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Background. **Blood transfusions have been linked to increased morbidity and mortality. Bleeding during and after cardiac operations and the hemodilution effects of cardiopulmonary bypass commonly result in blood transfusions. Because we could not find any studies evaluating the effects of transfusion on long-term survival after cardiac operation, we sought to determine these effects.**

Methods. **We studied 1,915 patients who underwent first-time isolated coronary artery bypass operations between July 6, 1994 and December 31, 1997 at our institution. Patients with transfusions were compared with those who had not been transfused. Long-term survival data were obtained from the United States Social Security Death Index. Groups were compared by Cox proportional hazard models, Kaplan-Meier survival plots, and hazard functions.**

Results. **Six hundred forty-nine of 1,915 study patients (34%) received a transfusion during their hospitalization. Transfused patients were older, smaller, and more likely to be female, and had more comorbidity. Transfused patients also had twice the 5-year mortality (15% vs 7%) of nontransfused patients. After correction for comorbidities and other factors, transfusion was still associated with a 70% increase in mortality (risk ratio = 1.7; 95% confidence interval = 1.4 to 2.0; $p = 0.001$). By multivariate analysis, transfusion, peripheral vascular disease, chronic obstructive pulmonary disease, New York Heart Association functional class IV, and age were significant predictors of long-term mortality.**

Conclusions. **We found that blood transfusions during or after coronary artery bypass operations were associated with increased long-term mortality.**

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Despite institutional efforts to curtail the frequency of blood transfusions in cardiac operations, the frequency remains high. Annually in the United States, more than 3 million patients receive more than 11 million units of transfused blood [1]. The decision to transfuse patients is invariably done to promote hemostasis or improve the carrying capacity of oxygen in the blood. However, there is little consensus on who should be transfused. Deciding when a patient requires transfusion of blood products varies significantly among surgeons and intensivists, even those at the same institution [2]. Moreover, a recent study suggests that up to two thirds of completed transfusions may be clinically inappropriate [3]. If transfusions were completely safe, differing thresholds would not matter. However, adverse reactions are associated with transfusion. Although febrile reactions appear to be benign, hemolytic [4] and infectious complications [5] may occur. Most recently, blood transfusions have been linked to postoperative wound infections [6], pneumonia [7], renal dysfunction [8], severe sepsis [9], hospital mortality [10], and a poorer prognosis after cancer operations [11–13]. Yearly, more than 600,000 cardiac operations are performed on adults in the United States [14]. Bleeding during and after cardiac operation and the hemodilution effects of cardiopulmonary bypass commonly result in blood transfusions [15–17]. However, we could not find any studies evaluating the effects of transfusion on long-term survival after cardiac operation. The purpose of this study was to determine if the long-term survival of patients was influenced by transfusions that were done either during or after cardiac operations.

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Material and Methods

This study was approved by the Institutional Review Board. Informed consent was waived because it was a retrospective database review. The study was powered to provide a 95% probability of detecting a 30% difference in late mortality between any transfusion and no transfusion groups, assuming a 10% overall mortality and half the patients transfused.

Subjects

All patients who underwent first-time, isolated coronary artery bypass grafting with cardiopulmonary bypass (n =

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1,953) between July 6, 1994 and December 31, 1997, were considered for this study. Patients who had valvular, carotid endarterectomy, or other operation simultaneously with coronary artery bypass grafting were excluded, as were redo operations. The start date of the study was chosen as the first date when intraoperative and postoperative transfusions were prospectively separated in the database, whereas the end date was chosen to achieve the power analysis requirements and maintain a minimum 2-year follow-up for all patients. Thirty-five patients (1.8%) with operative mortality (defined by The Society of Thoracic Surgeons as in-hospital death or out-of-hospital death within 30 days of operation) were excluded. Three patients were excluded for missing intraoperative data. The remaining 1,915 patients comprised the study population. All data were prospectively entered into the database. The definitions of The Society of Thoracic Surgeons were used for all entries in the database.

Data Analysis

Long-term patient survival data were secured from the United States Social Security Death Index database (http://ssdi.genealogy.rootsweb.com), which was queried in September 2001, using patient name and social security number combinations for all patients. This corresponds to minimum and maximum follow-up times of 39 months (December 1997 patients) and 81 months (July 1994 patients), respectively. Then the database of cardiac operations was updated for all deceased patients with the exact date of death. Then 5-year Kaplan–Meier survival plots were determined and compared for all study subgroups. Hazard functions depicting the rate of death per month for each of the groups were derived from the survival data. These functions are useful to identify the between-group variation in survival trends, and the most critical period determining postoperative survival [18].

Statistical Methods

The effect of transfusion on survival was tested in two ways: (1) a two-level approach of transfusion (any) versus no transfusion, and (2) a four-level approach of transfusion (intraoperative only, postoperative only, or both intraoperative and postoperative) versus no transfusion. Thirty-two preoperative, intraoperative, and postoperative variables were analyzed. Univariate analysis for categorical variables was done with either χ^2 statistic or Fischer's exact test depending on applicability (Windows Version 8; SAS, Cary, NC). Continuous variables were analyzed using either the unpaired *t*-test or the nonparametric Mann-Whitney rank sum test depending on normality. A p value less than 0.05 was used to indicate significance.

Next, Cox proportional hazard models were used to explain the affect of explanatory variables (including transfusion) on survival times. Given the biphasic nature (Figs 1 and 2) of the survival, differentiating postoperative year 1 from the succeeding years, these Cox proportional hazard models were applied separately to (1) all patients and (2) only those patients surviving at least 1 year. In

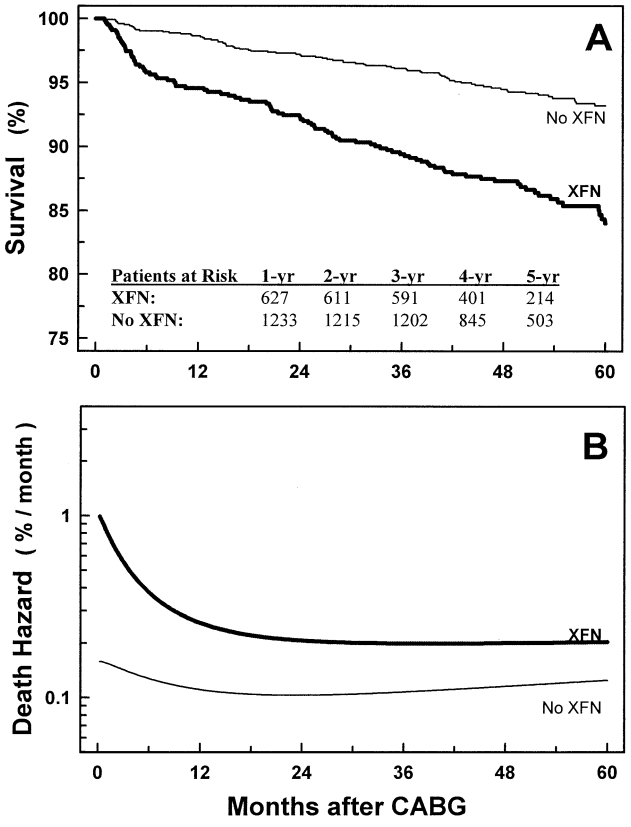

Fig 1. Kaplan-Meier estimates of survival and hazard functions in the no transfusion (No XFN) *and any transfusion* (XFN) *groups. (A) Five-year (60-month) Kaplan-Meier survival curves in patients transfused versus not transfused. (B) The respective hazard functions for these two groups.* (CABG = *coronary artery bypass grafting.)*

either case, model selection was first done with backward elimination, and variables significant at the p less than 0.05 level were retained in the model as independent predictors. The model was then confirmed using forward selection and stepwise selection. After confirming with the two-level approach that any transfusion was a highly significant risk factor for increased mortality, the Cox proportional hazard model was repeated using the four-level approach for the variables.

Because transfusion was not randomly assigned in this patient population, and the concern that multivariate analysis may not adequately control for confounding and bias, the data were further analyzed using propensity scoring. The propensity for transfusion was determined without regard for death using logistic regression analysis. All 32 preoperative, intraoperative, and postoperative variables were entered into the model. Variables were evaluated first univariately, then multivariately. Variables that remained in the model at the p less than 0.05 level were then used to calculate a propensity score for each patient. This propensity score represented the probability that a patient would receive a transfusion. Each transfused patient was then matched to a unique nontransfused patient using propensity scores identical to within 1%. If no match could be achieved at this thresh-

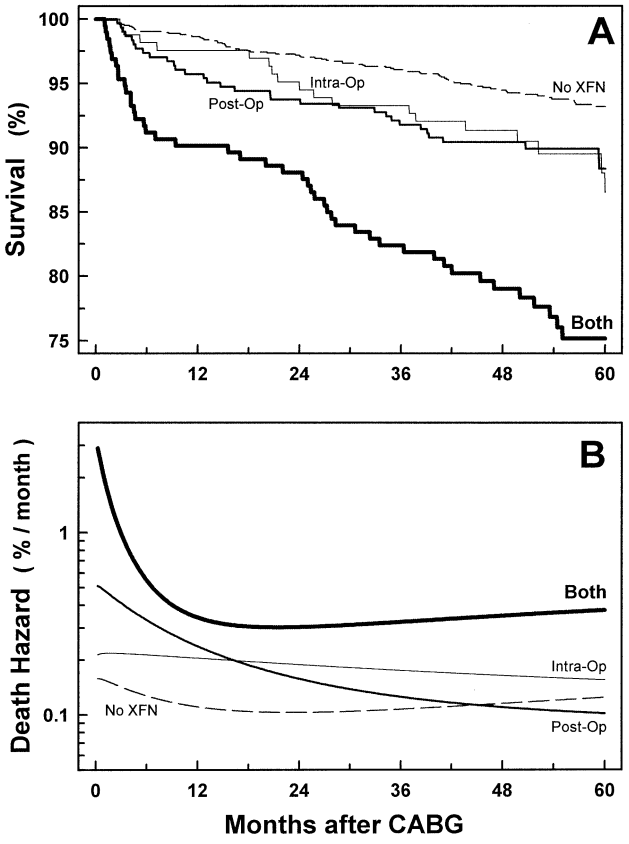

Fig 2. Kaplan-Meier estimates of survival and hazard functions in the transfused groups. (A) Five-year (60-month) Kaplan-Meier survival curves for patients who were transfused both intraoperatively and postoperatively (Both)*, only intraoperatively* (Intra-Op)*, only postoperatively* (post-Op)*, and not transfused* (No XFN)*. (B) The respective hazard functions for these four groups.* (CABG = *coronary artery bypass grafting.)*

old, the transfused patient was excluded. Five hundred forty-six of 659 transfused patients (83%) were matched.

Then the 1,092 patients matched by propensity scores were analyzed using the previously described Cox proportional hazard model with the two-level approach. The propensity score was forced to remain in the model.

Results

Six hundred fifty-nine of 1,915 study patients (34%) received a transfusion during their hospitalization. Of these patients, 356 patients (19%) had an intraoperative transfusion, 495 (26%) had a postoperative transfusion, and 192 (10%) had both. Alternatively, isolated intraoperative and postoperative transfusions occurred in 164 patients (9%) and 303 patients (16%), respectively.

We found that transfused patients were older, smaller, and stayed longer in the hospital, and were more likely to be female and to have cerebrovascular disease, peripheral vascular disease, hypertension, higher Society of Thoracic Surgeons (STS) scores, New York Heart Association (NYHA) functional class IV symptoms, and intraaortic balloon pumps. Their operation was more commonly done on an emergency basis and required greater cardiopulmonary bypass time (Table 1). They also had twice the late mortality (15% vs 6%) of nontransfused patients. After correction for comorbidities and other factors, transfusion was still associated with a 70% increase in mortality (risk ratio, 1.7; 95% confidence interval, 1.4 to 2.0; $p = 0.001$). By multivariate analysis, older age, the presence of peripheral vascular disease (PVD), the presence of chronic obstructive pulmonary disease (COPD), a worse NYHA functional class status, and transfusion were significant predictors of late mortality (Table 2).

When dividing the transfused group into its 3 subgroups of (1) intraoperative only, (2) postoperative only, and (3) both intraoperative and postoperative, then PVD, COPD, NYHA functional class IV, and older age remained significant predictors of 5-year mortality. Of the three subgroups, the postoperative only group (risk ratio, 1.6; 95% confidence interval, 1.2 to 2.0; $p = 0.029$) and the both intraoperative and postoperative group (risk ratio, 2.4; 95% confidence interval, 2.0 to 2.8; $p < 0.001$) were significant predictors of 5-year mortality (Table 3).

Kaplan-Meier survival plots suggested both early and late differences in survival with the transfused groups having poorer survival (Fig 1A, 2A). As confirmed by the hazard function (Fig 1B, 2B), there is a biphasic risk of death associated with transfusion. Mortality was severalfold higher in the transfused group for the first several months after operation (Fig 1B); however, by 1 year, mortality had decreased in the transfused group and was now only twice that of the nontransfused group.

After removing the 53 patients who died within 12 months of operation, and reanalyzing the remaining 1,862 patients, transfusion remained a significant predictor of death (risk ratio, 1.5; 95% confidence interval, 1.1 to 1.9; $p = 0.04$) from 1 to 5 years after operation. By multivariate analysis, older age, the presence of PVD or COPD, NYHA functional class IV status, and transfusion were significant predictors of late mortality (1 to 5 years) (Table 4).

By subgroup analysis, PVD, COPD, and age remained significant predictors of 1- to 5-year mortality, as were body mass index and both intraoperative and postoperative transfusions (risk ratio, 2.2; 95% confidence interval, 1.7 to 2.8; $p = 0.003$) (Table 5).

When the data were reanalyzed using propensity analysis, we found similar results. Predictors of transfusion for the propensity score were older age, female gender, lower weight, longer length of stay, longer perfusion time, and higher STS risk. The 546 transfused patients were well matched to the 546 nontransfused patients (transfused patients and nontransfused patients had a mean $\pm$ standard deviation propensity score of 0.576 ± 0.233 and 0.575 ± 0.231, respectively; $p = 1.00$). Any transfusion compared with no transfusion remained a risk factor for death at follow-up (risk ratio, 1.35; 95% confidence interval, 1.18 to 1.54; $p < 0.001$) (Fig 3).

Patients with NYHA functional class IV symptoms have a poorer prognosis after a coronary artery bypass

Table 1. Statistically Significant Characteristics of Patients

	No Transfusion	Any Transfusion	Intraoperative Transfusion	Postoperative Transfusion	Both Transfusions
Number of patients	1,266 (66%)	659 (34%)	164 (9%)	303 (16%)	192 (10%)
Actual mortality	82 (6%)	99 (15%)[a]	20 (12%)[b]	33 (11%)[b]	46 (24%)[a]
Median time to death (y)	2.1	1.7	2.1	1.4	1.4
Male (%)	80	45[a]	26[a]	58[a]	37[a]
Cerebral vascular disease (%)	27	41[a]	42[a]	37[a]	50[a]
Peripheral vascular disease (%)	12	20[a]	18[b]	18[c]	28[a]
Hypertension (%)	78	82[b]	89[a]	78	83
Diabetes mellitus (%)	30	34	38	30	40[b]
New York Heart Association functional class IV (%)	37	52[a]	56[a]	45[c]	63[a]
Emergency surgery (%)	5	10[a]	9	8[b]	13[c]
IABP (%)	6	17[a]	19[a]	13[a]	22[a]
Age (years)	62 ± 10	67 ± 10[a]	69 ± 9[a]	66 ± 9[a]	68 ± 10[a]
Weight (kg)	89 ± 16	78 ± 16[a]	74 ± 15[a]	82 ± 16[a]	76 ± 15[a]
Height (cm)	174 ± 9	167 ± 10[a]	163 ± 9[a]	169 ± 10[a]	165 ± 10[a]
Body surface area (m^2)	2.1 ± 0.2	1.9 ± 0.2[a]	1.8 ± 0.2[a]	2.0 ± 0.2[a]	1.9 ± 0.2[a]
Body mass index	30 ± 5	28 ± 5[a]	28 ± 5[a]	29 ± 5[a]	28 ± 5[a]
Cardiopulmonary bypass time (min)	85 ± 29	96 ± 36[a]	94 ± 33[a]	91 ± 32[a]	102 ± 44[a]
Society of Thoracic Surgeons predicted risk score (%)	1.95 ± 1.80	4.46 ± 5.00[a]	4.39 ± 3.28[a]	3.23 ± 3.11[a]	6.46 ± 7.42[a]
Hospital length of stay (days)	5 ± 2	10 ± 12[a]	6 ± 3[a]	9 ± 9[a]	14 ± 18[a]

[a] $p < 0.001$ compared with no transfusion; [b] $p < 0.05$; [c] $p < 0.01$.

Any Transfusion = transfused either intraoperatively or postoperatively, or both; Intraoperative Transfusion = transfused intraoperatively only; Postoperative Transfusion = transfused postoperatively only; Both Transfusions = transfused both intraoperatively and postoperatively.

graft operation. Even within this group, those who were transfused were more likely to die (Fig 4).

Comment

The primary result of this study showed that transfusion is a risk factor for 5-year mortality after cardiac operation. In addition, we identified several other risk factors for long-term mortality: older age, the presence of peripheral vascular disease, or COPD, and worse cardiac symptoms (NYHA functional class IV). Prior evidence has shown that age [19, 20], peripheral vascular disease [21], and COPD [22] are risk factors for 5-year mortality after coronary artery bypass operations. Severity of anginal symptoms, as measured by NYHA classification, has also been shown to predict late mortality [23]. Transfusion has not been described previously as a risk factor and, unlike the other risk factors, is notable for the fact that it is partially under physician control.

Transfusion with cardiac operations is not inevitable. Lowering the transfusion threshold had no effect on hospital morbidity or mortality [24]. High hematocrits (≥

Table 2. Predictors of Total 5-Year Mortality

Variable Transfusion	Risk Ratio	95% Confidence Interval	*p* Value
None	1.0 (reference)		
Any	1.7	1.4–2.0	0.001
Peripheral vascular disease	2.0	1.6–2.3	< 0.001
Chronic obstructive pulmonary disease	2.2	1.9–2.6	< 0.001
New York Heart Association functional class IV	1.5	1.2–1.8	0.01
Age	1.045	1.027–1.063	< 0.001

Risk ratio = the risk of death for a patient with that factor compared with a patient without that factor, or for continuous variables it is the increased risk for each year's increase in age. The risk ratio of the No Transfusion group is defined as 1.0 and called the reference.

Table 3. Predictors of Total 5-Year Mortality

Variable Transfusion	Risk Ratio	95% Confidence Interval	*p* Value
None	1.0 (reference)		
Intraoperative	1.2	0.6–1.7	0.534
Postoperative	1.6	1.2–2.0	0.029
Both	2.4	2.0–2.8	< 0.001
Peripheral vascular disease	1.9	1.5–2.2	< 0.001
Chronic obstructive pulmonary disease	2.2	1.9–2.6	< 0.001
New York Heart Association functional class IV	1.5	1.2–1.8	0.013
Age	1.045	1.027–1.063	< 0.001

Risk Ratio = the risk of death for a patient with that factor compared with a patient without that factor, or for continuous variables it is the increased risk for each year's increase in age. The risk ratio of the No Transfusion group is defined as 1.0 and called the reference.

Table 4. Predictors of 1- to 5-Year Mortality

Variable Transfusion	Risk Ratio	95% Confidence Interval	*p* Value
None	1.0 (reference)		
Any	1.5	1.1–1.9	0.04
Peripheral vascular disease	1.7	1.4–2.2	0.01
Chronic obstructive pulmonary disease	2.3	1.9–2.7	< 0.001
New York Heart Association functional class IV	1.5	1.1–1.9	0.01
Age	1.040	1.019–1.061	< 0.001

Risk ratio = the risk of death for a patient with that factor compared with a patient without that factor, or for continuous variables it is the increased risk for each year's increase in age. The risk ratio of the No Transfusion group is defined as 1.0 and called the reference.

34%) may even be harmful. Spiess and colleagues [25] found that patients with hematocrits 34% or greater on arrival to the intensive care unit after cardiac operation were more likely to suffer a myocardial infarction and cautioned against transfusion to an arbitrary value. Aprotinin decreased blood transfusion, surgical reexploration for bleeding, and perioperative mortality (odds ratio, 0.55; 95% confidence interval, 0.34 to 0.90) [26]. Using a thromboelastograph to guide coagulation [27], or using a smaller cardiopulmonary bypass circuit or prime volume decreased transfusions [28, 29].

We found that blood transfusion during or after cardiac operation is associated with an increased risk of death over the subsequent 5 years. Although we could not find any previous study that evaluated long-term transfusion risk after cardiac operation, several studies have found transfusion to have short-term deleterious effects after cardiac operation. It increases the risk of nosocomial pneumonia [7], sternal wound infections [6], severe sepsis [9], and renal dysfunction [8]. Utley and colleagues [30] found that transfusion explained the

Table 5. Predictors at 1- to 5-Year Mortality

Variable Transfusion	Risk Ratio	95% Confidence Interval	*p* Value
None	1.0 (reference)		
Intraoperative	1.6	0.9–2.2	0.16
Postoperative	1.4	0.9–1.9	0.19
Both	2.2	1.7–2.8	0.003
Peripheral vascular disease	1.7	1.2–2.1	0.02
Chronic obstructive pulmonary disease	2.4	2.0–2.8	< 0.0001
Age	1.04	1.02–1.06	0.0002
Body mass index	1.04	1.01–1.07	0.04

Risk ratio = the risk of death for a patient with that factor compared with a patient without that factor, or for continuous variables it is the increased risk for each year's increase in age or 1 kg/m^2 increase in BMI. The risk ratio of the No Transfusion group is defined as 1.0 and called the reference.

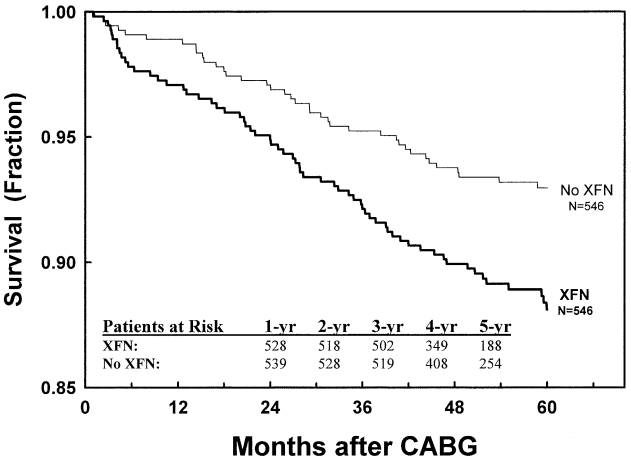

*Fig 3. Kaplan-Meier estimates of survival based on equal propensity scores of any transfusion (*XFN*) versus no transfusion (*No XFN*). (*CABG = *coronary artery bypass grafting.)*

increased perioperative mortality in women. In addition the number of units of blood transfused intraoperatively or on the first postoperative day was a significant predictor of hospital mortality [10]. Using leukocyte-depleted blood for transfusion decreased 60-day mortality after cardiac operation [31]. Defoe and colleagues [32] found that patients who had a lower hematocrit during cardiopulmonary bypass were associated with a higher risk of in-hospital mortality. However they did not provide data on transfusion or try to separate the effect of transfusion

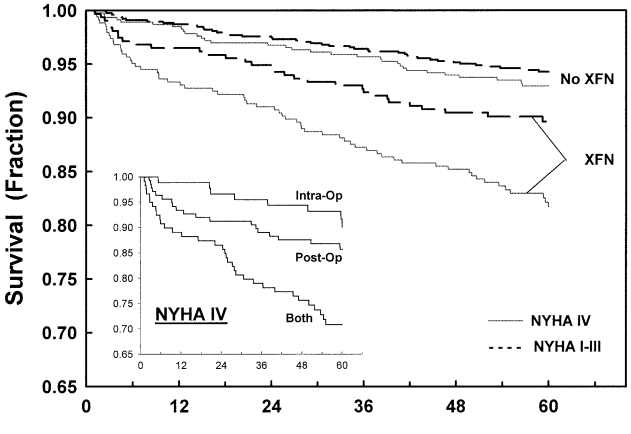

*Fig 4. Kaplan-Meier estimates of survival for patients separated into New York Heart Association (*NYHA*) functional classes I-III and class IV. The* inset *shows Kaplan-Meier survival for NYHA functional class IV patients transfused intraoperatively only (*Intra-Op*), postoperatively only (*Post-Op*), and intraoperatively and postoperatively (*Both*). (*CABG = *coronary artery bypass grafting;* XFN = *transfusion.)*

versus anemia on in-hospital mortality. They also did not evaluate long-term mortality.

The effects of transfusion on survival after an oncologic operation is controversial, with some studies finding increased mortality in transfused patients [11–13] and others finding no difference in mortality [33, 34]. Similar conflicting data were reported by Corry and colleagues, [35] who found decreased survival in patients transfused before undergoing renal transplant, and Solheim and colleagues [36], who found no difference in survival among transfused and nontransfused renal transplant recipients. Both the beneficial effects of transfusion on renal graft survival and the deleterious effects on cancer patients have been attributed to suppression of immune function by an unknown factor in the transfusion. However, blood transfusion given to women during childbirth did not influence the development of malignant tumors, but there was a trend toward higher long-term mortality (22 to 32 years) in the transfused group (5.5 vs 4.2%) [37]. A population-based epidemiological study found that transfusion was an independent predictor of long-term mortality (10 years), with the increased risk being present from all three components of transfusion: packed red cells, fresh frozen plasma, and platelets [38]. Recently a randomized study examined hospital mortality in intensive care unit patients transfused to maintain higher hemoglobin endpoints and found that transfusion was associated with an increased risk of death [39].

The biphasic response we found (ie, a short-term large increase in mortality and then a sustained, long-term increase in mortality in the transfused patients), suggests two separate processes (Fig 1A, 1B). This short-term increase may be caused by the transfusions or the transfusions may be a marker for functionally sicker patients. For example, we may have been more likely to check hemoglobin levels and transfuse patients if they had more dyspnea on exertion from cardiopulmonary dysfunction. Therefore the increased short-term mortality would be caused by the cardiopulmonary dysfunction, and the transfusion would only indicate the marker of a sicker patient. However, with the increased long-term mortality, we find it difficult to hypothesize that transfusion acted as a marker of a sicker patient. In addition there was greater mortality in those patients who received transfusions Both intraoperatively and postoperatively compared with those who received transfusions only intraoperatively or postoperatively (Fig 2A, 2B). Although the number of units transfused was not available, the higher mortality in patients who received transfusions at both times may indicate a dose-dependent relationship.

A limitation of this study is its retrospective nature, which can only find associations and not show causality. Because criterion for transfusion was not established a priori and patients were not randomized to different thresholds for transfusion, transfusion may merely be a marker for sicker, more symptomatic patients. That is, given two patients with equally severe anemia (one symptomatic and transfused and one not symptomatic and therefore not transfused), the increased risk of mortality may be related to the cause of the symptoms, such as worse cardiopulmonary function or muscle deconditioning and not to the transfusion itself. Against this, we found that intraoperative transfusion is a risk factor for increased mortality. In our practice, blood is usually transfused intraoperatively based on hemoglobin levels and not on signs and symptoms.

Another limitation is that hemoglobin levels were not included in the study. Because we routinely do not check hemoglobin levels more than 24 hours postoperatively, but check it only as clinically indicated (eg, elevated sanguineous chest tube drainage, pallor, or dyspnea), including hemoglobin levels would have introduced a bias. Because virtually all patients who died in-hospital or within 30 days of operation received transfusions, we eliminated these patients from the study. Including them would have overestimated the risk of blood transfusions. A fourth limitation is that we examined all-cause mortality and were unable to determine the cause of death (cardiac or noncardiac). Although death certificates may have been helpful, they may be less than accurate in the absence of autopsies. A final limitation is that while the study was designed to look for and did find a difference in mortality between transfused and nontransfused patients, the study may have been underpowered for the four-group analysis.

In conclusion, we found that transfusing blood during or after cardiac operation is associated with an increased 5-year mortality.

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