

The impact of blood transfusion on morbidity and mortality after cardiac surgery

O impacto da hemotransusão na morbimortalidade pós-operatória de cirurgias cardíacas

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Abstract

Objectives: To analyze the impact of blood transfusion on the incidence of clinical outcomes postoperatively (PO) from cardiac surgery.

Methods: Retrospective cohort study. We analyzed 4028 patients undergoing coronary artery bypass grafting (CABG), valve (TV), or both, in Brazilian tertiary university hospital between 1996 and 2009. We compared the postoperative complications between patients with blood transfusion (n = 916) and non-blood transfusion (n = 3112). Univariate analysis was performed using the Student t test, and multivariate logistic regression bivariate (stepwise

forward). Were considered significant variables with $P < 0.05$.

Results: Patients who received blood transfusions had more infectious episodes as mediastinitis (4.9% vs. 2.2%, $P < 0.001$), respiratory infection (27.8% vs 17.1%, $P < 0.001$) and sepsis (6.2% vs. 2.5%, $P < 0.001$). There were more episodes of atrial fibrillation (AF) (27% vs. 20.4%, $P < 0.001$), acute renal failure (ARF) (14.5% vs 7.3%, $P < 0.001$) and stroke (4.8% vs. 2.6%, $P = 0.001$). The length of PO hospital stay was higher in transfused (13 ± 12.07 days vs. 9.72 ± 7.66 days, $P < 0.001$). However, mortality didn't differ between groups (10.9% vs. 9.1%, $P = 0.112$). The transfusion was shown to be a risk factor for: respiratory infection (OR: 1.91, 95%

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CI 1.59-2.29, $P < 0.001$), AF (OR: 1.35, 95% CI 1.13-1.61, $P = 0.01$), sepsis (OR: 2.08, 95% CI 1.4-3.07, $P < 0.001$), mediastinitis (OR: 2.14, 95% CI: 1.43-3.21, $P < 0.001$), stroke (OR: 1.63, 95% CI 1.1-2.41, $P = 0.014$) and ARF (OR 1.8, 95% CI: 1.39-2.33, $P < 0.001$).

Conclusion: The blood transfusion is associated with increased risk of infectious events, episodes of AF, ARF and stroke, as well as the increased length of hospital stay but not mortality.

Descriptors: Blood Transfusion. Postoperative Complications. Hospital Mortality. Cardiac Surgical Procedures.

Resumo

Objetivos: Analisar o impacto da hemotransfusão sanguínea na incidência de desfechos clínicos no pós-operatório (PO) de cirurgias cardíacas.

Métodos: Estudo de coorte retrospectiva. Foram analisados 4.028 pacientes submetidos à cirurgia de revascularização miocárdica (CRM), troca valvar (TV) ou ambas, em hospital terciário universitário brasileiro, entre 1996 e 2009. Foram comparadas as complicações no PO entre os pacientes hemotransfundidos ($n=916$) e não-hemotransfundidos ($n=3112$). Foi realizada análise univariada através do teste *t* de Student, e análise multivariada com o uso de regressão

logística Bivariada (*Stepwise Forward*). Foram consideradas significativas as variáveis com $P < 0,05$.

Resultados: Os pacientes que receberam hemotransfusão apresentaram mais episódios infecciosos como mediastinite (4,9% vs. 2,2%, $P < 0,001$), infecção respiratória (27,8% vs 17,1%, $P < 0,001$), e sepse (6,2% vs. 2,5%, $P < 0,001$). Ocorreram mais episódios de fibrilação atrial (FA) (27% vs. 20,4%, $P < 0,001$), insuficiência renal aguda (IRA) (14,5% vs. 7,3%, $P < 0,001$) e acidente vascular cerebral (AVC) (4,8% vs. 2,6%, $P = 0,001$). O tempo de internação hospitalar no PO foi maior nos transfundidos ($13 \pm 12,07$ dias vs. $9,72 \pm 7,66$ dias, $P < 0,001$). Porém, a mortalidade não apresentou diferença entre os grupos (10,9% vs. 9,1%, $P = 0,112$). A transfusão mostrou-se como fator de risco para: infecção respiratória (OR: 1,91; IC95%: 1,59-2,29; $P < 0,001$), FA (OR: 1,35; IC95%: 1,13-1,61; $P = 0,01$), sepse (OR: 2,08; IC95%: 1,4-3,07; $P < 0,001$), mediastinite (OR: 2,14; IC95%: 1,43-3,21; $P < 0,001$), AVC (OR: 1,63; IC95%: 1,1-2,41; $P = 0,014$) e IRA (OR: 1,8; IC95%: 1,39-2,33; $P < 0,001$).

Conclusão: A hemotransfusão está associada ao aumento do risco de eventos infecciosos, episódios de FA, IRA e AVC, bem como aumentou o tempo de permanência hospitalar, mas não a mortalidade.

Descritores: Transfusão de Sangue. Complicações Pós-Operatórias. Mortalidade Hospitalar. Procedimentos Cirúrgicos Cardíacos.

INTRODUCTION

Blood transfusion and hemocomponents are important technologies in modern therapy. If it is appropriately used in significant morbidity or mortality conditions, and when its not effectively prevented or controlled in any other way, it can save lives and improve patients' health. However, as any other therapeutic interventions, it can lead to acute or late complications, such as the risk for transmission of infectious agents, among other clinical complications [1].

Blood transfusion is related to the occurrence of a transfusion reaction, transmission of infection, increased postoperative morbidity and mortality, risk of immunosuppression and the cost of hospitalization [2-4]. Cardiac surgery is associated with high rates of blood transfusion, ranging from 40% to 90% in most studies [5-7]. Transfusions have been associated with high morbidity and mortality in patients and some recent studies have demonstrated worse outcomes, including increased

occurrence of renal failure and infection, as well as respiratory, cardiac and neurological complications in transfused patients compared to those who were not transfused after cardiac surgery [7-9].

The occurrence of bleeding is a frequent complication of cardiovascular surgery [10]. Approximately one-third of the operated patients require blood transfusion, being responsible for the consumption of 10% to 25% of the hemoderivatives in the United States [10-13].

The aim of this study was to recognize the risk factors associated with blood transfusion in the postoperative period of cardiac surgery, thus, it allows strategies to be drawn to reduce these comorbidities in this group of patients.

METHODS

We conducted a retrospective cohort study using data from the Cardiovascular Surgery Department of Sao Lucas

Hospital at PUCRS, from 4028 patients who underwent coronary artery bypass graft (CABG), valve replacement (VR) or combined surgeries (CABG and VR) between January 1996 and December 2009. Patients who received two or more units of red packed blood cells in the postoperative period (PO) of the surgeries. The patients received blood transfusions when there was excessive bleeding after surgery (above 400 ml in the first postoperative hours or above 100 ml / hour for the first 6 postoperative hours) requiring surgical intervention.

The pre and perioperative variables analyzed were: female gender, age over 65 years, smoking, obesity (BMI $\geq 30\text{kg} / \text{m}^2$), chronic obstructive pulmonary disease (COPD) clinically diagnosed and / or through chest X-ray and / or spirometry, and / or drug therapy (corticosteroids or bronchodilators), chronic renal failure (creatinine $> 1.5\text{ mg} / \text{dL}$ or prior hemodialysis), active infectious process (through laboratory tests), prior cardiac surgery, history of previous diseases as diabetes (DM), systemic arterial hypertension (SAH), peripheral vascular disease (PVD), cerebrovascular accident (CVA), atrial fibrillation (AF) and acute myocardial infarction (AMI), unstable angina (UA), functional class 3 and 4 of heart failure according to criteria of the New York Heart Association (NYHA), ejection fraction below 40% (measured by echocardiography), surgical priority (emergency surgery / emergency as a single variable and defined as the need for intervention up to 48 hours due to imminent risk of death or unstable hemodynamic condition), extracorporeal circulation time over 120 minutes, use of intra-aortic balloon pump (IABP).

The postoperative variables analyzed as possible complications related to transfusion of hemoderivatives were: sepsis and respiratory infection diagnosed by isolated organisms in culture associated with fever and elevated white blood cell count; mediastinitis diagnosed from the presence of pain, warmth, redness, and pus in the wound of the sternum, presence of sternal instability and fever, as well as through a tomography of the thorax, postoperative AMI, diagnosed by the evidence of subepicardial current with the onset of Q wave, subendocardial injury current with increased markers of myocardial necrosis (troponin I above 10ng/dL and CK-MB five times higher than the reference value or above 10% of total CK) or new bundle branch block with elevation of markers, atrial fibrillation (AF) confirmed by electrocardiographic analysis, acute renal failure (ARF), with an increase of creatinine and need for dialysis, acute respiratory distress syndrome (ARDS), with chest radiograph showing alveolar-interstitial infiltrates, micro and / or macronodular, bilateral and asymmetric and an oxygenation index ($\text{PaO}_2/\text{FiO}_2$) $< 200\text{ mmHg}$, cerebrovascular accident (CVA), diagnosed by clinical signs of neurological deficit and CT compatible; the death rate within 30 days after surgery and hospitalization time in

patients receiving hemoderivatives or not were also analyzed.

The quantitative variables were described by mean and standard deviation and the categorical variables were described by means of absolute and relative frequencies. In addition to the descriptive analysis, univariate analysis was performed from the Student t test for the quantitative variables and Pearson's chi-square test and / or Fisher exact test for the categorical variables. To assess the possible intervening variables, multivariate analysis was performed by the bivariate logistic regression (stepwise forward), in which all pre-and perioperative factors were adjusted as possible confounding factor, with $P < 0.1$ for entry logistic regression. The variables with $P < 0.05$ were considered significant. The software SPSS (Statistical Package for the Social Sciences, version 18.0) were used for statistical analysis.

This study research project was submitted and approved by the PUCRS Research Ethics Committee.

RESULTS

In this retrospective study, 4,028 patients were included, 62.9% ($n = 2,533$) were male and 37.1% ($n = 1,495$) were female. Regarding the type of surgery, 67.2% ($n = 2706$) underwent CABG, 27.4% ($n = 1,102$) CTV and 5.6% ($n = 225$) underwent combined surgery (CABG + VR). Considering these patients, 22.7% ($n = 916$) required blood transfusion in the postoperative period of cardiac surgery. Only 139 (3.45%) patients in the study sample underwent surgery without extracorporeal circulation. In Table 1, the patients pre-and perioperative data are shown.

Ten postoperative complications were evaluated in relation to the use of packed red blood cells (RBC) (Table 2). Patients who received blood transfusions had significantly more infectious episodes as mediastinitis (4.9% vs. 2.2%; $P = 0.001$) respiratory infection (27.8% vs. 17.1%; $P = 0.001$), and sepsis (6.2% vs. 2.5%; $P = 0.001$). This group of patients also had more episodes of AF (27% vs. 20.4%; $P = 0.001$), ARF (14.5% vs. 7.3%; $P = 0.001$) and CVA (4.8% vs. 2.6%; $P = 0.001$). AMI and ARDS were not statistically significant, but showed a tendency. Moreover, the length of hospital stay after surgery was higher in the group that received blood transfusion (13 ± 12.07 days vs. 9.72 ± 7.66 days; $P = 0.001$). However, mortality did not differ between patients who received RBC as compared to those who were not transfused (10.9% vs. 9.1%; $P = 0.112$).

The postoperative complications were included in multivariate analysis (Table 3), and adjusted for pre-and perioperative factors mentioned above, and were related as risk factors due to blood transfusion: respiratory infection (OR: 1.91; CI95%: 1.59-2.29; $P < 0.001$), ARDS (OR: 2.35; CI95%: 0.97-5.67; $P = 0.058$), (NRAF (OR: 1.35; CI95%:

Table 1. Baseline characteristics of patients in pre and peri-operative period of cardiac surgery.

Variables	Patients who underwent hemotransfusion n=916 n(%)	Patients who did not undergo hemotransfusion n = 3112 n(%)	P
Female gender	393 (43)	1102 (35.4)	<0.001
Age > 65 years	375 (40.9)	1074 (34.5)	<0.001
Smoking	255 (27.8)	1027 (33)	0.004
Obesity	94 (10.3)	300 (9.6)	0.622
DM	237 (25.9)	680 (21.8)	0.012
COPD	138 (15.1)	524 (16.8)	0.222
CRF	108 (11.8)	210 (6.7)	<0.001
CVA	52 (5.7)	180 (5.8)	0.967
Pre-hemodialysis	20 (2.2)	26 (0.8)	0.001
Preinfection	58 (6.3)	185 (5.9)	0.724
UA	285 (31.1)	832 (26.7)	0.01
AMI	303 (33.1)	939 (30.2)	0.103
AF	69 (7.5)	240 (7.7)	0.913
SAH	616 (67.2)	1864 (59.9)	<0.001
Ef < 40%	768 (83.8)	2685 (86.3)	0.072
EC>120min	196 (21.4)	357 (11.5)	<0.001
PVD	95 (10.4)	230 (7.4)	0.004
IABP	80 (8.7)	216 (6.9)	0.079
Cir. Emergency surgery	16 (1.7)	26 (0.8)	0.028
CHF 3 and 4 (NYHA)	234 (25.5)	667 (21.4)	0.03

P: statistical significance; DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease; CRF: Chronic Renal Failure; CVA: Cerebrovascular Accident; UA: Unstable angina; AMI: Acute Myocardial Infarction; AF: Atrial Fibrillation; SAH: Systemic Arterial Hypertension; Ef: Ejection fraction; EC: Extracorporeal Circulation; PVD: Peripheral Vascular Disease; IABP: Intra-aortic Balloon Pump; CHF: Congestive Heart Failure; NYHA: New York Heart Association

Table 2. Complications presented in the postoperative period.

Complications	Patients who underwent hemotransfusion n=916 n(%)	Patients who did not undergo hemotransfusion n=3112 n(%)	P
AF	247 (27)	635 (20.4)	<0.0001
Sepsis	57 (6.2)	77 (2.5)	<0.0001
Mediastinitis	45 (4.9)	68 (2.2)	<0.0001
Respiratory infection	255 (27.8)	532 (17.1)	<0.0001
ARF	133 (14.5)	227 (7.3)	<0.0001
ARDS	10 (1.1)	12 (0.4)	0.022
Post AMI	123 (13.4)	366 (11.8)	0.193
CVA	44 (4.8)	81 (2.6)	0.001
Death	100 (10.9)	283 (9.1)	0.112
HS*	13±12.07	9.72±7.66	<0.0001

*Days. Mean ± Standard deviation.

P: statistical significance; AF: Atrial Fibrillation; ARF: Acute Renal Failure; ARDS: Acute Respiratory Distress Syndrome; Post AMI: AMI up to 30 days after surgery; CVA: Cerebrovascular Accident; HS: Hospital Stay

1.13-1.61; P<0.01), sepsis (OR: 2.08; CI95%: 1.4-3.07; P<0.001), mediastinitis (OR: 2.14; CI95%: 1.43-3.21; P<0.001), CVA (OR: 1.63; CI95%: 1.1-2.41; P=0.014) and ARF (OR: 1.8; CI95%: 1.39-2.33 days; P <0.001). AMI and death rate were not statistically significant.

Table 3. Multivariate analysis of postoperative complications due to blood transfusion.

Complications	OR	95% CI	P
Respiratory infection	1.91	1.59 – 2.29	<0.001
Post AMI	0.93	0.74 – 1.18	0.567
AF	1.35	1.13 – 1.61	0.01
Sepsis	2.08	1.40 – 3.07	<0.001
Mediastinitis	2.14	1.43 – 3.21	<0.001
ARF	1.8	1.39 – 2.33	<0.001
ARDS	2.35	0.97 – 5.67	0.058
CVA	1.63	1.1 – 2.41	0.014
Death	0.85	0.64 – 1.13	0.259

OR: odds ratio, CI 95%: 95% confidence interval, P: statistical significance; AF: Atrial Fibrillation; ARF: Acute Renal Failure; ARDS: Acute Respiratory Distress Syndrome; Post AMI: AMI up to 30 days after surgery; CVA? Cerebrovascular Accident

DISCUSSION

The study results suggest that blood transfusion in the studied sample is related to the risk of infectious events (such as mediastinitis, respiratory infection, sepsis). The transfused patients had also more episodes of AF, ARF and CVA. ARDS appears as a tendency to risk factor and can not be dismissed.

The association between packed red cells transfusion and postoperative complications (PO) for cardiac surgery is often described in the literature. In a study conducted by Koch et al. [14], when analyzing the ratio of units of packed red cells administered to adult patients and the risk of morbidity and mortality in patients undergoing CABG, it was concluded that from the 11,963 patients analyzed, 5,184 (49%) received at least one unit of RBC.

The authors also concluded that there is a relationship between each RBC unit transfused and the risk of morbimortality in the postoperative period. According to the study, each administered unit increases by 77% the postoperative mortality risk and 100% the risk of developing any renal complication, 76% the risk of developing postoperative infections, cardiac complications in 55% and 37% the risk of neurological complications. These associations remained strong even after the risk adjustment

factors causing postoperative complications. The authors also reported the importance of stratifying high-risk groups for transfusion and then, modulate the pre- and perioperative interventions that help to reduce blood transfusion in the postoperative period, and, consequently, the risk of complications.

In a study conducted by Möhnle et al. [15] in patients who had low risk of developing postoperative complications of cardiac surgery, it was observed that, despite the low risk patients who received blood transfusion had an increased risk of developing cardiac events, as well as an increase in surgical site infections. However, the authors report that the study's findings related to infectious, renal complications and hospital mortality should be carefully analyzed, mainly due to the fact that the group of transfused patients differs in several characteristics from the group that did not receive blood transfusions in the postoperative period.

Karkouti et al. [16] also reported that the need for blood transfusion in the postoperative period of cardiac surgeries is directly associated with complications such as sepsis, ARDS, ARF and death.

In this study, a tendency toward higher pulmonary complication rates in transfused patients was noted, reaching statistical significance for lower respiratory tract infection, but not for ARDS. The design of the study, however, did not allow to differentiate ARF due to TRALI (Transfusion-related Acute Lung Injury) from other causes such as ARDS and lower respiratory tract infection.

Specifically in relation to risk of pulmonary complications, Koch et al. [17], in another study reported that blood transfusion is associated with high risk of ARF, ARDS, need for reintubations due to pulmonary causes, long-term intubations and longer hospitalization period in the intensive care unit. The same study concludes that the use of plasma is associated with more pulmonary complications after surgery when compared to other hemoderivatives.

Another acute pulmonary complication caused by blood transfusion, known as TRALI, the receiver of hemoderivatives develops signs and symptoms of respiratory compromise due to a non-cardiogenic pulmonary edema. Evidence of hypoxemia with a ratio of PaO₂/FiO₂ <300, associated with bilateral pulmonary infiltrates and without fluid overload, are diagnostic criteria for TRALI. But the most common criterion for diagnosis is the temporal criterion between the transfusion and the onset of signs and symptoms. They usually occur 1 or 2 hours after the transfusion, with 100% of the patients presenting the symptoms 6 hours after transfusion.

Rogers et al. [6] found a significant increase in infections during hospitalization in patients who received blood transfusion, and the most prevalent are the genitourinary,

respiratory, digestive tract, skin and subcutaneous tissue, as well as sepsis. In this study, the risk of infections during hospitalization in transfused patients was two times higher compared to those who did not receive hemoderivatives. In this group of patients, the risk of death was five times higher in the case of elective surgery and four times higher in case of non-elective surgeries, as well as the risk of death after 30 days of hospital discharge was three times higher in patients undergoing elective surgery and four times higher in non-elective surgeries.

In Magedanz study et al. [18], in which a risk score for mediastinitis was created, an association between blood transfusion and risk of postoperative mediastinitis was found (OR: 2.5; CI95%: 1.5 - 4.1, $P = 0.001$), that also agrees with a study that found a strong association between transfusion and risk of infections, which reflects the immunosuppressive effect of blood transfusion [19].

The study conducted shows that transfusion of hemocomponents is directly related to increased risk of infectious processes in the postoperative period of cardiac surgery and the onset of AF during this period.

Studies have reported that blood transfusion, particularly platelets, is associated with the development of comorbidities such as AF, low cardiac output syndrome, AMI, CVA, renal failure and sepsis [14,16].

Atrial fibrillation is a common complication after cardiac surgery, ranging from 10% to 43% of the operated patients, contributing to morbidity and increased hospital stay of these patients. Koch et al. [20] in a study that evaluated the risk of developing AF in patients undergoing blood transfusion after cardiac surgery, it was concluded that transfusion is associated with the risk of AF in the postoperative period, and the risk increases for each unit transfused (OR: 1.2; 95% CI: 1.1-1.3 days; $P < 0.0001$). Although the precise mechanism is not known, the authors speculate that the inflammatory response associated with transfusion may be exacerbated, contributing to the occurrence of AF. This may be due to leukocyte activation, leading to injury of the atrial tissue.

Some studies report that the ischemic process, blood loss and blood transfusion are known to cause severe systemic inflammatory response. Blood transfusion can also initiate a secondary inflammatory response by modifying the systemic inflammatory response of the patients and the direct introduction of bioactive substances into circulation, in addition to the primary inflammatory response initiated by the extracorporeal circulation [21-23].

In this study, patients who received hemoderivatives required longer hospital stays, however, there was no difference in mortality compared to patients who were not transfused.

In the study conducted by Hajjar et al. [7], 502 patients who underwent cardiac surgery with extracorporeal

circulation (EC) were randomized to receive blood transfusion in a liberal manner (to maintain a hematocrit \geq 30%) or in a more restrictive way (hematocrit \geq 24%). This study demonstrates that a more conservative blood transfusion does not alter the rates of comorbidities (such as ARDS, ARF or cardiogenic shock) and mortality between the groups, demonstrating the importance of a more careful selection of patients who must undergo a blood transfusion.

In a study conducted by McGrath et al. [24], with 32,298 patients, no association between transfusion and increased morbidity and mortality after cardiac surgery was found. However, this study analyzed only the platelet transfusion, regardless of other hemoderivative components.

According to the study conducted by van Straten et al. [21], the number of units transfused may be a predictor of early mortality (up to 30 days in the postoperative period), but not of late mortality. Comparing the expected survival, the authors concluded that in patients who received three or more units of RBC, the survival rate drops significantly when compared to patients who did not receive hemoderivative products. These patients have also high incidence of postoperative complications, which could explain the high early mortality in this study.

By analyzing the relationship between blood transfusion and cardiac surgery in an older population, Veenith et al. [25] showed that blood transfusion is associated with a significant increase in mortality and length of hospital stay. The authors also report that this possible association is a result of the poor health status of patients in the preoperative period. Another factor that increases the risk of postoperative morbimortality would be that the blood transfusion may increase the risk of ischemic processes and infectious complications. This would also explain the long-term ICU and hospital stay.

Some studies also report strategies for reducing the use of hemoderivatives in postoperative cardiac surgery. Some authors report the importance of a careful preoperative evaluation, because it can reduce the risk of bleeding and the need for blood transfusion during the postoperative period. The measurement of serum iron and iron administration and preoperative erythropoietin may reduce the need for hemoderivatives. The perioperative interventions play an important role in reducing the risk of bleeding during and after surgery [4]. The use of antifibrinolytic, such as aprotinin, attenuates the systemic inflammatory response in patients undergoing EC [26]. The use of miniEC (reduction of the prime, the tubes and vacuum drainage) and the use of centrifugal pumps (Bio Pump) can reduce the excessive use of heparin [27,28]. Hypothermia (between 30° and 32° C) during the surgical procedure may

also reduce bleeding during surgery and in the postoperative period. The autologous blood donation is another method used, but still requires further studies, when the patient's blood is collected prior to surgery in order to be used after the procedure. It is considered a simple, inexpensive, safe and effective method to reduce homologous blood transfusion in a wide variety of elective surgical procedures, including cardiac surgeries [4,29].

New hemoconcentration techniques during EC have also been studied. Souza & Braille [30] propose a new method of hemoconcentration, which revealed a reduction of blood and plasma used during and after EC, as well as a reduced water balance compared to the group that did not use the hemoconcentrator.

In this study, however, there were some limitations. The number of units that were transfused in each patient or the effects of other hemoderivatives in the postoperative period was not taken into consideration. Another factor that was not taken into account was the storage time of the blood transfusion bags. Thus, we conclude that the data collected revealed a tendency demonstrating that more detailed studies are needed to show the effects of each hemocomponent transfused in patients undergoing cardiac surgery.

CONCLUSION

The analysis of this study results shows that blood transfusion is associated with increased risk of infectious events (such as mediastinitis, respiratory infection, sepsis), risk of developing AF, ARF, CVA and ARDS. The blood transfusion increased the length of hospital stay, but not mortality in these patients.

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