Intraoperative transfusion and an increased preoperative C-reactive protein level are associated with higher mortality after off-pump coronary artery bypass grafting

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ABSTRACT

Objective: The effects of transfusion on clinical outcomes after cardiac surgery remain inconclusive. We hypothesized that the risk of postoperative cumulative long-term, all-cause mortality after transfusion in patients undergoing cardiac surgery would differ by individual inflammatory status reflected by C-reactive protein level; thus, we performed a retrospective study.

Methods: All patients who underwent isolated off-pump coronary artery bypass grafting between October 2004 and October 2015 were retrospectively included. Patients were divided into 4 categories according to whether the preoperative C-reactive protein level was greater than or less than 1 mg/dL and whether red cells were transfused intraoperatively. The 4 categories were as follows: low C-reactive protein without transfusion; low C-reactive protein with transfusion; high C-reactive protein without transfusion; and high C-reactive protein with transfusion. A multivariable Cox regression was then performed. Sensitivity analysis in subgroup (<3 units of red cells transfused) was also performed.

Results: A total of 1636 patients were analyzed. Of the 4 categories, patients in the high C-reactive protein with transfusion group were at significantly higher risk of mortality than the low C-reactive protein without transfusion (hazard ratio, 1.86; 95% confidence interval, 1.24-2.79) or with transfusion group (hazard ratio, 1.47; 95% confidence interval, 1.13-1.93). A sensitivity analysis of patients who received only 1 or 2 units of red cells showed similar results.

Conclusions: Intraoperative red blood cell transfusion in patients with increased C-reactive protein level was significantly related to the risk of mortality after off-pump coronary artery bypass grafting. (*J Thorac Cardiovasc Surg* 2020;159:558-65)

The HR for mortality according to the amount of RBCs and preoperative CRP level.

Central Message

The effect of intraoperative RBC transfusion on postoperative mortality after OPCAB can be affected by preoperative CRP level.

Perspective

Most studies have focused only on Hb levels in terms of transfusion triggers, yielding inconsistent results. In this study, intraoperative RBC transfusion in patients with elevated CRP level was related to significantly increased mortality after OPCAB. These results suggest that patients may need individualized transfusion triggers.

See Commentary on page 566.

The question of whether perioperative red blood cell (RBC) transfusion is hazardous is unanswered in the field of

cardiac surgery. Given the higher transfusion rate associated with such surgery compared with noncardiac surgery,¹ an understanding of the risk of transfusion is of particular importance. However, the effects of transfusion on clinical outcomes after cardiac surgery remain inconclusive. Perioperative transfusion was reported to increase both short-term²⁻⁵ and long-term mortality⁵⁻⁸ after cardiac surgery. Transfusion of as few as 1 or 2 units of RBCs increased

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The study was approved by the Institutional Review Board of Seoul National University Hospital (No. 1803-097-930) on May 27, 2018.

Received for publication Sept 7, 2018; revisions received Jan 8, 2019; accepted for publication Jan 21, 2019; available ahead of print Feb 26, 2019.

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0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.01.078>

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Abbreviations and Acronyms

CI	= confidence interval
CRP	= C-reactive protein
Hb	= hemoglobin
HR	= hazard ratio
MI	= myocardial infarction
OPCAB	= off-pump coronary artery bypass grafting
RBC	= red blood cell

postoperative morbidity and mortality.² In contrast, some studies found no association between transfusion and adverse outcomes after adjusting for perioperative risk factors.⁹⁻¹²

Hypoperfusion and ischemia–reperfusion injury trigger inflammation after cardiac surgery, particularly when cardiopulmonary bypass is used.^{13,14} Even off-pump procedures do not completely abolish (but may reduce) inflammation,¹⁵⁻¹⁷ which plays a major role in the pathogenesis of atherosclerosis, which in turn triggers vascular occlusive disease.^{18,19} C-reactive protein (CRP), a general marker of inflammation, both mediates and predicts the development of vascular occlusive diseases such as myocardial infarction (MI) and stroke,¹⁹⁻²¹ and predicts postoperative outcomes.²²⁻²⁵ Transfusion aggravates inflammation by stimulating the release of inflammatory cytokines, including interleukin-6, interleukin-8, and secretory phospholipase A2.^{26,27}

Thus, the adverse effects of transfusion in patients undergoing cardiac surgery may be influenced by preexisting inflammation. To date, no study has explored a potential relationship between inflammation and transfusion, or the prognostic significance thereof. We hypothesized that patient outcomes would differ by individual inflammatory status reflected by preoperative CRP level; we performed a large, single-center, retrospective observational study to explore this possibility.

MATERIALS AND METHODS**Study Population**

The study was approved by the Institutional Review Board of Seoul National University Hospital (No. 1803-097-930); the requirement for written informed consent was waived because of the retrospective nature of the work. All consecutive patients who underwent isolated, off-pump coronary artery bypass grafting (OPCAB) in our tertiary teaching hospital from October 2004 to October 2015 were retrospectively included. Patients without preoperative CRP data obtained within 1 month before surgery were excluded.

Perioperative Management and Transfusion Strategy

Target-controlled infusions of propofol and remifentanyl, volatile anesthetics, or continuous infusion of a mixture of midazolam and sufentanil was used for general anesthesia. Pulmonary arterial pressure, mixed venous oxygen saturation, cerebral oxygen saturation, and transesophageal echocardiography were monitored intraoperatively. Intraoperative RBC

transfusion was standardized. Intraoperative hemoglobin (Hb) or hematocrit measurements were routinely performed every 1 to 2 hours after anesthesia induction, and additional tests were performed when necessary. RBCs were transfused to maintain the Hb level at greater than 9 g/dL (hematocrit >27%). The Hb or hematocrit level was reassessed after completion of transfusion, and additional transfusion scheduled as necessary. Blood cell salvage was routinely performed.

All patients were transferred to the intensive care unit after surgery. Aspirin 100 mg/d was administered to all patients until the day of surgery and resumed as soon as possible after the surgery, mostly on the first postoperative day. Clopidogrel 75 mg/d was also added along with aspirin for 1 year after the surgery. Statin therapy was commenced if a patient had a low-density lipoprotein cholesterol level greater than 100 mg/dL.

Data Collection

We collected the following data from electronic medical records: demographics, medication histories, comorbidities, preoperative laboratory data, preoperative ejection fraction, operative information including RBC transfusions, and postoperative morbidities (acute kidney injury defined using the creatinine criteria of the Kidney Disease: Improving Global Outcomes study, reintubation, and reoperation to control bleeding). We also recorded preoperative high-sensitivity CRP levels. Data on all-cause mortality were obtained from the database of the National Population Registry of the Korean National Statistical Office.

Statistical Analysis

The primary outcome was the risk of long-term all-cause mortality after OPCAB according to preoperative CRP level and intraoperative RBC transfusion. Secondary outcomes were 30-day, 90-day, 1-year, and 3-year mortality. Continuous variables are expressed as means (with standard deviations) or as medians (with interquartile ranges [IQRs]), as appropriate, and categorical variables are expressed as numbers (with % values). Categorical variables were compared using the chi-square test or Fisher exact test, and continuous variables were compared using the analysis of variance or the Kruskal–Wallis test where appropriate. The 4 categories reflected whether the preoperative CRP level was greater than or less than 1 mg/dL, based on previous studies,^{22,28} and whether RBCs were transfused intraoperatively. The categories were as follows: low CRP without transfusion, low CRP with transfusion, high CRP without transfusion, and high CRP with transfusion. To compare the risk of mortality, we performed Cox proportional hazards regression to calculate the hazard ratio (HR) of each group. Univariable analyses included demographic data, medical histories, preoperative medications, laboratory profiles, operative data, and postoperative morbidities, which are listed in Table 1. Three different multivariable Cox regressions were performed, permitting separate investigation of different types of the perioperative confounders. Model 1 was adjusted for preoperative variables including demographic data, medical history, preoperative medication, and preoperative clinical data. In Model 2, intraoperative and surgical data were adjusted for, as well as the preoperative variables. Postoperative comorbidities were added in Model 3.

Kaplan–Meier curves were then created, and survival was compared using the log-rank test. In addition, we performed the cubic spline analysis to see the change in the risk of mortality according to the amount of RBC transfusion, in which preoperative CRP level was adjusted for.

Sensitivity analysis was performed in a subgroup (<3 units of RBCs transfused) to evaluate whether the primary outcome was biased by including patients who received large amounts of RBCs, possibly because of excessive surgical bleeding. The multivariable Cox regression analysis was repeated in this subgroup.

All statistical analyses were performed with the aid of R software (ver. 3.4.3; R Development Core Team, Vienna, Austria). The cubic spline function curves were drawn using the *rms* package (ver. 5.1-2).

TABLE 1. Baseline characteristics and perioperative data

Variables	Low CRP, no RBC (n = 338)	Low CRP, yes RBC (n = 952)	High CRP, no RBC (n = 64)	High CRP, yes RBC (n = 282)	P
Preoperative CRP (mg/dL)	0.14 (0.05-0.31)	0.18 (0.05-0.37)	2.33 (1.46-3.31)	2.38 (1.59-4.77)	
Intraoperative RBC (units)	-	3 (2-4)	-	3 (2-4)	
Demographic data					
Age (y)	60.9 (10.6)	66.6 (8.6)	61.5 (10.3)	68.7 (8.5)	<.001
Female	92 (27.2%)	280 (29.4%)	20 (31.3%)	75 (26.6%)	.706
BMI (kg/m ²)	25.5 (3.1)	24.5 (3.0)	24.5 (2.9)	23.3 (3.0)	<.001
Medical history					
Hypertension	189 (55.9%)	646 (67.9%)	36 (56.3%)	199 (70.6%)	<.001
Diabetes	128 (37.9%)	461 (48.4%)	24 (37.5%)	156 (55.3%)	<.001
Myocardial infarction	26 (7.7%)	69 (7.2%)	13 (20.3%)	47 (16.7%)	<.001
Congestive heart failure	12 (3.6%)	46 (4.8%)	12 (18.8%)	43 (15.2%)	<.001
Chronic liver disease	40 (11.8%)	106 (11.1%)	9 (14.1%)	31 (11.0%)	.891
Atrial fibrillation	25 (7.4%)	72 (7.6%)	8 (12.5%)	28 (9.9%)	.319
Cerebrovascular disease	29 (8.6%)	124 (13.0%)	5 (7.8%)	42 (14.9%)	.051
Previous PCI	55 (16.3%)	125 (13.1%)	4 (6.3%)	31 (11.0%)	.082
Preoperative medication					
Aspirin	241 (71.3%)	676 (71.0%)	21 (32.8%)	162 (57.4%)	<.001
Clopidogrel	79 (23.4%)	305 (32.0%)	17 (26.6%)	69 (24.5%)	.006
ACEi/ARB	119 (35.2%)	412 (43.3%)	13 (20.3%)	102 (36.2%)	<.001
β-blocker	82 (24.3%)	219 (23.0%)	8 (12.5%)	54 (19.1%)	.102
Calcium channel blocker	154 (45.6%)	461 (48.4%)	15 (23.4%)	123 (43.6%)	.001
Diuretics	30 (8.9%)	160 (16.8%)	10 (15.6%)	52 (18.4%)	.002
Statin	170 (50.3%)	522 (54.8%)	13 (20.3%)	110 (39.0%)	<.001
Preoperative clinical data					
LV ejection fraction (%)	57 (52-63)	57 (52-63)	52 (33-57)	53 (40-60)	<.001
LV ejection fraction <35%	24 (7.1%)	63 (6.6%)	17 (26.6%)	51 (18.1%)	<.001
Serum creatinine (mg/dL)	1.00 (0.90-1.10)	1.01 (0.87-1.20)	1.00 (0.93-1.21)	1.10 (0.90-1.70)	.004
Hematocrit (%)	34.4 (4.6)	34.8 (4.7)	33.6 (4.9)	33.7 (4.5)	.004
IABP use within 72 h before surgery	11 (3.3%)	66 (6.9%)	5 (7.8%)	27 (9.6%)	.015
No. of diseased vessels					<.001
1-vessel disease	18 (5.3%)	17 (1.8%)	0 (0.0%)	8 (2.8%)	
2-vessel disease	49 (14.5%)	100 (10.5%)	15 (23.4%)	24 (8.5%)	
3-vessel disease	212 (62.7%)	666 (70.0%)	35 (54.7%)	203 (72.0%)	
Not specified	59 (17.5%)	169 (17.8%)	14 (21.9%)	47 (16.7%)	
Left main disease	33 (9.8%)	139 (14.6%)	5 (7.8%)	32 (11.3%)	.057
Operative data					
Re-do surgery	11 (3.3%)	17 (1.8%)	0 (0%)	2 (0.7%)	.073
Emergency surgery	7 (2.1%)	40 (4.2%)	0 (0%)	8 (2.8%)	.099
No. of distal anastomoses	3 (2-4)	3 (3-4)	3 (3-4)	3 (3-4)	.002
Coronary graft					
Left internal thoracic artery	320 (94.7%)	908 (95.4%)	62 (96.9%)	253 (89.7%)	.003
Right internal thoracic artery	36 (10.7%)	98 (10.3%)	8 (12.5%)	50 (17.7%)	.007
Right gastroepiploic artery	97 (28.7%)	282 (29.6%)	28 (43.8%)	79 (28.0%)	.086
Saphenous vein	193 (57.1%)	621 (65.2%)	35 (54.7%)	182 (64.5%)	.026
Intraoperative dobutamine use	44 (13.0%)	193 (20.3%)	12 (18.8%)	92 (32.6%)	<.001
Intraoperative dopamine use	46 (13.6%)	124 (13.0%)	20 (31.3%)	54 (19.1%)	<.001
Intraoperative epinephrine use	5 (1.5%)	24 (2.5%)	5 (7.8%)	19 (6.7%)	<.001
Intraoperative norepinephrine use	176 (52.1%)	541 (56.8%)	32 (50.0%)	186 (66.0%)	.003
Duration of surgery (min)	357 (310-400)	375 (335-415)	360 (316-400)	376 (340-425)	<.001
Intraoperative colloid (ml)	1025 (0-1700)	1500 (500-2000)	0 (0-1500)	1150 (150-1900)	<.001
Average minimum hematocrit (%)*	27.2 (3.9)	24.7 (3.7)	27.4 (4.5)	24.6 (3.7)	<.001

(Continued)

TABLE 1. Continued

Variables	Low CRP, no RBC (n = 338)	Low CRP, yes RBC (n = 952)	High CRP, no RBC (n = 64)	High CRP, yes RBC (n = 282)	P
Postoperative morbidity					
Postoperative AKI	74 (21.9%)	320 (33.6%)	12 (18.8%)	91 (32.3%)	<.001
Reintubation	10 (3.0%)	60 (6.3%)	9 (14.1%)	47 (16.7%)	<.001
Reoperation for bleeding control	1 (0.3%)	28 (2.9%)	1 (1.6%)	16 (5.7%)	.001

Data are expressed as mean (SD), median (IQR), or number (%). CRP, C-reactive protein; RBC, red blood cell; BMI, body mass index; PCI, percutaneous coronary intervention; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricle; IABP, intra-aortic balloon pump; AKI, acute kidney injury. *The numbers of patients of each group were 292, 852, 47, and 254, respectively, because of missing values (n = 191).

RESULTS

Of the 1663 patients who underwent isolated OPCAB, 27 were excluded because preoperative CRP data were lacking. The remaining 1636 patients were analyzed. Baseline characteristics and operative data are presented in Table 1. The median CRP levels were 0.14 mg/dL, 0.18 mg/dL, 2.33 mg/dL, and 2.38 mg/dL in the low CRP without transfusion, low CRP with transfusion, high CRP without transfusion, and high CRP with transfusion groups, respectively. The CRP levels were measured at a median (IQR) of 4 days (2-6) before surgery. The median (IQR) RBC transfusion level was 3 units (2-4) in patients who received transfusions.

The results of univariable and multivariable analyses are summarized in Table 2. The median (IQR) follow-up duration was 55 (23-89) months. The number (%) of all-cause mortality was 341 (20.8%); low CRP without transfusion, 40 (11.8%); low CRP with transfusion, 178 (18.7%); high CRP without transfusion, 14 (21.9%); and high CRP with transfusion, 109 (39.5%). The combined variable was significantly associated with the risk of mortality after OPCAB in the Wald test ($P = .003$, Table 2). Of the 4 categories, only patients in the high CRP with transfusion group were at significantly higher risk of mortality than the low CRP without transfusion group in all multivariable models (Model 3, HR, 1.86; 95% confidence interval [CI], 1.24-2.79) (Table 2). In addition, the mortality risk was significantly greater in the high CRP with transfusion group than in the low CRP with transfusion group (HR, 1.47; 95%

CI, 1.13-1.93) or the high CRP without transfusion group (HR, 2.00; 95% CI, 1.09-3.65), although the risk of the low CRP with transfusion group was similar to that of the low CRP without transfusion group (HR, 1.26; 95% CI, 0.87-1.83) (Table 2). There was no statistical difference between the low CRP with transfusion group and the high CRP without transfusion group (data not shown).

The Kaplan-Meier curves showed that cumulative survival after OPCAB differed significantly among the groups (Figure 1). Compared with the low CRP without transfusion group, the other 3 groups exhibited significantly poorer survival. In particular, the high CRP with transfusion group exhibited the poorest survival. The low CRP with transfusion and high CRP without transfusion groups survived to similar extents. The cubic spline function curves revealed that the HR associated with the same extent of transfusion was higher in patients with CRP levels greater than 1 mg/dL than less than 1 mg/dL; the rate of HR increase was more pronounced in patients with higher CRP levels (Figure 2).

Sensitivity analysis of 964 patients who received less than 3 units of RBCs showed that the mortality risk remained significantly higher in the high CRP with transfusion group than in the low CRP with transfusion group (HR, 2.07; 95% CI, 1.20-3.57); the mortalities of the other groups were not affected (Table 3).

Secondary outcomes are summarized in Table 4. Thirty-day, 90-day, 1-year, and 3-year mortality were higher in the

TABLE 2. Cox proportional hazard model for long-term mortality after off-pump coronary artery bypass grafting

Groups	Event n (%)	Univariable		Multivariable 1*		Multivariable 2†		Multivariable 3‡	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Inflammation-transfusion			<.001		<.001		<.001		.003
Low CRP-no RBC	40 (11.8%)	Reference		Reference		Reference		Reference	
Low CRP-yes RBC	178 (18.7%)	1.72 (1.22-2.43)		1.20 (0.84-1.72)	.316	1.31 (0.91-1.89)	.153	1.26 (0.87-1.83)	.215
High CRP-no RBC	14 (21.9%)	1.83 (0.99-3.37)		1.24 (0.66-2.33)	.511	1.09 (0.58-2.08)	.786	0.93 (0.48-1.79)	.833
High CRP-yes RBC	109 (38.7%)	4.32 (3.00-6.23)		2.07 (1.40-3.04)	<.001	2.09 (1.40-3.13)	<.001	1.86 (1.24-2.79)	.003

The adjusted HR§ (95% CI) of High CRP-yes RBC was 1.47 (1.13-1.93), $P = .004$ and 2.00 (1.09-3.65), $P = .024$, compared with Low CRP-yes RBC and High CRP-no RBC, respectively. HR, Hazard ratio; CI, confidence interval; CRP, C-reactive protein; RBC, red blood cell. *Multivariable model 1 was adjusted for demographic data, medical history, preoperative medication, and preoperative clinical data listed in Table 1. Left ventricular ejection fraction was dichotomized into whether less than 35% or not. †Multivariable model 2 was adjusted for all variables used in Multivariable model 1 and operative data listed in Table 1 except for the lowest intraoperative hematocrit. Data on coronary graft used were entered in the model as a binary variable; total arterial graft versus at least on saphenous vein graft. ‡Multivariable model 3 was adjusted for all variables used in Multivariable model 2 and postoperative morbidities listed in Table 1. §Adjusted for all variables used in Multivariable model 3.

FIGURE 1. Kaplan–Meier survival curves according to inflammation-transfusion strata. The cumulative survival differed significantly among the strata. Compared with the low CRP without transfusion group, the high CRP with transfusion group showed poorer survival. *CRP*, C-reactive protein; *RBC*, red blood cell.

high CRP with transfusion group compared with the other groups (Table 4).

DISCUSSION

In this large retrospective study, we found that the effect of intraoperative RBC transfusion on postoperative mortality after OPCAB may be affected by preoperative CRP level (Video 1). The mortality of patients who received intraoperative RBC transfusions differed by their baseline CRP levels. Patients in the high CRP with transfusion group had a significantly higher risk of mortality than the low CRP without transfusion group or with transfusion group (1.9- and 1.5-fold higher risk, respectively). Similar results were observed in subgroup analysis including only patients receiving less than 3 units of RBCs.

Traditionally, many clinicians set the transfusion trigger higher (Hb level <9–10 g/dL) for patients undergoing cardiac surgery than noncardiac surgery, seeking to maintain adequate tissue perfusion. As the adverse effects of transfusion became more widely recognized,^{3,29,30} many studies have addressed transfusion strategies/triggers for patients undergoing cardiac surgery. However, most have focused only on Hb levels, yielding inconsistent results. Several

observational studies reported that perioperative RBC transfusion negatively affected outcomes,^{2–8} but others advocated transfusion, observing that the harmful effects were not significant after adjusting for various clinical confounders.^{9–12} Even large, multicenter randomized trials have drawn different conclusions.^{31,32} The Transfusion Indication Threshold Reduction (TITRe2) trial favored a liberal transfusion threshold (Hb level <9 g/dL) over a restrictive threshold (Hb level <7.5 g/dL).³¹ In that study, all-cause mortality at 90 days was significantly higher in the restrictive group than in the liberal group (4.2% vs 2.6%), although this was a secondary outcome. Moreover, the restrictive threshold was not superior to the liberal threshold in terms of the primary outcome (a composite of serious wound infection, sepsis, MI, intestinal infarction, and acute kidney injury).³¹ The TITRe2 investigation raised uncertainty regarding whether transfusion should be restricted in patients undergoing cardiac surgery (who usually have marginal cardiovascular reserves and are thus at high risks of frequent transfusion).^{33,34} However, in the Transfusion Requirements in Cardiac Surgery (TRICS III) trial, a restrictive transfusion strategy was not inferior to a liberal strategy in terms of a composite outcome

FIGURE 2. Cubic spline function curves for HR according to the amount of transfusion in patients with high and low CRP level, respectively. The HR for mortality was higher and increased more rapidly in patients with CRP levels greater than 1 mg/dL than less than 1 mg/dL. Blue bands refer to 95% CI. CRP, C-reactive protein; RBC, red blood cell.

consisting of death, MI, stroke, and renal failure (11.4% vs 12.5%).³² The TRICS investigators favored the restrictive strategy; the risk of the composite outcome was lower compared with that of the liberal strategy in an elderly subgroup.³²

The adverse effects of RBC transfusion may be multifactorial.^{29,30} Leucocyte microchimerism after RBC transfusion is immunomodulatory, increasing the risk of infection, organ failure, and inflammation.^{35,36} However,

leucocyte-depleted RBC transfusion did not reduce microchimerism.³⁷ Patients with coronary artery disease, particularly those undergoing coronary artery bypass grafting, may be more susceptible to the adverse effects of RBC transfusion^{4,6}; thrombosis, intimal hyperplasia, or atherosclerosis may be aggravated by leucocyte-mediated inflammation, triggering graft occlusion or failure after revascularization.³⁸ The pivotal role played by inflammation is emphasized by the fact that an elevated, perioperative CRP level was associated with increased risks of long-term mortality, length of hospital stay,²⁴ and major adverse cardiovascular and cerebral events after coronary artery bypass grafting.²² Thus, we consider that the effect of transfusion on mortality after OPCAB is potentiated by preoperative inflammation. To the best of our knowledge, this is the first study to explore the effects of the relationship between inflammation and transfusion on patient outcomes. As mentioned earlier, previous studies focused only on Hb levels. Given our results and those of a previous study on anemia/transfusion interactions,³⁸ the present approach may be inappropriate for some patients. Unknown interactions may be in play between transfusion and other clinical variables affecting patient outcomes. Further studies are required.

We dichotomized preoperative CRP levels using the cut-off of 1 mg/dL used in previous studies.^{22,28} Although higher CRP levels do not necessarily indicate inflammation, Ridker and colleagues^{25,39} showed that

TABLE 3. Subgroup analysis on patients with less than 3 units of red blood cell transfused

Groups	Event, n (%)	Adjusted HR*	95% CI	P
Inflammation-transfusion				
Low CRP-no RBC (n = 338)	40 (11.8%)	Reference		
Low CRP-yes RBC (n = 449)	57 (12.7%)	1.28	0.82-2.00	.278
High CRP-no RBC (n = 64)	14 (21.9%)	0.92	0.44-1.89	.813
High CRP-yes RBC (n = 113)	31 (27.4%)	2.07	1.20-3.57	.009

The adjusted HR (95% CI) of High CRP-yes RBC was 1.61 (0.98-2.66), $P = .060$ and 2.26 (1.06-4.83), $P = .036$, compared with Low CRP-yes RBC and High CRP-no RBC, respectively. HR, Hazard ratio; CI, confidence interval; CRP, C-reactive protein; RBC, red blood cell. *Adjusted for all variables of Multivariable model 3 in Table 2.

TABLE 4. Postoperative outcomes after off-pump coronary artery bypass grafting

Outcomes	Low CRP no RBC	Low CRP yes RBC	High CRP no RBC	High CRP yes RBC	P
30-d mortality	3/331 (0.9%)	26/930 (2.8%)	1/62 (1.6%)	18/275 (6.5%)	.001
90-d mortality	6/310 (1.9%)	44/867 (5.1%)	4/58 (6.9%)	43/253 (17.0%)	<.001
1-y mortality	13/246 (5.3%)	76/725 (10.5%)	6/48 (12.5%)	62/205 (30.2%)	<.001
3-y mortality	16/193 (8.3%)	80/534 (15.0%)	7/39 (17.9%)	51/152 (33.6%)	<.001

CRP, C-reactive protein; RBC, red blood cell.

CRP levels of even 0.1 to 0.3, thus not only greater than 0.3 mg/dL, were associated with moderate and high risks of future cardiovascular events in healthy females.

Study Limitations

Our study had several limitations. First, the work was retrospective in nature. Although we adjusted for many perioperative clinical variables, some bias may be in play. Tran and colleagues⁴⁰ indicated that the association between transfusion and mortality became insignificant after adjusting for postoperative complications such as renal failure, prolonged intubation, a need for reintubation, acute MI, or cardiac dysfunction. We adjusted for postoperative covariates, including acute kidney injury, any need for reintubation, and reoperation to control bleeding. However, adjustments for other postoperative morbidities, especially cardiac conditions, may be required. Second, we used only CRP as a marker of inflammation; the levels of other markers also may be clinically significant. However, CRP is an exquisitely sensitive marker, predicting postoperative outcomes.^{22,28} Third, we did not assess the dose-response effect of the inflammation/transfusion relationship. When defining transfusion triggers for patients undergoing cardiac surgery with preexisting inflammation, data on changes in patient outcome according to transfusion volume are required. Fourth, we do not answer the (important)

question: What is the cause of death of patients in the high CRP with transfusion group? Considering the key role played by inflammation in the development of atherosclerosis,^{18,19} we infer that such patients would more frequently experience recurrent vascular occlusive disease or graft failure.

CONCLUSIONS

We found that the effect of intraoperative RBC transfusion on mortality after OPCAB was influenced by preoperative CRP level. The risk of mortality after transfusion was significantly higher in patients with preexisting inflammation. These patients may need individualized transfusion triggers.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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VIDEO 1. The effect of transfusion on mortality after OPCAB grafting can be affected by preoperative CRP level. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30292-2/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30292-2/fulltext).

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Key Words: coronary artery bypass grafting, C-reactive protein, inflammation, mortality, transfusion