Perioperative blood transfusions are not associated with overall survival in elderly patients receiving surgery for fractured hips

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Abstract

Background: Whether perioperative blood transfusions are associated with long-term outcomes remains controversial. This study aimed to evaluate the effect of blood transfusions on overall survival in hip fracture patients.

Methods: This retrospective survey was conducted at a single medical center and enrolled patients aged ≥ 70 years who received hip fracture surgery between 2013 and 2015. Multivariate Cox regression analysis was used to estimate the effect of blood transfusions on overall survival after surgery. Furthermore, patients who received a blood transfusion were further matched to those who did not receive a blood transfusion by patient characteristics. Stratified Cox regression analysis was used to assess the effect of transfusions on overall survival after matching.

Results: A total of 718 patients with a median follow-up period of 25.9 months were included in the analysis, of whom 495 (68.9%) received a blood transfusion. Four independent risk factors for mortality were identified, including male sex (hazard ratio [HR], 1.48; 95% CI, 1.01-2.17), aging (HR, 1.03; 95% CI, 1.0-1.06), general anesthesia (HR, 1.61; 95% CI, 1.11-2.31), and anemia status (mild vs no anemia: HR, 1.67; 95% CI, 0.96-2.90 and moderate versus no anemia: HR, 4.14; 95% CI, 2.35-7.3). The effect of blood transfusions on overall survival was nonsignificant after adjusting for the selected risk factors (HR, 1.44; 95% CI, 0.87-2.36). After matching, the effect of blood transfusions on overall survival remained nonsignificant (HR, 1.7; 95% CI, 0.78-3.71).

Conclusion: No association was found between blood transfusions and overall survival among elderly patients undergoing hip fracture surgery. More prospective studies are necessary to elucidate the association between blood transfusions and long-term outcomes in patients receiving hip fracture surgery.

Keywords: Anemia; Blood transfusion; Hemoglobin; Hip fracture

1. INTRODUCTION

Hip fractures have become a severe public health challenge in many countries due to the aging population.[1,2] Slow recovery and disabilities after hip fractures are common, even with surgical interventions.[3,4] Increasing evidence suggests that anemia is common in elderly patients receiving hip fracture surgery and that this adversely affects morbidity and mortality after surgery.[5,6] Although blood transfusions are usually used to treat perioperative anemia in patients undergoing hip fracture surgery, some studies have reported that transfusions may increase morbidity and mortality after surgery.[7,8] The potential causal relationship between blood transfusions and worse outcomes after surgery remains unclear. Some studies have reported an association between the storage time of erythrocytes and increased mortality,[9,10] while another focused on cytokine release and immune activation.[11] However, conflicting results are not uncommon,[5] so that the effect of transfusions on long-term outcomes after hip fracture surgery has become an important issue in clinical practice and research.

The aim of this retrospective cohort study was to investigate the association between perioperative blood transfusions and overall survival after hip fracture surgery in elderly patients using various statistical analytical strategies, including traditional regression approaches and propensity score-based methodologies. Based on positive findings observed in previous studies,[7,8] we hypothesized that blood transfusions may increase the risk of mortality after hip fracture surgery. The purpose of our analysis was to offer health care providers with detailed information about the risk of blood transfusions in order to guide clinical decision-making in the perioperative period of hip fracture surgery.

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2. METHODS

After approval from our Institutional Review Board (IRB-TPEVGH No. 2016-10-004CC), we reviewed the electronic medical records of patients aged ≥ 70 years who received general or spinal anesthesia for hip fracture surgery at Taipei Veterans General Hospital between January 2013 and December 2015. The exclusion criteria were pathologic hip fractures, high-energy injuries and those with incomplete data. The patients were further classified into two groups based on whether or not they received perioperative blood transfusions. Medical records of the recruited patients were extracted by research assistants who were not involved in data analysis. The quality of the obtained data was verified through random sampling by the authors.

The following variables were collected from our electronic medical record system: age, sex, American Society of Anesthesiologists (ASA) physical status classification, hemoglobin level, platelet count, international normalized ratio, history of chronic renal insufficiency, perioperative blood transfusion, anesthesia time, and intraoperative blood loss. Anemia status was defined using the criteria of the World Health Organization[12] as being mild (hemoglobin: 11-11.9 g/dL in women and 11-12.9 g/dL in men), moderate (8-10.9 g/dL), and severe (< 8 g/dL).

The primary endpoint was overall survival after surgery, which was defined as the interval from the date of surgery to the date of mortality. For those who survived, their survival times were regarded as the corresponding censored observations. All patients were followed up until the endpoint, censor date or the end of January 2018, whichever occurred first.

2.1. Statistical analysis

All patients were classified into transfusion and no transfusion groups, and comparisons of patient characteristics between these two groups were conducted using the χ^2 test for categorical variables and either the *t* test or Mann-Whitney *U* test for continuous variables, as appropriate. Log transformation was conducted to reduce skewness of non-normal continuous variables. Univariate Cox regression analysis was used to evaluate the effects of transfusion status and other collected variables on overall survival. Multivariate Cox regression analysis was also used with a stepwise model selection strategy with entry and removal significance criteria of 0.1 and 0.05, respectively, to select factors associated with overall survival from the significant outcome predictors in the univariate analysis. Due to the possibility of imbalances in patient characteristics, logistic regression analysis was conducted to generate propensity scores by including the collected variables in the model (the analytical results are presented in the Appendix). Propensity score matching was carried out using a caliper width of 0.2 times the SD of the logit-transformed propensity scores to ensure sufficient balance in the collected variables between matched pairs.[13] Comparisons of patient variables between the paired groups were conducted as mentioned above and stratified using a Cox regression model with the matched pairs to evaluate associations between blood transfusions and overall survival. For sensitivity analysis, we used quintiles of the obtained propensity scores to divide the study subjects into five groups of equal size, and stratified Cox regression analysis was performed to estimate the pooled hazard ratio (HR) of transfusion effect on overall survival across these strata. A p value < 0.05 was considered to be statistically significant. We used IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA) for all statistical analyses.

3. RESULTS

Among the 718 hip fracture patients included in the analysis, 495 (68.9%) received a blood transfusion. The median follow-up duration after surgery was 25.9 months. Table 1 presents the patient characteristics of those who did and did not receive a transfusion. There was an obvious imbalance in the distributions of age, ASA classification, anemia status, anesthesia time and blood loss between the transfusion and no transfusion groups. However, after propensity score matching, no significant differences in patient characteristics between the two groups were found in the 149 matched pairs (Table 1).

Table 2 shows the univariate analysis results. Seven of the collected variables were found to be significant predictors of overall survival after hip fracture surgery, including blood transfusion (crude odds ratio, 2.14; 95% CI, 1.35-3.39), aging, sex, anemia status, chronic renal insufficiency, general anesthesia, and anesthesia time. ASA classification was of borderline significance (p = 0.05), and international normalized ratio, platelet count, and blood loss during surgery were not associated with overall survival after hip fracture surgery in the univariate analysis.

Table 1

Patient characteristics before and after propensity score matching

	Before matching					After matching				
	No transfusion (N = 223)		Transfusion (N = 495)			No transfusion (N = 149)		Transfusion (N = 149)		
	Count (mean)	% (SD)	Count (mean)	% (SD)	SDD	Count (mean)	% (SD)	Count (mean)	% (SD)	SDD
Age, y	(81)	(6)	(85)	(6)	50.8	(81)	(7)	(82)	(7)	7.7
Sex (male)	111	49.8%	245	49.5%	0.6	71	47.7%	76	51.0%	6.7
ASA ≥ 3	156	70.0%	426	86.1%	39.6	109	73.2%	115	77.2%	9.3
Anemia					72.4					3.2
Nil	112	50.5%	87	17.6%		57	38.3%	56	37.6%	
Mild	98	44.1%	273	55.3%		80	53.7%	78	52.3%	
Moderate	12	5.4%	134	27.1%		12	8.1%	15	10.1%	
INR	(1.05)	(0.10)	(1.05)	(0.14)	1.2	1.05	0.11	1.05	0.15	6.4
Platelet (× 1000)	(215)	(81)	(209)	(86)	7.0	213	85	221	110	7.6
Chronic renal insufficiency	41	18.5%	138	28.0%	22.7	31	20.8%	32	21.5%	1.6
General anesthesia	87	39.0%	240	48.5%	19.2	60	40.3%	59	39.6%	1.4
Anesthesia time (min)[a]	150	120-165	165	135-195	50.7	150	120-180	150	120-180	7.6
Blood loss (mL)[a]	150	100-200	200	150-350	73.8	150	100-250	150	100-200	11.3

SDD, the difference in mean, proportion, or rank divided by the pooled SE, expressed as a percentage; absolute values > 20 indicate potential imbalance.

ASA = American Society of Anesthesiologists physical status classification; INR = international normalized ratio; SDD = standardized difference.

[a]Anesthesia time and blood loss are presented as median with interquartile range.

Table 2

Univariate and multivariate regression analyses of the effects of the collected variables on overall survival after hip fracture surgery

Univariate	HR (95% CI)	*p*
Blood transfusion	2.14 (1.35-3.39)	0.001
Age	1.04 (1.01-1.07)	0.004
Sex (female vs male)	0.60 (0.42-0.86)	0.006
ASA ≥ 3	1.69 (1.00-2.86)	0.050
Anemia		< 0.001
Mild vs nil	1.95 (1.15-3.31)	0.013
Moderate vs nil	4.42 (2.55-7.68)	< 0.001
INR	0.67 (0.15-2.93)	0.593
Platelet	1.00 (1.00-1.00)	0.648
Chronic renal insufficiency	2.00 (1.37-2.91)	< 0.001
General anesthesia	1.54 (1.08-2.21)	0.018
Anesthesia time[a]	1.62 (1.14-2.31)	0.007
Blood loss[a]	1.01 (0.81-1.27)	0.910
Multivariate model selection		
Age	1.03 (1.00-1.06)	0.046
Sex (female vs male)	0.68 (0.46-0.99)	0.045
Anemia		< 0.001
Mild vs nil	1.67 (0.96-2.90)	0.067
Moderate vs nil	4.14 (2.35-7.30)	< 0.001
General anesthesia	1.61 (1.11-2.31)	0.011

ASA = American Society of Anesthesiologists physical status classification; HR = hazard ratio; INR = international normalized ratio.

[a]Anesthesia time and blood loss are log transformed.

After the model selection processes, only four independent predictors of overall survival after hip fracture surgery were identified in the multivariate model (Table 2). Female sex was associated with a lower risk of mortality after surgery; however, general anesthesia and aging were associated with a higher risk. In addition, patients with moderate anemia had a higher risk of mortality after surgery than those with mild anemia or without anemia (Table 2). Nevertheless, the effect of blood transfusions on overall survival after hip fracture surgery was no longer significant after further adjustments for the four selected risk factors (HR, 1.44; 95% CI, 0.87-2.36) (Table 3). After propensity score matching, the effect of transfusions was still not significant in stratified Cox regression analysis (HR, 1.7; 95% CI, 0.78-3.71). In sensitivity analysis, the quintile-stratified method also generated nonsignificant results (HR, 1.41; 95% CI, 0.82-2.44).

4. DISCUSSION

In this study, we demonstrated that perioperative blood transfusions were not associated with a higher risk of long-term mortality after hip fracture surgery in elderly patients (≥ 70 y). In contrast, anemia status was an independent risk factor for mortality after surgery. Although transfusions are commonly used to treat acute anemia during hip fracture surgery, the hypothetical relationship between transfusions and overall survival after surgery was not found in multivariate regression modeling or propensity score-based methods. This finding is consistent with a study by Smeets et al[5] but in contrast to a study by Engoren et al[7]. The strength of our study was using rigorous statistical methods to control for the effects of other potential confounders in a sample size large enough to achieve the aims of the study. Our findings provide new evidence to guide the treatment of perioperative anemia with regards to blood transfusions in elderly patients undergoing hip fracture surgery.

Table 3

Methods used to evaluate the effect of blood transfusions on overall survival after hip fracture surgery

Method	HR (95% CI)	*p*
Model adjusted[a]	1.44 (0.87-2.36)	0.154
Propensity score matching	1.70 (0.78-3.71)	0.183
Quintile stratified	1.41 (0.82-2.44)	0.211

HR = hazard ratio.

[a]Multivariate model adjusted for age, sex, anemic status, and general anesthesia.

Carson et al[14] found that low hemoglobin levels were associated with a higher rate of cardiac complications in patients with preexisting cardiac comorbidities. Potter et al[15] also investigated preoperative anemia and blood transfusions in hip fracture patients using meta-analysis and suggested that anemia on hospital admission was associated with increased mortality. However, their analysis failed to demonstrate an association between postoperative transfusions and mortality after adjusting for covariates. These findings are consistent with our results and imply that anemia seems to be a major determinant affecting long-term survival after hip fracture surgery. The possible mechanism of the association between anemia and worse outcomes after surgery remains unclear, although some researchers have suggested that it may be related to underlying systemic diseases, inflammation processes, insufficient oxygen delivery resulting in organ dysfunction during stress, or a combination of multiple factors.[8]

Although the effect of perioperative transfusions on postoperative outcomes has been extensively investigated, there is still much controversy over this issue. The causal relationships between perioperative transfusions and long-term mortality remain uncertain, and only one large randomized trial has had sufficient power to assess the effect of optimal transfusion strategies on mortality in patients undergoing hip fracture surgery. The functional outcomes in cardiovascular patients undergoing surgical hip fracture repair trial randomized more than 2000 elderly patients undergoing hip fracture surgery with moderate to severe anemia and cardiovascular diseases or other risk factors to a liberal or restrictive transfusion strategy.[16] They concluded that although patients in the liberal transfusion group had a greater chance of receiving a blood transfusion, there were no differences in the occurrence of acute coronary syndrome or short-term mortality between the two transfusion arms. These results are compatible with other related randomized trials of nonsurgical populations in critical care settings.[17,18] On the other hand, observational studies have reported conflicting results concerning the effect of blood transfusions on morbidity and mortality after hip fracture surgery. Vochteloo et al[6] reported that blood transfusions were a risk factor for mortality with a main effect within the first 3 months. Johnston et al[19] studied a cohort of more than 3000 patients to explore this issue, and found a negative correlation at 120 and 365 days only in univariate but not in multivariate analysis. Carson et al[14] also used a large cohort and found no effect on 30- and 90-day mortality. In addition, Engoren et al[7] reported that blood transfusions were associated with higher long-term mortality after hip fracture surgery. The inconsistencies in these findings may be due to different transfusion targets, patient characteristics, and analytical methods, and further large-scale investigations are needed to elucidate the causal relationships among anemia, transfusion and long-term outcomes in elderly patients receiving hip fracture surgery.

From the results of logistic regression analysis used to generate propensity scores, we identified five independent risk factors for perioperative blood transfusions in our elderly patients undergoing hip fracture surgery, including age (HR, 1.08), female sex (HR, 2.18), ASA classification ≥ 3 (HR, 2.16), anemia

(mild vs nil: HR, 3.5; moderate vs nil: HR, 14.6), and intraoperative blood loss (HR, 3.04, in logarithmic scale). These findings could be considered to be a clinical guide for perioperative blood transfusions. For the patients receiving hip fracture surgery with related risk factors, and particularly multiple factors in combination, the risk of perioperative blood transfusions was substantially higher, and thorough preparation for transfusion therapy should be considered in advance.

There are several limitations to this study. First, the decision to treat perioperative anemia with a transfusion was not standardized but based on the clinical judgment of the physicians or surgeons in charge. Second, the retrospective study design cannot exclude potential selection bias. Third, the effects of unmeasured confounders cannot be further assessed and included in the analysis. Fourth, propensity score matching has some inherent problems, such as the inability to balance unmeasured characteristics.[20]

In conclusion, we found no association between blood transfusions and overall survival in elderly patients undergoing hip fracture surgery, and that anemia status was an independent risk factor for long-term mortality after surgery. The current study provides useful information about transfusion strategies for hip fracture surgery in elderly patients. More prospective studies are necessary to elucidate the association between blood transfusions and long-term outcomes in patients receiving hip fracture surgery.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jcma.2018.01.013.

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