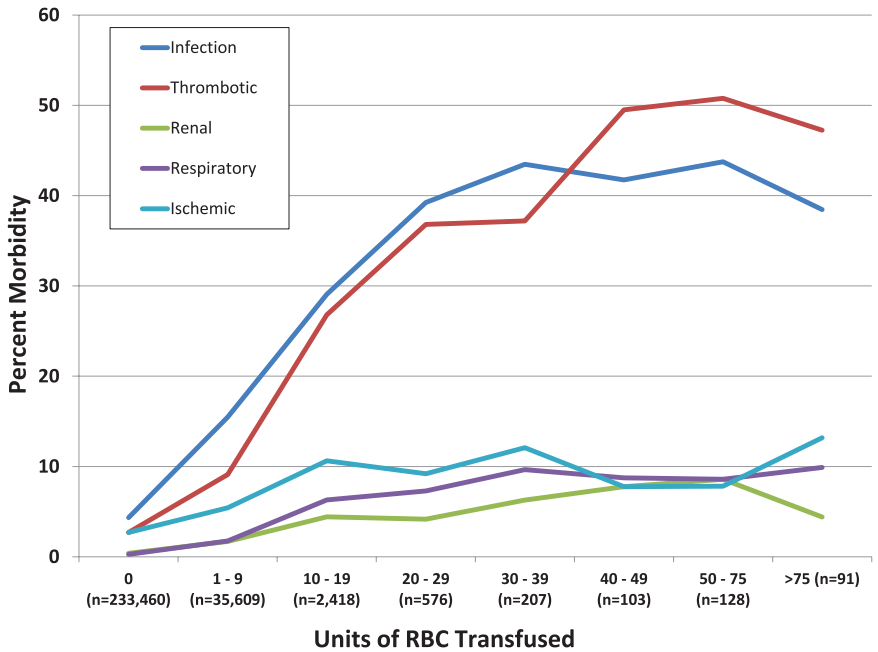

Fig. 2. Event rates for five morbid outcomes are plotted according to the number of erythrocyte units transfused. In high-dose transfused patients, hospital-acquired infections and thrombotic events were four to five times more prevalent than renal, respiratory, or ischemic events. The incidence of infection increased with erythrocyte dose up to 40% and then plateaued. Thrombotic events increased up to a rate of 50% before reaching a plateau. Renal, respiratory, and ischemic event rates increased gradually up to rates of 5 to 10% at an erythrocyte dose of 20 units. RBC = erythrocyte.

of blood than in those who received 1 to 4 units. In addition, Yang *et al.*[10] found that mortality increased with the increase in volume of erythrocyte transfusion for patients receiving 10 or greater units within 72 h. However, that study had only 52 patients who received more than 30 units. An additional study revealed a 39% mortality in patients who were massively transfused (10 or greater units),[15] and Koch *et al.*[8] showed a dose-dependent, risk-adjusted increase in postoperative morbidity

and mortality in isolated patients who underwent coronary artery bypass graft surgery, focusing on the 0 to 10 unit range.

The novelty of our study lies in describing the outcomes in relation to transfusion dose in patients who received very high transfusion doses of 20, 40, 60, or even greater than 75 units of erythrocytes. Furthermore, we report dose–response curves illustrating the relative incidence of specific morbid events in these patients. In addition, a large cohort of high-dose transfused patients (n = 3,532) allowed us to identify the clinical characteristics that are predictive of adverse outcomes. The number of erythrocyte units was significantly associated with increased morbidity and mortality in both the risk-unadjusted and risk-adjusted models. Of note, patients with congestive heart failure had increased risk of mortality in the risk-adjusted model of high-dose transfused patients. Patients with poor ventricular function may be more susceptible to transfusion-associated circulatory overload than their healthy counterparts. This factor may account for the increased risk of morbidity and mortality among patients with congestive heart failure. Transfusion-associated circulatory overload is the second leading cause of transfusion-related death,[16] with an incidence recently estimated at 3 to 5% of transfused patients,[17] a rate higher than historically believed. Such evidence would suggest that a more cautious approach should be used in patients with poor cardiac function who require high-dose transfusion. It is also important to avoid severe anemia or hypovolemia in patients with poor ventricular function because these conditions can worsen heart failure.

Although the composite outcomes are commonly used in clinical studies, our findings were perhaps more revealing when the composite outcome was broken out into five individual morbid events. Surprisingly, infections and thrombotic events occurred not only with much greater frequency than other morbidities (renal, respiratory, and ischemic events), but they were also more dose-dependent with transfusion, showing steep curves from 0 units up to 40 to 50 units, followed by a plateau at higher doses. These findings are consistent with those of previous studies that indicate that transfusion-related immune suppression[18] results in higher infection rates.[19,20] Thrombotic events have also been associated with transfusion[20–22] and are thought to be dose-dependent,[23] but the mechanism is not entirely clear. High-dose transfusion has not been assessed previously with regard to thrombotic event rates. Our findings did show increased renal, respiratory, and ischemic event rates with increasing transfusion dose, but these events were much less common than infections and thrombosis and reached a plateau at approximately 20 erythrocyte units. These findings indicate that clinicians may need to be vigilant to prevent, diagnose, and treat infections and thrombosis in patients who undergo high-dose transfusion in order to improve outcome and reduce mortality.

Interestingly, surgical patients had lower mortality compared with nonsurgical patients across all blood doses, and this association remained in the risk-adjusted model for high-dose transfused patients. We hypothesize that this is because most surgical patients with massive bleeding are having surgery to correct and control the bleeding (splenectomy, trauma, aortic aneurysm repair, and many more). Therefore, these patients who have surgically correctable problems fare better than medical patients who are bleeding profusely (end-stage liver disease, gastrointestinal bleeding, and many more) that are not amenable to surgery or the patients not healthy enough to undergo surgery.

Allocation of blood, a precious resource, is a contentious point among medical providers. In one study, 3% of trauma patients who underwent massive transfusion accounted for 71% of all erythrocytes administered in a calendar year at the R Adams Cowley Shock Trauma Institute (Baltimore, Maryland).[15] The quantification of survival at high doses of transfusion, which we have shown, can help with the allocation of these resources. After 50 units of transfusion, our data show that mortality was approximately 50%; therefore, our findings would discourage the practice of terminating erythrocyte transfusion due to futility at a set number of units, but rather to follow individual case-based clinical decision-making taking into account the patient's clinical course. For instance, one patient in our cohort survived after receiving 129 units of erythrocytes.

The most significant limitations in our study stem from its retrospective nature. The primary findings, however, such as the dose–response for transfusion and outcomes, as well as the clinical predictors of adverse outcomes, should be valid, even with the retrospective design. Furthermore, we attempted risk adjustment using a multivariable analysis, although some residual confounding may remain, with sicker patients receiving higher-dose transfusions. Another potential limitation is that we analyzed transfusion data from each patient's entire hospital stay. Therefore, a substantial number of the high- and even very-high-dose transfused patients may not have met the classic definition of massive transfusion (10 or greater units within 24 h). Nonetheless, we describe what we believe has not been previously shown—the dose–response curves over a wide range of transfusion volumes for in-hospital morbidity and mortality as well as the relative incidence of specific morbid events in relation to transfusion dose. Another potential limitation is the use of ICD-9 codes from an administrative database to assess morbid outcomes. Based on the nuances of coding charts, this method may not be as reliable as prospectively collected event rates for morbidity. Furthermore, the timing of these hospital-acquired morbidities relative to the transfusions cannot be established (*e.g.*, we cannot specify that the transfusion occurred before the morbidity). To minimize this limitation, we did, however, exclude morbidity that was present on admission, which is a required data element at our institution. It should also be emphasized that our findings do not support a cause and effect relation between transfusion and outcomes, but rather an association between the two.

In summary, high-dose transfused patients are at high risk for hospital-acquired infections and thrombotic events, which were four to five times more prevalent than renal, respiratory, and ischemic events. Mortality increased in a linear manner, such that for every 10 erythrocyte units, mortality increased approximately 10%, and mortality exceeded

50% after 50 erythrocyte units. In the high-dose transfused cohort, those with high Charlson scores or congestive heart failure had worse clinical outcomes. Our findings may help guide treatment for high-dose transfusion patients by encouraging physicians to avoid volume overload in high-risk patients and to be vigilant for infectious and thrombotic complications. In addition, our data may allow ethical decisions to be made when considering the futility question of giving huge quantities of blood products to patients.

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Competing Interests

Dr. Frank has received consulting fees from Haemonetics (Braintree, Massachusetts), Medtronic (Minneapolis, Minnesota), and Biomet (Warsaw, Indiana), none of which have products discussed in this article. Dr. Ness has been a consultant for Terumo BCT (Lakewood, Colorado), which does not have products discussed in this article. The other authors declare no competing interests.

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Appendix. ICD-9 Codes Used to Define Morbid Outcomes

Infection/Complication	ICD-9 Code	Diagnosis Description
Clostridium difficile	008.45	*C. difficile*
Cerebral vascular accident	434.01	Cerebral thrombosis with cerebral infarction
Cerebral vascular accident	434.11	Cerebral embolism with cerebral infarction
Cerebral vascular accident	434.91	Cerebral artery occlusion unspecified with cerebral infarction
Cerebral vascular accident	997.02	Iatrogenic cerebrovascular infarction
Deep vein thrombosis	453.40	Deep venous thrombosis leg not otherwise specified
Deep vein thrombosis	453.41	Deep venous thrombosis proximal leg
Deep vein thrombosis	453.42	Deep venous thrombosis distal leg
Deep vein thrombosis	453.81	Acute venous embolism and thrombosis of superficial veins of upper extremity
Deep vein thrombosis	453.82	Acute venous embolism and thrombosis of deep veins of upper extremity
Deep vein thrombosis	453.83	Acute venous embolism and thrombosis of upper extremity, unspecified
Deep vein thrombosis	453.84	Acute venous embolism and thrombosis of axillary veins
Deep vein thrombosis	453.85	Acute venous embolism and thrombosis of subclavian veins
Deep vein thrombosis	453.86	Acute venous embolism and thrombosis of internal jugular veins
Deep vein thrombosis	453.87	Acute venous embolism and thrombosis of other thoracic veins
Deep vein thrombosis	453.89	Acute venous embolism and thrombosis of other specified veins
Disseminated intravascular coagulation	286.0	Congenital factor VIII disorder
Disseminated intravascular coagulation	286.1	Congenital factor IX disorder
Disseminated intravascular coagulation	286.2	Congenital factor XI disorder
Disseminated intravascular coagulation	286.3	Congenital deficient clotting factor not elsewhere classified
Disseminated intravascular coagulation	286.4	Von Willebrand disease
Disseminated intravascular coagulation	286.5	Intrinsic circulating anticoagulants disorder
Disseminated intravascular coagulation	286.6	Defibrination syndrome
Disseminated intravascular coagulation	286.7	Acquired coagulation factor deficiency
Disseminated intravascular coagulation	286.9	Coagulation defect not elsewhere classified/not otherwise specified
Drug-resistant antibiotic infection	V09.0	Penicillin-resistant infection
Drug-resistant antibiotic infection	V09.1	Cephalosporin-resistant infection
Drug-resistant antibiotic infection	V09.2	Macrolides-resistant infection
Drug-resistant antibiotic infection	V09.3	Tetracyclines-resistant infection
Drug-resistant antibiotic infection	V09.4	Aminoglycosides-resistant infection
Drug-resistant antibiotic infection	V09.50	Quinolones-/fluoroquinolones-resistant infection
Drug-resistant antibiotic infection	V09.51	Quinolones-/fluoroquinolones-resistant infection
Drug-resistant antibiotic infection	V09.6	Sulfonamides-resist infection
Drug-resistant antibiotic infection	V09.70	Antimycobacterial-resistant infection
Drug-resistant antibiotic infection	V09.71	Other antimycobacterial-resistant infection
Drug-resistant antibiotic infection	V09.80	Specific drug-resistant infection, not multiple drugs
Drug-resistant antibiotic infection	V09.81	Multidrug-resistant infection
Drug-resistant antibiotic infection	V09.90	Drug-resistant microorganisms
Drug-resistant antibiotic infection	V09.91	Multidrug-resistant microorganism
Myocardial infarction	410.00	Acute myocardial infarction anterior/lateral wall/unspecified episode
Myocardial infarction	410.01	Acute myocardial infarction anterior/lateral wall/first episode
Myocardial infarction	410.02	Acute myocardial infarction anterior/lateral wall/substernal episode
Myocardial infarction	410.10	Acute myocardial infarction anterior wall/unspecified episode
Myocardial infarction	410.11	Acute myocardial infarction anterior wall/first episode
Myocardial infarction	410.12	Acute myocardial infarction anterior wall/substernal episode
Myocardial infarction	410.20	Acute myocardial infarction inferior lateral wall/unspecified episode
Myocardial infarction	410.21	Acute myocardial infarction inferior lateral wall/first episode
Myocardial infarction	410.22	Acute myocardial infarction inferior/lateral wall/substernal episode
Myocardial infarction	410.30	Acute myocardial infarction inferior/posterior wall/unspecified episode
Myocardial infarction	410.31	Acute myocardial infarction inferior/posterior wall/first episode
Myocardial infarction	410.32	Acute myocardial infarction inferior/posterior wall/substernal episode
Myocardial infarction	410.40	Acute myocardial infarction inferior wall/unspecified episode
Myocardial infarction	410.41	Acute myocardial infarction inferior wall/first episode
Myocardial infarction	410.42	Acute myocardial infarction inferior wall/substernal episode
Myocardial infarction	410.50	Acute myocardial infarction other wall/unspecified episode
Myocardial infarction	410.51	Acute myocardial infarction lateral wall/first episode

(*Continued*)

Appendix. Continued

Infection/Complication	ICD-9 Code	Diagnosis Description
Myocardial infarction	410.52	Acute myocardial infarction lateral wall/substernal episode
Myocardial infarction	410.60	Acute myocardial infarction posterior wall/unspecified episode
Myocardial infarction	410.61	Acute myocardial infarction posterior wall/first episode
Myocardial infarction	410.62	Acute myocardial infarction posterior wall/substernal episode
Myocardial infarction	410.70	Subendocardial acute myocardial infarction/unspecified episode
Myocardial infarction	410.71	Subendocardial acute myocardial infarction/first episode
Myocardial infarction	410.72	Subendocardial acute myocardial infarction/substernal episode
Myocardial infarction	410.80	Acute myocardial infarction other site/unspecified episode
Myocardial infarction	410.81	Acute myocardial infarction other site/first episode
Myocardial infarction	410.82	Acute myocardial infarction other site/substernal episode
Myocardial infarction	410.90	Acute myocardial infarction unspecified/unspecified episode
Myocardial infarction	410.91	Acute myocardial infarction/unspecified site/first episode
Myocardial infarction	410.92	Acute myocardial infarction/unspecified site/substernal episode
Postoperative wound infection	998.51	Infected postoperative seroma
Postoperative wound infection	998.59	Other postoperative infection
Pulmonary embolism	415.11	Iatrogenic pulmonary embolism
Pulmonary embolism	415.12	Septic pulmonary embolism
Pulmonary embolism	415.19	Other pulmonary embolism/infarction
Pulmonary embolism	673.00	Obstetrics air embolism-unspecified
Pulmonary embolism	673.01	Obstetrics air embolism-delivery
Pulmonary embolism	673.02	Obstetrics air embolism-delivery with postpartum Complication
Pulmonary embolism	673.03	Obstetrics air embolism-antepartum complication
Pulmonary embolism	673.04	Obstetrics air embolism-postpartum complication
Pulmonary embolism	673.10	Amniotic embolism-unspecified
Pulmonary embolism	673.11	Amniotic embolism-delivery
Pulmonary embolism	673.12	Amniotic embolism-delivery with postpartum complication
Pulmonary embolism	673.13	Amniotic embolism-antepartum complication
Pulmonary embolism	673.14	Amniotic embolism-postpartum complication
Pulmonary embolism	673.20	Obstetrics pulmonary embolism not otherwise specified-unspecified
Pulmonary embolism	673.21	Pulmonary embolism not otherwise specified-delivered
Pulmonary embolism	673.22	Pulmonary embolism not otherwise specified-delivery with postpartum complication
Pulmonary embolism	673.23	Pulmonary embolism not otherwise specified-antepartum complication
Pulmonary embolism	673.24	Pulmonary embolism not otherwise specified-postpartum complication
Pulmonary embolism	673.30	Obstetrics pyemic embolism-unspecified
Pulmonary embolism	673.31	Obstetrics pyemic embolism-delivery
Pulmonary embolism	673.32	Obstetrics pyemic embolism-delivery with postpartum complication
Pulmonary embolism	673.33	Obstetrics pyemic embolism-antepartum complication
Pulmonary embolism	673.34	Obstetrics pyemic embolism-postpartum complication
Pulmonary embolism	673.80	Obstetrics pulmonary embolism not elsewhere classified-unspecified
Pulmonary embolism	673.81	Pulmonary embolism not elsewhere classified-delivery
Pulmonary embolism	673.82	Pulmonary embolism not elsewhere classified-delivery with postpartum complication
Pulmonary embolism	673.83	Pulmonary embolism not elsewhere classified-antepartum complication
Pulmonary embolism	673.84	Pulmonary embolism not elsewhere classified-postpartum complication
Renal complications	997.5	Surgical complication-urinary tract
Respiratory complications	997.31	Ventilator-associated Pneumonia
Respiratory complications	997.39	Other surgical complication-respiratory
Sepsis	038.9	Septicemia not otherwise specified
Sepsis	670.20	Puerperal sepsis—unspecified as to episode of care or not applicable
Sepsis	670.22	Puerperal sepsis, delivered, with mention of postpartum complication
Sepsis	670.24	Puerperal sepsis—postpartum condition or complication
Sepsis	771.81	Newborn septicemia
Sepsis	995.91	Sepsis
Transient ischemic attack	435.0	Basilar artery syndrome
Transient ischemic attack	435.1	Vertebral artery syndrome
Transient ischemic attack	435.2	Subclavian steal syndrome
Transient ischemic attack	435.3	Vertebrobasilar artery syndrome
Transient ischemic attack	435.8	Transient cerebral ischemia not elsewhere classified
Transient ischemic attack	435.9	Transient cerebral ischemia not otherwise specified

ICD-9 = *International Classification of Diseases*, 9th edition.