Journal of Biometrics & Biostatistics
ISSN: 2155-6180

Tsai et al., J Biom Biostat 2018, 9:5
DOI: 10.4172/2155-6180.1000414

Research Article
Open Access

Potential Factors Affecting Transfusion Policy and Length of Hospitalization in Patients with Thermal Injury

Shin-Yi Tsai*, Chon-Fu Lio, Leiyu Shi, Shou-Chuan Shih, Yi-Fang Chang, Yu-Tien Chen, Sheng-Kai Kevin Ma and Chien-Feng Kuo

Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, USA

Abstract

Background: To explore the potential factors affecting time to discharge alive among burn patients and to determine the appropriateness of restrictive and liberal transfusion policies for burn patients.

Study design and method: A retrospective analysis of 66 burn patients was conducted from 2013 to 2015. The average age was 26.7 and TBSA was 42.1% (± 25.9%). Data exploration of all dependent variables was performed to determine the normality and non-normally distributed variables were converted using Templeton's two-step transformation involving percentile ranking. We assessed associations between significant clinical factors from and the outcome using Cox proportional hazards regression models with fixed and time-varying covariates. Impact of different transfusion threshold on the LOS was estimated by Cox proportional hazards regression and Kaplan-Meier curve.

Results: A higher ABSI score (adj. HR, 0.28; P=0.017), present of bacteremia (adj. HR, 0.19; P=0.002) and pRBC transfusion (adj. HR, 0.55; P=0.001) were associated with significantly lower hazards of hospital discharge, suggesting a longer hospital stay. Further, the "restrictive" group also had a better outcome regarding the length of ICU stay (P=0.006) and hospital stay (P=0.003). There was a longer length of hospital stay in hemoglobin threshold greater than 8.5 g/dl patients. (Log rank test, P=0.001). Transfusion threshold per se played an important role in extending the length of hospitalization (P=0.019).

Conclusions: Restrictive RBC transfusion policy is more favorable to order appropriate blood components and helps the healthcare system to shorten LOS, reduce cost and complications.

Keywords: Restrictive transfusion policy; Liberal transfusion policy; Length of hospital stay (LOS); Abbreviated Burn Severity Index (ABSI); Formosa dust explosion; Bacteremia; Trauma-induced coagulopathy; Blood management of burn care; Postburn anemia; Thromboelastometry

Introduction

The etiologies of postburn anemia are various [1]. The activation of inflammation and coagulation of thermal injuries both destroy erythrocytes that are sequestrated within the thrombosed microcirculation of acute-stage wounds [2,3]. Furthermore, patients can experience acute anemia related to the surgical management of wounds, iatrogenic blood loss, and critical illness [4]. Risk factors for increased blood loss include the surface area of wound that is excised, percentage of third degree burns, and a prolonged time to first wound excision [5]. Acute burn excision results in at least a 2% loss in blood volume per percent that is excised; hence, massive blood loss (>50% total blood volume) occurs during major burn excisions [6]. Additionally, if a long time passes between injury and operation, bacteria may colonize the wound, which may increase blood loss and impair hemostasis. Papers have reported that extensive blood loss caused by excision and grafting is a major factor leading to acute blood loss anemia [7-9]. Another category of blood loss is iatrogenic blood loss; 17% of the total blood lost from patients during intensive care unit (ICU) stays may be iatrogenic [10,11]. Regarding red blood cells (RBCs), total body surface area (TBSA) and patient age are major predictors of increased packed red blood cell (pRBC) transfusion; one study indicated that anticoagulants substantially increase the risk of iatrogenic bleeding [12]. Thus, multiple factors such as burn size, age, and percentage of third degree burn, time to the first operation, operation count, and ICU length of stay can affect the demand for blood product transfusion among flame burned patients.

Some studies have indicated that patient mortality and morbidity might not be affected by the policy that governs transfusion thresholds [12,13]. One study reported on both restrictive RBC transfusion policy (transfusion when hemoglobin concentration falls below approximately 80 g/L) and liberal RBC transfusion policy (transfusion when hemoglobin concentration falls below approximately 100 g/L) [14]. However, a large cluster randomized trial to assess the effectiveness of transfusion strategies for acute upper gastrointestinal bleeding indicated that both restrictive and liberal policies are feasible because no significant difference exists in their clinical outcomes [15]. Therefore, transfusion policy is still controversial regarding some critical illnesses. In terms of cohorts with thermal injuries, conventional theory suggests that hemoglobin levels must be maintained at >10 g/dL to promote wound healing. When comparing blood transfusions with lower volumes (target Hb of 7-8 g/dL) and conventional volumes (target Hb >10 g/dL) for a large cohort of patients, the authors believe that more definitive clinical guidelines regarding blood transfusion volumes would be beneficial [16].

After a powder explosion, massive blood products including whole blood, pRBCs, albumin, fresh plasma, and frozen plasma are required for transfusion to explosion casualties. The financial burdens of health

***Corresponding author:** Shin-Yi Tsai, Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, USA, Tel: 886225433535; E-mail: stsai22@jhu.edu

Received November 04, 2018; **Accepted** November 19, 2018; **Published** November 26, 2018

Citation: Tsai SY, Lio CF, Shi L, Shih SC, Chang YF, et al. (2018) Potential Factors Affecting Transfusion Policy and Length of Hospitalization in Patients with Thermal Injury. J Biom Biostat 9: 414. doi: 10.4172/2155-6180.1000414

care systems and the adverse effects of blood transfusions are known to increase hospital costs. Blood transfusion was indicated to prolong hospital stay and increase possible readmissions, causing unnecessary expenditure [17].

This study aims to explore the potential factors affecting time to discharge alive among patients with flame burn injuries caused by the powder explosion at Formosa Fun Coast and some other fire events in Taiwan and to determine the appropriateness of restrictive and liberal transfusion policies for patient with thermal injuries. This is the first study of patient blood management in Taiwan to refine current policy on blood product management and to facilitate forecasting the demand for blood production, reducing the number of transfusions and the in-hospital costs incurred by catastrophic events.

Method

Study design and patient selection

This was a retrospective study conducted through claims data from chart review of adult acute burn referrals to Mackay Memorial Hospital, Taiwan, one of the largest medical centers in downtown Taipei, from 2013 to 2015. All adult patients who were admitted to the hospital with acute burns requiring burn specialist were enrolled. Patients who did not survive the initial acute phase to the point of successful discharge, or whose clinical information from electronic record was incomplete were excluded. Additionally, only patients who received all essential acute managements suggested by burn specialists were involved. We felt that these criteria of patient selection ensured the reliability in length of stay estimation and applicability of the results. Patients with more than 20% TBSA of burn would transfer to the intensive care unit (ICU). Standard operating procedures such as fluid resuscitation for thermal injury management were written in the emergency room and burns unit protocol. The study was approved by the Institutional Review Board of MacKay Memories Hospital (15MMHIS127).

Data collection

The patients' demographic and laboratory data were obtained by reviewing electronic medical records. The TBSA of burn was estimated using the Wallace "rule of nines" method. Full-thickness injury was defined as an injury extended to all layers of the skin. Endotracheal tube placement was performed during initial resuscitation in the patients having evidence of inhalation injury or respiratory failure, and these patients were classified as having an inhalation injury. The severity of burn injury was measured using the Abbreviated Burn Severity Index (ABSI) [18]. Additionally, various clinical sepsis indicators were calculated including quick Sequential Organ Failure Assessment (qSOFA) and the American Burn Association (ABA) sepsis criteria for patients with burn [19,20]. The parameter of this sepsis criteria includes temperature (>39°C or <36°C), progressive tachycardia (>110 beats/min), progressive tachypnea (>25 breaths/min without ventilation or >12 breaths/min under ventilation), thrombocytopenia (<100 000/μL; not until 3 d after initial resuscitation), hyperglycemia (untreated plasma glucose >200 mg/dL, an intravenous drip of >7 units of insulin/h, or >25% increase in insulin requirement over 24 hours), and feed intolerance >24 hours (abdominal distension, containing residual that is 2 times the feeding rate, or diarrhea >2500 mL/d). The patients with burn injury who met ≥ 3 of these criteria plus documented infection (such as culture positive infection) were considered the presence of sepsis. Wound infection was considered in patients with clinical symptoms and positive wound culture. Patients with clinical suspicion of pneumonia and having a positive culture from sputum or bronchoalveolar lavage specimen were regarded as respiratory tract infection. Bacteremia was defined by a positive blood culture in patients with warning signs of sepsis. In this study, we focused some variables as indicators of outcomes, such as operation count, debridement count, length of hospital stay (LOS), mechanical ventilation days and length of ICU stay. Instead of strict regulations on transfusion threshold for burn injuries, the hospital used computerized physician order entry (CPOE) to provide clinicians the recent lab data of the blood receipts, so clinicians can easily correlate patients' profiles to decide the execution or cancelation of transfusion orders flexibly. Thus, different physician may have an individual hemoglobin threshold for blood transfusion. All hemoglobin levels prior to the transfusion on the day were documented, and the average of the data was regarded as threshold for blood transfusion.

Statistical analysis

Descriptive statistic of demographic and clinical characteristics of burn severity and prognosis was summarized in Table 1.

The demographic data could be reflective of our results in any burns patient. Before the analysis, data exploration of all dependent variables was performed to determine the normality by Kolmogorov-Smirnov and Shapiro-Wilk tests. Those non-normally distributed variables were converted using Templeton's two-step transformation involving percentile ranking (first step; resulting in uniformly distributed probabilities) followed by applying the inverse-normal transformation (second step; yielding normally distributed z-scores), in order to warrant adequate normality [21]. Statistic descriptions of the transformed variable were displayed in Table 2.

Although transformed variables of pRBC and Frozen Plasma failed the normality tests, the distribution of both variables was acceptable to perform regression analysis (skewness<1). Univariate analysis was performed by Pearson's correlation to determine factors that influence the total length of hospital stay (Table 3).

We assessed associations between significant clinical factors from Table 3 and the outcome using Cox proportional hazards regression models with fixed and time-varying covariates (Table 4).

Moreover, we divided the cohort into three groups depending on the average hemoglobin threshold for transfusion (Table 5).

Population (N=66)	Mean	Median	Std. Deviation
Gender (male%)	45.45	-	-
Age (years)	26.74	23	11.04
TBSA[a] (%)	42.06	47.5	25.88
Present of full thickness burn (%)	65	-	-
Present of inhalation injury (%)	31.82	-	-
Major comorbidity[b] (%)	12.12	-	-
ABSI[c] score at admission (mean)	8.58	8	3.77
Required ICU admission (%)	25.38	-	-
Mechanical ventilation (days)	4.75	0	8.27
ICU stay (days)	18.11	0	28.02
Length of hospital stay (days)	47.82	31.5	39.24
pRBC transfusion (packs)	14.2	4	19.64
Frozen Plasma transfusion	12.21	0	27.65
Total cost (10K TWD)	170.9	88.47	181.51

[a]Total Burn Surface Area of burn; [b]History of major comorbidities including hypertension, type 2 diabetes mellitus, coronary heart disease and/or hepatitis; [c]Abbreviated Burn Severity Index

Table 1: Demographic and clinical characteristics of enrolled burn injured patients.

	Skewness	Kurtosis	P value (Kolmogorov-Smirnov)	P value (Shapiro-Wilk)
ABSI[a] score	0.07	-0.52	0.196	0.208
Length of hospital stay	0.06	-0.39	0.2	0.674
pRBC transfusion	0.66	-0.64	<0.001	<0.001
Frozen Plasma transfusion	0.85	-0.4	<0.001	<0.001

[a]Abbreviated Burn Severity Index.

Table 2: Normality tests of various dependent and independent continuous variables for regression analysis.

	Pearson's coefficient	P value
	Burn severity	
ABSI[a]	0.64	<0.001
Comorbidity[b]	–0.296	0.016
	Complication	
Wound infection	0.395	0.001
Respiratory tract infection	0.263	0.034
Bacteremia	0.583	<0.001
	Transfusion	
Amount of pRBC	0.793	<0.001
Amount of Frozen Plasma	0.529	<0.001

Table 3: Univariate estimative of Pearson's product-moment coefficient between length of hospital stay and various independent variables.

	Adjusted Hazard ratio		95% Confidence interval	
	Time to Hospital Discharge Alive	P value	Lower	Upper
ABSI[a]	0.28	0.017	0.099	0.796
Comorbidity[b]	2.467	0.064	0.948	6.42
Wound infection	1.539	0.162	0.841	2.815
Respiratory tract infection	0.746	0.63	0.227	2.457
Bacteremia	0.185	0.002	0.063	0.541
pRBC transfusions	0.547	<0.001	0.424	0.705
Flozen Plasma transfusions	0.972	0.759	0.881	1.166

[a]Abbreviated Burn Severity Index; [b]History of major comorbidities including hypertension, type 2 diabetes mellitus, coronary heart disease and/or hepatitis.

Table 4: Associations between length of hospital stay and variables relating to burn injury severity, complication and blood transfusion.

	Not received pRBC (N=30)	Thresholds for pRBC transfusion		P value[§]
		"Liberal" Hemoglobin levels>8.5 g/dL (N=26)	"Restrictive" Hemoglobin levels ≤ 8.5 g/dL (N=10)	
Gender (male%)	43.33	42.31	60	0.341
Age (years)	29.43	23.69	26.6	0.389
TBSA[a] (%)	23.1	61.15	43.3	0.021
Present of full thickness burn (%)	46.67	76.92	90	0.375
Present of inhalation injury (%)	3.33	65.38	30	0.056
Major comorbidity[b] (%)	23.33	10	0	0.102
ABSI[c] score at admission (mean)	6	11.46	8.8	0.028
Required ICU admission (%)	6.67	68	40	0.127
Mechanical ventilation (days)	0	10.68	4.2	0.07
ICU stay (days)	2.54	37	12	0.006
Operation count	1.23	8.42	4.1	0.009
Debridement count	0.93	4.65	2.6	0.031
Wound infection (%)	33.33	69.23	70	0.964
Respiratory tract infection (%)	0	11.54	30	0.183
Bacteremia (%)	0	38.46	20	0.293
The length of stay with ABA score[d] ≥3 (days)	0	9.38	3.2	0.211
The length of stay with qSOFA score[e] ≥2 (days)	0	8.19	2.5	0.185
Length of hospital stay (days)	16.77	83.92	47.1	0.003
Mean pRBC transfusion trigger (Hemoglobin, g/dL)	-	9.51	7.82	<0.001
pRBC transfusion (packs)	-	29.88	15.4	0.053
Pre-transfusion hemoglobin level (median; g/dL)		9.51	7.83	<0.001
Post-transfusion Hb (median; g/dL)		9.66	10.26	0.302
Frozen plasma transfusion	0.67	23.92	16.4	0.568

[§]Comparison between "Hemoglobin levels>8.5 g/dL" and "Hemoglobin levels≤8.5 g/dL" groups. [a]Total Burn Surface Area of burn; [b]Abbreviated Burn Severity Index; [c]History of major comorbidities including hypertension, type 2 diabetes mellitus, coronary heart disease and/or hepatitis; [d]American Burn Association sepsis criteria; [e]Quick Sequential Organ Failure Assessment.

Table 5: Demographic and clinical characteristics of burn injured patients stratified by the various hemoglobin thresholds for packed Red blood cell transfusion.

Citation: Tsai SY, Lio CF, Shi L, Shih SC, Chang YF, et al. (2018) Potential Factors Affecting Transfusion Policy and Length of Hospitalization in Patients with Thermal Injury. J Biom Biostat 9: 414. doi: 10.4172/2155-6180.1000414

An unpaired Student's t test and chi-squared test were used to compare demographic and clinical characteristics between "Hemoglobin levels >8.5 g/dl" and "Hemoglobin levels ≤8.5 g/dl" groups. Pre-transfusion hemoglobin and post-transfusion hemoglobin level were compared as well. The pre-transfusion hemoglobin was defined as the last hemoglobin level before transfusion without the hemoglobin level in between consecutive transfusion days. The post-transfusion level was defined as the hemoglobin level after the last day if transfusion were done in consecutive days. A Mann-Whitney U test was performed when continuous data did not follow a normal distribution (Figure 1).

Another model of Cox proportional hazards regression (Table 6) and Kaplan-Meier curve (Figure 1) were used to estimate the impact of different transfusion threshold on LOS. We used the ABSI as an indicator with which to adjust burn severity instead of calculating all the component factors (age, sex, TBSA, inhalation injury, etc.) due to multi collinearity (TBSA, R^2=0.853) and a low number of degrees of freedom. In all the comparisons, a P value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software, Version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 66 patients with burn injury were enrolled. The average age of the consecutive patients was 26.74 years. The average TBSA percentage of burn was 42.06%. The mean ABSI score was 8.58. More than half of the patients (65.00%) had full-thickness burn injury, and one third had inhalation injury (31.82%). Only seven of them had the history of major comorbidities such as hypertension, type 2 diabetes mellitus, coronary heart disease or hepatitis. Hence, this cohort reflected a group of patient with young, severely burned, but relatively healthy before admission. We believe the homogeneity of the enrolled patients can help us better understand the influence of blood transfusion on the outcome. Overall, the average LOS per patient was 47.82 days. A quarter of patients required intensive care unit (ICU) and mean ICU stay was 18.112 days. On average, every patient received 14.20 units of pRBC and 12.21 units of Frozen Plasma, and total cost was about 1.7 million TWD per person.

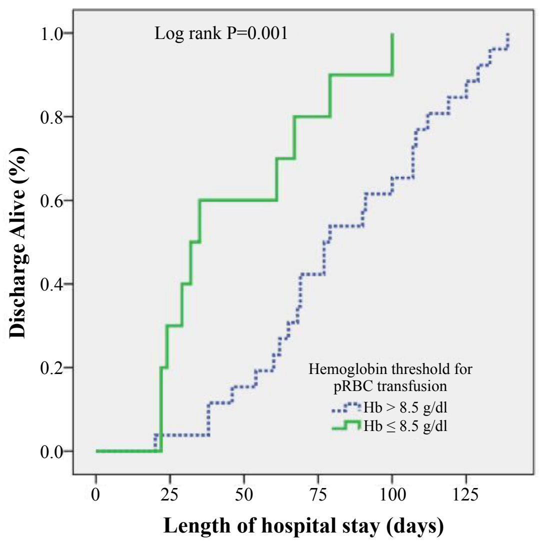

Figure 1: Kaplan-Meier curve demonstrated that there was a longer length of hospital stay in patient with a hemoglobin threshold greater than 8.5 g/dL (Log rank test, P=0.001).

The first step was to explore what factors might affect the length of hospital stay. We tried to apply a variety of clinical factors such as burn severity, complication and blood transfusion for a linear analysis. Table 3 showed that all significant factors related to the hospital stay by Pearson's correlation.

Unexpectedly, comorbidity was negatively correlated with hospital stay (r=-0.30, P=0.02). We believed that this result was attributed to the fact that this population had less area of burn and severity comparing to the victim of "Formosa dust explosion accident" admitted on 27 June 2015. Next, all potential LOS -related factors were further investigated in a multivariate Cox regression model as shown in Table 4.

A higher ABSI score (adj. HR, 0.28; 95% CI, 0.10-0.80; P=0.017), present of bacteremia (adj. HR, 0.19; 95% CI, 0.06-0.54; P=0.002) and pRBC transfusion (adj. HR, 0.55; 95% CI, 0.42-0.71; P <0.001) were associated with significantly lower hazards of hospital discharge, suggesting a longer time to hospital discharge. In order to further analyze the impact of pRBC transfusion on the prognosis, we stratified the patient depending on their average hemoglobin threshold for transfusion. A cutoff of 8.5 g/dL was used and patients were separated into three groups accordingly as shown in Table 5.

There was a significant difference in mean transfusion trigger between "liberal" (Hb=9.51 g/dL) and "restrictive" (Hb=7.82 g/dL) groups (P<0.001). We found that the burn severities, such as TBSA (P=0.021) and ABSI (P=0.028), were higher in patients with "liberal" transfusion threshold (Hb trigger >8.5 g/dL). This group of patients also had a higher operation and debridement count, however, there was not much difference concerning the occurrence of complications including the infection of several sites. In addition, there were no significant differences in several sepsis screening markers, such as ABA score and qSOFA, between groups. It implied that frequent operations might not be caused by infection. Although the average hemoglobin level throughout hospitalization was similar between groups (P=0.165), the amount of transfused pRBC seemed to be lower in patients with "restrictive" threshold (15.40 vs. 29.88 units of pRBC), but did not reach statistically significance (P=0.053). Further, the

	Adjusted Hazard ratio		95% Confidence interval	
	Time to Hospital Discharge Alive	P value	Lower	Upper
Confounding factors				
ABSI[a]	0.228	0.014	0.07	0.743
Bacteremia	0.323	0.021	0.124	0.846
Transfusions threshold				
Hemoglobin >8.5 g/dl	1	-	-	-
Hemoglobin ≤8.5 g/dl	2.675	0.019	1.174	6.097
[a]Abbreviated Burn Severity Index				

Table 6: Associations between length of hospital stay and hemoglobin thresholds for packed Red Blood Cell transfusion adjusted by burn injury severity and bacteremia.

"restrictive" group also had a better outcome regarding the length of ICU stay (P=0.006) and hospital stay (P=0.003). The pre-transfusion Hb and post-transfusion Hb were compared, with post-transfusion Hb higher than pre-transfusion Hb shown, as expected.

A Kaplan-Meier curve (Figure 1) demonstrated that there was a longer length of hospital stay in patients with a hemoglobin threshold greater than 8.5 g/dL. (Log rank test, P=0.001), as shown.

As we want to clarify whether or not the extent of the injury or the transfusion threshold per second could affect the outcome of burn injured patients, we included ABSI and bacteremia as confounding factors for investigating the impact of transfusion threshold on the hospital stay by a multivariate Cox regression model as shown in Table 6.

Results suggested that although burn severity (ABSI, P=0.014) and complication (bacteremia, P=0.021) had certain impacts on hospital stay, transfusion threshold per second played an important role in extending the length of hospitalization (P=0.019).

Discussion

In our study population, three factors that reduced the rate of discharge alive were elevated ABSI score, bacteremia, and pRBC transfusion (Table 4). Furthermore, a comparison between the group with Hb levels >8.5 g/dL and the group with Hb levels ≤8.5 g/dL revealed that the rate of discharge alive was higher in the group with Hb levels ≤8.5 g/dL (aHZ=2.65; Table 5 and Figure 1). The results demonstrated that the LOS was higher in the cohort that was treated with the liberal strategy than in the group that received the restrictive strategy. Moreover, compared with the cohort that received the restrictive strategy, pRBC transfusion was higher in the cohort that was treated with the liberal strategy. A study of multiple trials across a range of clinical specialties (e.g., surgery, critical care) concluded that transfusions with allogeneic RBCs can be avoided in most patients with hemoglobin thresholds above 7-8 g/dL [22]. Several guidelines recommend a restrictive transfusion policy [23]. The transfusion of RBCs should be considered when Hb level<7-8 g/dL, depending on the patient's characteristics. The decision to transfuse RBCs should be based on a clinical assessment of the patient that weighs the risks associated with transfusion against the anticipated benefit. A restrictive transfusion threshold is safe in most clinical settings [24].

Liberal transfusion strategies are not necessarily associated with superior outcomes and may expose patients to unnecessary risks. The American Association of Blood Banks (AABB) recommends employing a restrictive transfusion strategy and considering transfusion when Hb level is 7-8 g/dL in hospitalized, stable patients [25]. Additional clinical practice guidelines exist that specify Hb targets for critical care patients with various conditions, including sepsis.

RBC transfusion is indicated in patients who are actively bleeding and should be based on clinical assessment in addition to laboratory testing. Adult critical care medical and surgical inpatients being treated for sepsis during the first 6 hours of resuscitation may receive transfusions if they have an Hb level ≤10 g/dL [26]. Blood product transfusion is a potential cost of burn care. After a powder explosion, the consumption of massive blood products (including whole blood, pRBC, albumin, fresh plasma, and frozen plasma) increases; blood products impose a prominent financial burden on modern health care systems. European and US studies have suggested that the mean cost of an RBC unit ranges from US$761-$821 [27-29]. Multiple studies have reported that ICU admission and stay, hospital LOS, operation count, debridement, and the risk of serious hospital-acquired infection were significantly higher in the cohort treated using the liberal strategy [30-35]. Hospital stay was the most expensive component of burn care [36]. Thus, reducing hospital stay length without compromising the quality of care is the main goal for lowering in-hospital costs [37].

The mean inpatient cost was 1.83 times higher in a transfused group than in a non-transfused group in Australia; RBC transfusions were independently associated with significantly higher hospital costs [38,39]. The number of blood transfusions received during hospitalization may be a marker of disease severity and survival [40-42]. Prospective studies have reported that blood transfusion was an independent predictor of mortality, ICU admission, systemic inflammatory response syndrome, ARDS, ventilator-associated pneumonia, organ dysfunction and failure, and hospital length of stay independent of injury severity [10,41,43-46].

Consequently, the administration of blood products has been linked to increased infection, immunosuppression, and infectious complications [47-49]. The compromise of the immune system by blood transfusion may increase a patient's susceptibility to infection, with each unit of blood transfused increasing the risk of infection by 13%; this may affect mortality [50-51].

The potential harm to burn patients receiving excessive blood transfusion was noted. The number of transfusions received was associated with mortality and infectious episodes in patients with major burns even after factoring for indices of burn severity [7].

In the aforementioned explosive event, the high survival rate following major acute burns has been attributed to the high use of early tangential wound excision and grafting, relatively appropriate antimicrobial therapies, and the use of specialized critical care facilities and nutritional support protocols. However, the necessary financial expenditure was drastic.

Our findings demonstrate that restrictive strategies in burn care are more favorable than liberal strategies because restrictive strategies shorten LOS and reduce costs. Restrictive strategies also have the potential to lower the incidence of health-care-associated infection [35]. Thus, clarifying the potential factors related to extensive blood product transfusion could facilitate forecasting the demand for blood production, reducing the amount of transfusion, and potentially lowering the in-hospital costs for treating flame burned patients. Based on the aforementioned concerns, several alternative health care policies can be considered to replace blood transfusion, as follows:

Hospitals can reduce the rate of RBC transfusions;

They can implement patient blood management programs, which can benefit patients by not only implementing restrictive transfusion policies, but also by evaluating patients' clinical signs so that appropriate blood is ordered. All RBC transfusions in non-bleeding inpatients could be considered as one single unit to be ordered;

Clinical symptoms could be monitored regularly to ensure that caregivers are aware of patients' conditions. In particular, if transfusion is indicated based on Hb level, post-transfusion Hb must be determined before ordering more units.

Additionally, CPOE systems can be configured to automatically query the most recent Hb level when any order for inpatient RBC transfusion is placed. If the most recent Hb level>7 g/dL or if Hb level has not been measured in the previous 24 hours, the physician can receive a best practice alert prompting selection from a limited menu of appropriate indications or cancelation of the transfusion order [26,52].

To assess safety, a prospective comparison was made on the effects of a 4:1 strategy versus a 1:1 strategy for pRBC–fresh frozen plasma (pRBC/FFP) transfusions. The outcomes of these strategies were compared in children with burns greater than 20% TBSA; the conclusion was that a 1:1 pRBC/FFP transfusion strategy increased FFP use, decreased overall pRBC use, and resulted in higher antithrombin AIII and protein C postoperatively without a difference in INR or PT/aPTT. This may represent compensatory changes in the 4:1 group in response to intraoperative blood loss [6].

According to epidemiological data from the United States and Europe, the influence of coagulation depends on the severity of injury and amounts of crystalloid infusion, ischemia, tissue plasminogen activator, tissue injury and shock, and hyperfibrinolysis [53].

The interactions between coagulation and inflammation systems are caused by sepsis, activation of coagulation proteases, and inappropriate inflammatory response. These factors operate through cell surface receptors and cascade activations, such as complement and platelet depletion. Factor dilution, clotting system depletion, and disseminated intravascular coagulation crystalloid infusion are known to dilute clotting factors after microvascular tissue injury, which in cases of severe inflammation, decreases coagulation factors, reduces clotting factors, and affects the coagulation state [54].

The pathophysiology of trauma-induced coagulopathy consists of coagulation activation, hyper fibrinogenolysis, and consumption coagulopathy. These pathophysiological mechanisms are the characteristics of DIC with the fibrinolytic phenotype [53]. Moreover, replacement fluid is suggested in blood management of burn care; for instance, isotonic solutions (4.5% and 5.0% in volumes of 50 to 500 mL) are often used to replace subacute plasma volume loss caused by burns or trauma [55].

An algorithm incorporating albumin use in the first 24 hours after burn injury was associated with the use of lower quantities of vasopressor agents and lower mortality. Early albumin use was associated with a shorter duration of mechanical ventilation in burn patients, and the use of 5% albumin and vasopressors, as required, decreased fluid resuscitation and burn mortality complications [56]. Furthermore, optimistic strategies for transfusion policy could refer to lab data for indications of when to order appropriate units of blood components.

Infection control is essential in burn care. Poor infection control may induce physicians to debride infected tissue; surgical wound management is a major cause of post burn anemia. In an early excision group, the blood transfusion requirement was significantly higher (potentially increasing the infection rate) but the LOS was significantly shorter [57]. Consequentially, blood transfusion inevitably creates a vicious circle. Nevertheless, early and correct diagnoses help clinicians to prescribe appropriate antibiotics to eradicate pathogens efficiently and thus to reduce the demand for operations and blood product transfusions. Several useful serum markers that signal infection have been recognized. For example, C-reactive protein (CRP), an inflammatory response marker, is associated with the presence and progression of certain infections and CRP serial measurement might be useful in pediatric burn patients [58-60]. CRP begins to rise after 12-24 hours and peaks at 48 hours [61]. The clinical utilization of CRP indication for sepsis still leaves some room for discussion, because CRP has not been indicated to be sufficient for detecting infection or sepsis in burn populations; CRP only reflects inflammatory responses caused by thermal injuries [62,63]. Procalcitonin (PCT) was reported to have a better discriminatory capacity than CRP for identifying infectious processes in patients with severe burn injury [64]. Burn shock leads to local injury at the site of the burn; severe thermal injuries to areas greater than or equal to 20% TBSA result in acute systemic responses [16]. Sensitive and reliable biomarkers for detecting sepsis in severe burn care would be optimal.

PCT levels are detectable within 2-4 hours, peak within 6-24 hours, and fall to normal levels after the immune system is under infection control. A meta-analysis demonstrated that determination of PCT levels can strongly discriminate between septic and non-septic burn patients; PCT can identify susceptibility to sepsis in a timely fashion so that physicians can initiate antimicrobial therapy to improve patients' outcomes [61,65].

Several studies on burn injury populations have observed that PCT levels (>0.5 ng/mL) were significantly higher in patients with systemic infections than in those without infections [58,66]. Platelet count (<100 000/mm^3) could be another predictor of sepsis, especially in pediatric patients [67]. One study reported that platelet count is a better predictor than PCT [60]. A PCT-guided strategy to treat suspected bacterial infections could reduce antibiotic exposure [68].

Ultimately, it would be desirable to establish a model for blood product transfusion based on patient characteristics and several types of lab data (such as CRP, PCT, complete blood count). Furthermore, culture reports and usage of antibiotics can be examined to discover the correlation between drug-resistant microbes and increased blood product transfusion. The aforementioned biomarkers could be considered; however, it might be more practical for clinicians to measure tissue oxygenation directly using noninvasive methods or plasma markers, such as base deficit, lactate, or other biomarkers. These biomarkers could be coupled with hemoglobin the iron-containing oxygen-transport metallo-protein in the red blood cells that will level to provide a more clinically relevant indication of the need for RBC transfusion, because most current guidelines are based on hemoglobin level [69,70].

The predictors for increased RBCs and plasma transfusions were high TBSA of burn patients, the use of argatroban, and the use of anticoagulants, which are suspected to cause heparin-induced thrombocytopenia (HIT) even though HIT is rare. The type and intensity of anticoagulant medication carries substantial risk for increased RBC usage and increased plasma usage [71]. Thus, to use appropriate doses of anticoagulants, to monitor patients by thromboelastometry, and to correct coagulopathy are effective actions that reduce transfusion requirements and improve survival in trauma victims [72].

Another promising alternative therapy is antioxidant vitamin therapy. Zinc was found to promote impaired post burn SOD activity; zinc prevents the entrenchment of tissular dysfunction because integral disturbance of O_2 metabolism is the principal pathological mechanism in burn patients. Intensity of oxidative stress is amplified by blood transfusions, which determine oxidative lesions and the death of healthy cells [73]. Appropriate nutritional supplementation is suggested. Nutritional deficiencies could aggravate the anemia of critical illness and approximately 13% of long-term ICU burn patients had abnormal levels of iron, vitamin B12, and folate in one study [5]. Nutritional deficiencies lead to abnormal erythrocyte morphology and then to decreased half-life or earlier sequestration of these cells and a decrease in RBC's [1,8].

Our study is the first transfusion policy in burn care and proposed several practical strategies to improve transfusion policy, but some limitations must be noted in our study. First, because the number of cases was too low to allow stratification of numerous potential factors, we used ABSI to represent some factors related to the severity of burns. However, ABSI includes TBSA, inhalation injury, age and other factors, so it should be representative. Nevertheless, future studies could consider using more cases to validate the results. Another limitation was the lack of data validating some theories regarding PCT, anticoagulants, and other factors. The implication of our study provides clinicians to aware of the restrictive RBC transfusion policy more favorable to order appropriate blood components and helps the healthcare system to open an avenue to shorten LOS, reduce cost and complications, and sequentially promote burn patients' life of quality in the long run.

Conclusions

Our study makes clinicians aware of the restrictive RBC transfusion policy more favorable to order appropriate blood components and helps the healthcare system to open an avenue to shorten LOS, reduce cost and complications, and sequentially promote burn patients' life of quality in the long run.

Declarations

Ethics approval and consent to participate

Approval was obtained from the local ethics committee of Mackay Memorial Hospital. Committee number: 15MMHIS127.

Clinical research name: "Healthcare policy analysis in response to powder explosion victims and general burn patients"

Consent for publication

Consents for publication were obtained.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests regarding the publication of this paper.

Funding

This study is supported in the Department of Medical Research at Mackay Memorial Hospital (MMH-105-87).

Authors' Contributions

Study conception and design: Shin-Yi Tsai, M.D.; M.S. DrPH, Chon-Fu Lio, M.D.,

Acquisition of data: Shin-Yi Tsai, M.D.; M.S. DrPH 1,2, Chon-Fu Lio, MD, Chien-Feng Kuo, M.D.

Analysis and interpretation of data: Shin-Yi Tsai, M.D.; M.S. DrPH 1,2, Chon-Fu Lio, M.D.1,3, Chien-Feng Kuo, M.D.5 Fang-Ju Sun, MS 7 Shou-Chuan Shih8, 9 M.D.

Drafting of manuscript: All authors.

Critical revision: Shin-Yi Tsai, M.D.; M.S. DrPH, Shou-Chuan Shih M.D.

Acknowledgements

This study is supported in the Department of Medical Research at Mackay Memorial Hospital (MMH-105-87). We express our appreciation to Fang-Ju Sun, who have given us some suggestions.

References

1. Posluszny JA, Gamelli RL (2010) Anaemia of Thermal Injury: Combined Acute Blood Loss Anemia and Anemia of Critical Illness. J Burn Care Res 31: 229-242.
2. Lavrentieva A, Houris I, Aspragathou S, Mitka K, Kazanas K, et al. (2008) The efficacy of antithrombin administration in the acute phase of burn injury. Thromb Haemost 100: 286-290.
3. Hatherill JR, Till GO, Bruner LH, Ward PA (1986) Thermal injury, intravascular haemolysis, and toxic oxygen products. J Clin Invest 78: 629-636.
4. Posluszny JA, Gamelli RL (2010) Anaemia of thermal injury: combined acute blood loss anaemia and anaemia of critical illness. J Burn Care Res 31: 229-242.
5. Hart DW, Wolf SE, Beauford RB, Lal SO, Chinkes DL, et al. (2001) Determinants of blood loss during primary burn excision. Surgery 130: 396-402.
6. Palmieri TL, Greenhalgh DG, Sen S (2013) Prospective comparison of packed red blood cell-to-fresh frozen plasma transfusion ratio of 4: 1 versus 1: 1 during acute massive burn excision. J Trauma Acute Care Surg 74: 76-83.
7. Palmieri TL, Caruso DM, Foster KN, Cairns BA, Peck MD, et al. (2006) Effect of blood transfusion on outcome after major burn injury: a multicentre study. Crit Care Med 34: 1602-1607.
8. Harris RL, Cottam GL, Johnston JM, Baxter CR (1981) The pathogenesis of abnormal erythrocyte morphology in burns. J Trauma 2: 13-21.
9. Loebl EC, Marvin JA, Curreri PW, Baxter CR (1974) Erythrocyte survival following thermal injury. J Surg Res 16: 96-101.
10. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L (2002) Anemia and blood transfusion in critically ill patients. JAMA 288: 1499-1507.
11. Ahsen VN, Müller C, Serke S, Frei U, Eckardt KU (2001) Important role of non-diagnostic blood loss and blunted erythropoietic response in the anaemia of medical intensive care patients. Crit Care Med 27: 2630-2639.
12. Lu RP, Lin FC, Ortiz-Pujols SM, Adams SD, Whinna HC, et al. (2013) Blood utilization in patients with burn injury and association with clinical outcomes (CME). Transfusion 53: 2212-2221.
13. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J (2015) Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ, 350 p: h1354.
14. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, et al. (2013) Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 368: 11-21.
15. Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, et al. (2015) Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 386: 137-144.
16. Rowan MP, Chung KK, LC Cancio (2015) Burn wound healing and treatment: review and advancements. J Crit Care 19: 137-144.
17. Hofmann A, Ozawa S, Farrugia A, Farmer SL, Shander A (2013) Economic considerations on transfusion medicine and patient blood management. Best Pract Res Clin Anaesthesiol 27: 59-68.
18. Tobiasen J, Hiebert JM, Edlich RF (1982) The abbreviated burn severity index. Ann Emerg Med 11: 260-262.
19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, et al. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315: 801-810.
20. Greenhalgh DG, Saffle JR, Holmes JH, Gamelli RL, Palmieri TL, et al. (2007) American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res 28: 776-790.
21. Templeton GF (2011) A two-step approach for transforming continuous variables to normal: implications and recommendations for IS research. CAIS 28: 41-58.
22. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D (2016)

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 10: CD002042.

23. Shander A, Gross I, Hill S, Javidroozi M, Sledge S (2013) A new perspective on best transfusion practices. Blood Transfus 11: 193.
24. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, et al. (2016) Clinical Practice Guidelines from the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 316: 2025-2035.
25. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, et al. (2012) Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med 157: 49-58.
26. Szczepiorkowski ZM, Dunbar NM (2013) Transfusion guidelines: when to transfuse. Hematology Am Soc Hematol Educ Program pp: 638-44.
27. Abraham I, Sun D (2012) The cost of blood transfusion in Western Europe as estimated from six studies. Transfusion 52: 1983-1988.
28. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, et al. (2012) Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 50: 753-765.
29. Leahy MF, Mukhtar SA (2012) From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice. Intern Med J 42: 332-338.
30. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB (2009) Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 208: 931-937.
31. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, et al. (2013) Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 368: 11-21.
32. Murphy GJ, Reeves BC, Rogers CA (2007) Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 116: 2544-2552.
33. Horvath KA, Acker MA, Chang H, Bagiella E, Smith PK, et al. (2013) Blood transfusion and infection after cardiac surgery. Ann Thorac Surg 95: 2194-2201.
34. Hofmann A, Farmer S, Shander A (2011) Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management. Oncologist 16: 3-11.
35. Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, et al. (2014) Health care–associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA 311: 1317-1326.
36. Hop MJ, Polinder S, van der Vlies CH, Middelkoop E, van Baar ME (2014) Costs of burn care: a systematic review. Wound Repair Regen 22: 436-450.
37. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA (1983) Early excision and grafting vs. non-operative treatment of burns of indeterminant depth: a randomized prospective study. J Trauma 23: 1001-1004.
38. Morton J, Anastassopoulos KP, Patel ST, Lerner JH, Ryan KJ, et al. (2010) Frequency and outcomes of blood products transfusion across procedures and clinical conditions warranting inpatient care: an analysis of the 2004 healthcare cost and utilization project nationwide inpatient sample database. Am J Med Qual 25: 289-296.
39. Trentino KM, Farmer SL, Swain SG, Burrows SA, Hofmann A, et al. (2015) Increased hospital costs associated with red blood cell transfusion. Transfusion 55: 1082-1089.
40. Hebert PC, Wells G, Martin C, Tweeddale M, Marshall J, et al. (1998) A Canadian survey of transfusion practices in critically ill patients. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. Crit Care Med 26: 482-7.
41. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, et al. (1999) A multi-centre, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian Critical Care Trials Group. N Engl J Med 340: 409-417.
42. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, et al. (2004) The CRIT Study: Anemia and blood transfusion in the critically ill: current clinical practice in the United States. Crit Care Med 32: 39-52.
43. Croce MA, Tolley EA, Claridge JA, Fabian TC (2005) Transfusions result in pulmonary morbidity and death after a moderate degree of injury. J Trauma 59: 19-23.
44. Whitson BA, Huddleston SJ, Savik K, Shumway SJ (2010) Risk of adverse outcomes associated with blood transfusion after cardiac surgery depends on the amount of transfusion. J Surg Res 158: 20-27.
45. Jagoditsch M, Pozgainer P, Klingler A, Tschmelitsch J (2006) Impact of blood transfusions on recurrence and survival after rectal cancer surgery. Dis Colon Rectum 49: 1116-1130.
46. Moore FA, Moore EE, Sauaia A (1997) Blood transfusion. An independent risk factor for post injury multiple organ failure. Arch Surg 132: 620-624.
47. Linkins LA, Dans AL, Col LKM, Bona R, Davidson BL, et al. (2012) Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: e495S-530S.
48. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, et al. (2010) Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 304: 1559-1567.
49. Bossola M, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, et al. (2005) Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg 241: 381.
50. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, et al. (2008) Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 248: 447-458.
51. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, et al. (2007) The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 63: 805-813.
52. Yazer MH, Deandrade DS, Triulzi DJ, Wisniewski MK, Waters JH (2016) Electronic enhancements to blood ordering reduces component waste. Transfusion 56: 564-570.
53. Hayakawa M (2017) Pathophysiology of trauma-induced coagulopathy: disseminated intravascular coagulation with the fibrinolytic phenotype. J Intensive Care 5: 14.
54. Martini WZ (2009) Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. J Trauma 67: 202-208.
55. Norfolk D (2013) 5th Handbook of Transfusion Medicine. United Kingdom Blood Services.
56. Park S, Hemmila M, Wahl W (2012) Early albumin use improves mortality in difficult to resuscitate burn patients. J Trauma Acute Care Surg 73: 1294-1297.
57. Ong YS, Samuel M, Song C (2006) Meta-analysis of early excision of burns. Burns 32: 145-150.
58. Barati M, Alinejad F, Bahar MA, Tabrisi MS, Shamshiri AR, et al. (2008) Comparison of WBC, ESR, CRP and PCT serum levels in septic and non-septic burn cases. Burns 34: 770-774.
59. Povoa P (2002) C-reactive protein: a valuable marker of sepsis. Intensive Care Med 28: 235-243.
60. Neely AN, Fowler LA, Kagan RJ, Warden GD (2004) Procalcitonin in pediatric burn patients: an early indicator of sepsis? J Burn Care Rehabil 25: 76-80.
61. Schuetz P, Albrich W, Mueller B (2011) Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med 9: 107.
62. Rosanova MT, Tramonti N, Taicz M, Martiren S, Basílico H, et al. (2015) Assessment of C-reactive protein and procalcitonin levels to predict infection and mortality in burn children. Arch Argent Pediatr 113: 36-41.
63. Jeschke MG, Finnerty CC, Kulp GA, Kraft R, Herndon DN (2013) Can we use C-reactive protein levels to predict severe infection or sepsis in severely burned patients? Int J Burns Trauma 3: 137-143.
64. Egea-Guerrero JJ, Martínez FC, Rodríguez RA, Bohórquez LA, Vilches AA, et al. (2015) The utility of C-reactive protein and procalcitonin for sepsis diagnosis in critically burned patients: A preliminary study. Plastic Surgery 23: 239-243.
65. Cabral L, Afreixo V, Almeida L, Paiva JA (2016) The Use of Procalcitonin (PCT) for Diagnosis of Sepsis in Burn Patients: A Meta-Analysis. PLoS ONE 11: e0168475.
66. Mann EA, Wood GL, Wade CE (2011) Use of procalcitonin for the detection

of sepsis in the critically ill burn patient: a systematic review of the literature. Burns 37: 549-558.

67. Housinger TA, Brinkerhoff C, Warden GD (1993) The relationship between platelet count, sepsis, and survival in pediatric burn patients. Arch Surg 128: 65-66.

68. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, et al. (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. Lancet 375: 463-474.

69. Maton A (1993) Human biology and health, Englewood Cliffs, NJ: Prentice Hall.

70. Yazer M (2016) AABB Red Blood Cell Transfusion Guidelines Something for Almost Everyone. The J Am Med Assoc 316: 1984-1985.

71. Lu R, Lin FC, Ortiz-Pujols SM, Adams SD, Whinna HC, et al. (2013) Blood utilization in patients with burn injury and association with clinical outcomes (CME). Transfusion 53: 2212-2221.

72. Schaden E, Kimberger O, Kraincuk P, Baron DM, Metnitz PG, et al. (2012) Perioperative treatment algorithm for bleeding burn patients reduces allogeneic blood product requirements, in Br J Anaesth 109: 376-381.

73. Ivona N, Novac M, Maria V (2011) Risk Factors Influencing the Oxidative Stress in Surgical Therapy of Skin Grafts. Curr Health Sci J 37: 1234-1242.