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Chee M. Chan
Georgetown University Medical Center, chee262@hotmail.com

Andrew F. Shorr
Georgetown University Medical Center

Jeremy G. Perkins
Walter Reed Army Medical Center

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Factors associated with acute lung injury in combat casualties receiving massive blood transfusions: A retrospective analysis☆,☆☆,★

Chee M. Chan MD, MPH[a,*], Andrew F. Shorr MD, MPH[a], Jeremy G. Perkins MD, FACP[b]

[a]*Pulmonary and Critical Care Department, Washington Hospital Center, Georgetown University Medical Center, Washington, DC 20010, USA*
[b]*Hematology and Oncology Department, Walter Reed Army Medical Center, Washington, DC, USA*

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Abstract

Purpose: We sought to determine if use of warm fresh whole blood (WFWB), rather than blood component therapy, alters rates of acute lung injury (ALI) in patients with trauma.

Materials and Methods: We retrospectively analyzed rates of ALI in patients undergoing massive blood transfusions while at a combat support hospital. Patients with ALI were compared with those not developing ALI with respect to demographics, trauma type, severity of illness, crystalloid volume given, and exposure to WFWB. Logistic regression was used to identify variables associated with ALI.

Results: The cohort included 591 subjects (mean age, 28 ± 8.1 years; male, 96.7%). Acute lung injury occurred in 11.2%, and 34.4% received WFWB. After adjusting for the type of trauma, severity of illness, and volume of crystalloid administered, WFWB remained independently associated with ALI (adjusted odds ratio [AOR], 1.06; 95% confidence interval [CI], 1.00-1.13). Nearly two thirds of persons with ALI never received WFWB; factors associated with the use of WFWB were also examined. Severity of illness (AOR, 1.18; 95% CI, 1.02-1.35), crystalloid volume (AOR, 1.12; 95% CI, 1.06-1.18), recombinant factor VIIa use (AOR, 1.94; 95% CI, 1.06-3.57), and US citizenship (AOR, 3.06; 95% CI, 1.74-5.37) correlated with WFWB use.

Conclusions: Warm fresh whole blood may be associated with an increased risk of ALI, but this is confounded by increased injury and crystalloid use in patients receiving WFWB.

☆ The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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* Corresponding author. Tel.: +1 202 877 7856; fax: +1 202 291 0386.
E-mail address: chee262@hotmail.com (C.M. Chan).

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1. Introduction

Traumatic injury represents a leading cause of critical illness, and respiratory failure is a common complication of severe trauma [1]. Approximately 2% to 4% of persons with trauma develop acute lung injury (ALI). More significantly, crude mortality rates in trauma-associated ALI approach 40% [2]. Appreciation of the potential factors contributing to ALI in trauma, therefore, represents a major focus of research.

Multiple factors help explain why individuals with trauma face an increased risk for ALI. The initial traumatic injury itself can promote a systemic inflammatory response facilitating the development of ALI [3]. Furthermore, focal chest trauma, whether blunt or penetrating, heightens the risk for ALI [4,5]. Similarly, the presence of hemorrhagic shock along with its treatment can potentiate ALI [1,6]. Thus, one aspect of trauma resuscitation, namely, blood transfusion, is independently linked to the development of ALI. Mechanistically, stored blood accumulates proinflammatory substances during storage even after leukoreduction, which may contribute to the development of ALI, independent of the presence of shock [7-11].

The correlation between packed red blood cell (pRBC) use and ALI suggests that a different strategy to trauma resuscitation might alter rates of ALI. The use of warm fresh whole blood (WFWB) is one potential alternative to pRBCs. Fresh blood lacks many of the factors that comprise the theoretical "storage lesion" found in stored pRBCs that have been associated with ALI [12]. Early studies of WFWB use suggest that it is a safe alternative in trauma resuscitation [13-15]. These prior analyses, though, have not explored specific complications associated with transfusion in trauma, nor have they addressed ALI after trauma. Furthermore, the absence of a mortality penalty related to the use of WFWB relative to other components such as apheresis platelets (aPLTs) does not preclude that WFWB itself might, nonetheless, increase morbidity or other complications.

We hypothesized that WFWB represents a safe option after trauma with respect to the potential for ALI. Specifically, we theorized that exposure to WFWB would decrease the risk for ALI in massive transfusion as compared with resuscitation with component therapy including pRBCs. To evaluate our hypothesis, we conducted a retrospective analysis of a large military trauma registry reflecting the US military experience in Iraq.

2. Materials and methods

2.1. Study overview

We retrospectively identified all patients with trauma (US military, coalition troops, contractors, Iraqi police/military, and Iraqi civilians) admitted to the Combat Support Hospital in Ibn Sina Hospital in Baghdad, Iraq, between January 2004 and December 2006. The specific cohort of interest, traumatic patients undergoing massive transfusion, has been described in part elsewhere [16]. The initial study creating the overall trauma registry at Ibn Sina was approved by the institutional review board at Brooke Army Medical Center in San Antonio, TX, and in accordance with the approved protocol. This de-identified subgroup analysis was exempted from institutional review board approval after review from the Office of Research at the Uniformed Services University of Health Sciences, Bethesda, MD.

During the study period, protocols that standardized the transfusion practice in trauma resuscitation existed [17]. At the Combat Support Hospital, physicians had access to various blood products including pRBCs, fresh-frozen plasma (FFP), and cryoprecipitate. Per the protocol, administration of blood products ensued within minutes of injury so as not to delay resuscitation efforts. All subjects in this cohort received pRBCs, and those given WFWB were transfused with a minimum 2 units of WFWB. These components were obtained almost exclusively from the United States via the Armed Services Blood Program Office. Warm fresh whole blood (collected and stored at 22°C for no longer than 24 hours) was donated by questionnaire-screened healthy volunteers no more frequently than every 8 weeks. Warm fresh whole blood units were nonleukoreduced, and most WFWB collected was transfused within 8 hours of collection [18]. Starting in November 2004, aPLTs were collected by certified apheresis technologists or technicians and performed strictly following the American Association of Blood Banks and US Food and Drug Administration guidelines using a mobile collection system (MCS+ 9000; Haemonetics, Braintree, Mass) and were stored for up to 5 days at 20°C to 24°C.

2.2. Subjects

We included patients undergoing massive transfusion in the current analysis. We defined *massive transfusion* as the receipt of 10 or more units of blood within 24 hours. We excluded the following: (1) patients treated initially at forward surgical units/local hospitals before transfer to Ibn Sina Hospital, (2) those who received their massive transfusion on a day other than on admission (after the first 24 hours), and (3) patients who died within 30 minutes from admission because WFWB required a minimum of 30 minutes to collect and process before transfusion. This latter group was excluded to control for potential survival bias.

2.3. End points and covariates

The development of ALI after massive transfusion served as our primary end point. The presence of ALI was based on discharge *International Classification of Disease* (*ICD-9*) codes: 518.82. Factors associated with the development of

ALI after massive transfusion served as a secondary end point. We recorded information regarding patient demographics (age, sex, race), initial vital signs, laboratory data, and mechanism of injury (eg, blunt vs penetrating). Disease severity was assessed via the revised Trauma Injury Severity Score (TRISS). The TRISS was calculated based on location of injury, age, physiologic characteristics, and type of trauma. Furthermore, we evaluated the types of blood products transfused and if the patient was given WFWB. To determine if there were any potential biases involved that may have driven preferential use of WFWB, we investigated variables independently linked to WFWB exposure as part of a tertiary, exploratory analysis.

Acute lung injury may be difficult to diagnose in patients with blunt trauma because chest contusion may mimic ALI. We therefore conducted a sensitivity analysis to address this concern by repeating our analyses after excluding patients of blunt trauma.

2.4. Statistics

Categorical variables were examined using the χ^2 test, whereas continuous variables were evaluated using the Student *t* test when normally distributed. The Fisher exact test was used for small sample sizes, and the Mann-Whitney *U* test was used for nonparametric variables, as appropriate. All tests were unpaired and 2 tailed, and a *P* value less than .05 was assumed to represent statistical significance.

Using the results from the univariate analysis, a multivariate logistic regression model was developed to determine patient characteristics and blood components associated with the occurrence of ALI. Covariates found to have a significant relationship with ALI with $P < .10$ on univariate analysis, and those found to affect the prevalence of ALI based on previous studies [2,19] were included in the model. Variables were assessed to address colinearity. Goodness of fit was assessed using the Hosmer-Lemeshow test.

A similar multivariate logistic regression model was developed to assess variables independently associated with the use of WFWB. To analyze this model, WFWB was converted from a continuous variable into a categorical variable, where in those who received any WFWB were compared with those who were never exposed to WFWB.

3. Results

The final cohort included 591 subjects (mean age, 28.0 ± 8.1 years; mean ± SD TRISS, 2.2 ± 2.2), and the overall mortality was 30.3%. Most of the cohort were men (96.7%) and experienced penetrating trauma wounds (92.6%). The following quantities were transfused in this study: 11 715 U of pRBCs, 933 U of WFWB, 7062 of FFP, and 4716 U of cryoprecipitate. All patients received RBCs, and approximately one fourth received WFWB. Acute lung injury developed in 11.2% of subjects; of these, 34% received WFWB transfusions. In contrast, among those who did not develop ALI, only 20% received WFWB transfusions ($P = .01$).

3.1. Factors associated with ALI

Baseline characteristics of those who developed ALI compared with those without ALI are documented in Table 1. Patients with ALI received more units of WFWB than individuals who did not develop ALI (mean, 3.0 vs 1.4; $P = .003$). However, increasing doses of WFWB did not correlate with the development of ALI. Also, more individuals experienced blunt trauma in the ALI group and received an average of 2.3 L more of crystalloid therapy ($P = .005$). The subjects did not differ with regard to severity of illness, physiologic and laboratory findings, and administration of other blood components or recombinant factor VIIa (rFVIIa).

In a multiple logistic regression model adjusting for multiple covariates (Table 2), the use of WFWB remained

Table 1 Comparison between those who did and did not develop ALI

	ALI	No ALI	*P*
Demographic characteristics			
Age (y), mean	28.9	27.9	.32
Sex, male (%)	98.5	97.5	.63
Trauma characteristics			
Injury Severity Index, mean	26.0	24.2	.26
Revised Trauma Score, mean	6.5	6.3	.66
TRISS, median [a]	2.3	2.9	.19
Wound, penetrating (%) [a]	83.3	94.3	.001
Physiologic parameters (on admission)			
Systolic blood pressure (mm Hg), mean	102.8	97.5	.26
Diastolic blood pressure (mm Hg), mean	56.6	54.2	.46
Heart rate (beats/min), mean	117.9	115.2	.48
Respiratory rate (breaths/min), mean	24.9	22.7	.10
Laboratory findings			
Hemoglobin (g/dL), mean	11.5	11.0	.11
Platelet count ($10^3/\mu$L), mean	263.5	253.6	.54
International normalized ratio, mean	1.7	1.8	.70
pH, mean	7.2	7.2	.78
Base deficit, mean	9.8	9.6	.86
Transfused blood products within 24 h of trauma			
WFWB (U), median [a]	3.0	1.4	.003
Red blood cells (U), mean	19.8	19.8	.98
Total RBC (U), RBC + WFWB	22.8	21.2	.36
FFP (U), mean [a]	13.4	11.8	.14
aPLTs (U)	1.2	1.4	.34
Other resuscitation measures			
Crystalloid use within 24 h (L), median [a]	11.4	9.0	.005
rFVIIa (%)	57.8	60.5	.68

[a] Variables included in logistic regression model (Table 2).

Table 2 Independent factors associated with the development of ALI

	AOR	95% CI	*P*
Whole fresh warm blood	1.06	1.00-1.13	.04
Wound, blunt	3.54	1.61-7.77	.002
Crystalloids	1.05	1.00-1.10	.04
FFP	0.99	0.96-1.03	.83
TRISS	1.03	0.89-1.18	.71

An AOR greater than 1 signified a higher risk for ALI. Thus, WFWB, crystalloid therapy, and blunt trauma wounds were associated with ALI.
[a]Hosmer-Lemeshow test ($P = .201$).

independently associated with the diagnosis of ALI. The adjusted odds ratio (AOR) related to ALI when WFWB was administered was 1.06 (95% confidence interval [CI], 1.00-1.13; $P = .044$). Other variables significantly associated with the development of ALI included the administration of crystalloids (AOR, 1.05; 95% CI, 1.00-1.10; $P = .040$) and the type of trauma, where blunt trauma conferred a higher risk (AOR, 3.54; 95% CI, 1.61-7.77; $P = .002$).

Because blunt chest trauma causes pulmonary contusions, which can be misdiagnosed as ALI, we conducted a sensitivity analysis excluding these patients. Our findings were similar in the penetrating trauma alone cohort where increasing WFWB (AOR, 1.08; 95% CI, 1.02-1.14; $P = .010$) and crystalloid (AOR, 1.06; 95% CI, 1.01-1.11; $P = .020$) administration correlated with the occurrence of ALI (Hosmer-Lemeshow test statistic = 0.299) [data otherwise not shown].

Table 3 Comparison of baseline characteristics between WFWB and non-WFWB groups

	WFWB	No WFWB	*P*
Demographic characteristics			
Age (y), mean	27.6	28.1	.56
Sex, male (%)	96.9	97.8	.53
Citizenship, United States (%) [a]	60.2	35.0	<.0001
Trauma characteristics			
Injury Severity Index, mean	27.5	23.5	.001
Revised Trauma Score, mean	6.0	6.5	.02
TRISS, median [a]	1.6	2.4	.001
Wound, penetrating (%)	92.9	93.1	.96
Physiologic parameters			
Systolic blood pressure (mm Hg), mean	92.2	99.6	.02
Diastolic blood pressure (mm Hg), mean	48.2	56.2	.001
Heart rate (beats/min), mean	113.1	116.1	.34
Respiratory rate (breaths/min), mean	23.0	23.0	.51
Temperature (°C), median [a]	36.3	36.4	.005
Laboratory findings			
Hemoglobin (g/dL), mean [a]	10.5	11.2	.007
Platelet count ($10^3/\mu$L), mean[a]	221.1	263.4	<.0001
INR, mean [a]	2.0	1.7	.003
pH, mean	7.1	7.2	<.0001
Base deficit (mEq/L), mean	11.8	9.0	<.0001
Transfused blood products within 24 h of trauma			
Red blood cells (U), mean	22.6	19.1	.05
FFP (U), mean	13.8	11.4	.23
aPLTs (U), mean [a]	1.1	1.5	<.0001
Cryoprecipitate (U), mean	11.0	7.2	.02
Other resuscitation measures			
Crystalloids (L), mean [a]	12.3	9.6	<.0001
rFVIIa (%) [a]	67.2	58.3	.07
Mortality			
48-h mortality (%)	21.1	22.8	.69
30-d mortality (%)	41.5	45.6	.47

INR indicates international normalized ratio.
[a] Variables included in logistic regression model (Table 4).

3.2. Factors associated with WFWB use and its prevalence

Approximately 66% of those who developed ALI never received WFWB. The characteristics of those given WFWB vs those resuscitated with pRBCs are shown in Table 3. More patients who received WFWB were US citizens and were more severely ill. Despite these differences, mortality was similar between the 2 groups (41.5% in the WFWB group vs 45.6% in the non-WFWB group, $P = .466$).

Table 4 reveals that severity of illness was significantly associated with WFWB administration, even after adjusting for covariates (AOR, 1.18; 95% CI, 1.02-1.35; $P = .021$). Furthermore, US citizenship (AOR, 3.06; 95% CI, 1.74-5.37; $P < .0001$), use of rFVIIa (AOR, 1.94; 95% CI, 1.06-3.57; $P = .032$), and increasing use of crystalloid therapy (AOR, 1.12; 95% CI, 1.06-1.18; $P < .0001$) were associated with the use of WFWB. Conversely, the transfusion of aPLT was linked with fewer transfusions of WFWB (AOR, 0.72; 95% CI, 0.60-0.87; $P = .001$).

In the stratified analysis, the prevalence of ALI in those who received any WFWB was approximately 18.0% compared with only 9.3% in those who did not receive

Table 4 Independent factors related to the use of WFWB

	AOR	95% CI	*P*
TRISS	1.179	1.02-1.35	.02
aPLTs	0.720	0.60-0.87	.001
Crystalloids	1.122	1.06-1.18	<.0001
rFVIIa	1.943	1.06-3.57	.03
Citizenship, United States	3.058	1.74-5.37	<.0001
Temperature	0.881	0.71-1.10	.26
Hemoglobin	0.901	0.81-1.01	.07
INR	0.943	0.74-1.20	.63
Platelets	0.997	0.99-1.00	.09

INR indicates international normalized ratio.
An odds ratio greater than 1 demonstrated an increased rate of exposure to WFWB. Severity of illness (TRISS), use of aPLTs, crystalloids, and rFVIIa were all associated with WFWB use.
[a]Hosmer-Lemeshow test ($P = .254$).

Table 5 Comparing characteristics associated with ALI in patients receiving WFWB and among those who are WFWB naïve

Prevalence of ALI (%)	WFWB experienced (18.0)			WFWB naïve (9.3)		
	ALI	No ALI	*P*	ALI	No ALI	*P*
Demographic characteristics						
Age (y), mean	28.7	27.4	.47	29.0	28.0	.42
Sex, male (%)	100.0	96.2	.34	97.7	97.9	.94
Type of trauma, penetrating (%) [a]	91.3	93.3	.74	79.1	94.5	.001
Trauma characteristics						
Injury Severity Index, mean	28.8	27.2	.58	24.4	23.4	.60
Revised Trauma Score, mean	6.3	5.9	.39	6.5	6.5	.80
TRISS, median [a]	1.7	1.6	.74	2.4	2.4	.85
Physiologic parameters						
Systolic blood pressure (mm Hg), mean	95.7	91.4	.61	106.6	98.9	.19
Diastolic blood pressure (mm Hg), mean	48.5	48.1	.93	60.7	55.7	.21
Heart rate (beats/min), mean	116.9	112.2	.49	118.4	115.9	.59
Respiratory rate (breaths/min), mean	26.7	22.2	.09	23.9	22.9	.49
Laboratory findings						
Hemoglobin (g/dL), mean	11.5	10.3	.06	11.6	11.1	.31
Platelet count ($10^3/\mu$L), mean	212.3	223.0	.67	288.4	260.8	.16
INR, mean	2.2	2.0	.41	1.5	1.7	.43
pH, mean	7.1	7.2	.33	7.2	7.2	.41
Base deficit (mEq/L), mean	13.4	11.5	.29	7.9	9.1	.29
Transfused blood products within 24 h of trauma						
Red blood cells (U), mean	22.7	22.6	.96	18.2	19.1	.55
FFP (U), mean	14.5	13.6	.71	12.7	11.3	.23
aPLTs (U)	0.9	1.2	.59	1.3	1.5	.62
Other resuscitation measures						
Crystalloid use (L), mean [a]	13.5	12.0	.40	11.5	9.4	.02
rFVIIa (%)	63.6	68.0	.69	54.8	58.6	.63
Outcome measures						
30-d mortality (%)	45.5	40.5	.67	50.0	45.1	.62

INR indicates international normalized ratio.
[a] Variables included in logistic regression model (Table 6).

WFWB. Within the WFWB group, there were no significant risk factors associated with the development of ALI (Table 5). However, in the subgroup that did not receive any WFWB, the occurrence of ALI was again found to be related to crystalloid therapy and type of trauma wound (Table 6).

4. Discussion

This retrospective analysis of a large group of patients with trauma requiring massive blood transfusions documents that the overall occurrence of ALI was low, but the transfusion of WFWB may be associated with its development. Our results suggest that WFWB transfusion might increase morbidity when massive transfusion is required. This relationship persisted even after controlling for selected other risk factors for ALI, such as severity of illness. In short, we cannot exclude the potential for harm related to WFWB use.

Prior studies have evaluated the relationship between ALI and the transfusion of various blood products. For example, in a recent nested case-control study consisting of 2024 intensive care unit patients who had a length of intensive care unit stay of more than 48 hours, 109 individuals developed ALI [20]. When compared with controls, the volume of platelets and plasma transfused was associated with ALI in a univariate analysis, but this association disappeared in the multivariate analysis. This contrasts prior epidemiologic studies that implicated FFP, rather than other blood products, as an independent risk factor for ALI [2,19,21]. In a

Table 6 Independent risk factors associated with ALI in those naïve to WFWB

	OR	95% CI	*P*
Wound, blunt	5.48	2.25-13.38	<.0001
TRISS	1.01	0.85-1.21	.88
Crystalloids	1.07	1.01-1.13	.02

[a]Hosmer-Lemeshow test ($P = .772$).

retrospective analysis focusing specifically on patients with trauma, the authors noted a trend toward increased respiratory failure in patients who received WFWB (7%) compared with component therapy (3%, $P = .08$) [13]. In addition, in a prospective observational study, the development of ALI in patients with trauma was associated with increasing transfusion of blood products. Using both the strict American-European Consensus Conference criteria for ALI and an equivocal definition where chest radiographs were difficult to interpret yielded the same findings that increasing units of blood were independently associated with ALI [22].

Our findings add to prior analyses exploring the effect of blood product transfusion on the development of ALI. Specifically, our findings are novel in that we document that both WFWB and crystalloid may be linked to ALI. The correlation between crystalloid therapy and ALI after trauma confirms several earlier reports examining damage control resuscitation [23]. In multiple animal studies, preferential administration of crystalloid therapy during hemorrhagic shock exacerbates the systemic inflammatory response, thus potentiating the risk for ALI [9,24]. Furthermore, aggressive intravenous fluid replacement interferes with hemostatic mechanisms that will exacerbate blood loss [23]. In combination, our study supports these prior studies and suggests that crystalloids should be judiciously administered during the resuscitation process.

No prior analyses have explored how the use of WFWB alters rates of ALI. Warm fresh whole blood has received attention as an alternate to component therapy because in some austere environments, select components of blood, such as aPLT, may not be readily available. Similarly, some suggest that WFWB may offer a relative safety advantage because it has not undergone processing and storage. Although our data suggest that WFWB may contribute to ALI in ways similar to other transfusion components, the fact that approximately 66% of individuals who developed ALI were never exposed to WFWB underscores that one cannot draw a firm causal connection between WFWB and ALI. The relationship between WFWB and ALI is, thus, likely weak, irrespective of the results of the logistic regression. On the one hand, WFWB transfusion may represent a necessary but, not of and within itself, sufficient step in the evolution of ALI after massive transfusion. As a corollary, eliminating its use would not necessarily lead to a decrease in the incidence of ALI in trauma. Conversely, WFWB was administered to sicker patients, and despite our efforts, we likely could not completely adjust for severity of illness as a potential confounder. In fact, more subjects in this subset also received rFVIIa, indirectly suggesting more extensive bleeding. Thus, we cannot exclude that the occurrence of ALI in this population may be confounded by issues related to severity of illness incompletely captured through TRISS. Indeed, the trauma itself may be the culprit event that triggers the evolution of ALI, and at worse, WFWB transfusions, or any blood product exposure, simply fuel the fire [10].

There are several mechanisms by which WFWB could precipitate ALI. First, the relatively large volume of plasma in WFWB contains leukocyte antibodies, which have been demonstrated to be associated with ALI [25]. Approximately 70% of individuals who receive WFWB during cardiac surgery also have transfusion of living leukocytes. Forty percent had leukoagglutinin formation, and another 30% developed incomplete antibodies. These fresh living leukocytes were distinct from leukocytes in stored blood and possess intact transplantation antigens [11]. Second, transfusion-associated microchimerism may occur where allogeneic leukocytes replicate in the host. Clinical manifestations of the chimerism can cause a graft-vs-host disease or an autoimmune process that precipitates ALI. Transfusion-associated microchimerism occurs in nearly 50% of transfused severely injured patients. More concerning, leukoreduction does not affect the likelihood of its occurrence, and it happens more frequently with younger fresher blood. These possibilities could explain the higher incidence of ALI in those who received WFWB in our cohort [26]. In essence, both WFWB and component therapy mechanistically share features that may potentiate the evolution of ALI.

Demonstrating the possibility that WFWB may cause harm illustrates the necessity to carefully study WFWB and future resuscitation measures. In the same vein, our observations indicate that the emergence of advanced blood products such as freeze-dried plasma or frozen platelets mandates that clinical trials of these products, as multiple regulations currently require, systematically collect information regarding the possible morbidity associated with ALI. Our results should not be interpreted as a call to prevent further use of WFWB. Rather, it is likely that all blood products, whether WFWB or component therapy, "fuel the fire" and foster the evolution of ALI. Similarly, the true contribution of WFWB to the burden of ALI after trauma is likely limited, given the frequency with which ALI is seen in those who are never exposed to WFWB.

Our study has several unique attributes. The cohort for this study predominantly consisted of patients who had penetrating trauma wounds as opposed to blunt trauma injuries. This distinction affords us the ability to examine lung injury because it pertains to penetrating wounds. Because blunt trauma is certainly easier to confuse with ALI because of the presence of pulmonary contusions, specifically studying the effects of various types of traumatic injuries helps us to control for confounding due to type of injury. That WFWB remains linked to ALI development after excluding those who experienced blunt trauma underscores the possible relationship between WFWB and ALI. This study is also unique because of the effort to standardize the approach to manage patients with trauma requiring massive blood transfusions. Treatment of these patients was standardized and was minimally influenced by the physicians employed or the patient's characteristics. In addition, a standard approach to harvesting and testing WFWB was available to ensure timely transfusion of fresh blood.

There are several limitations to this study. First, as a retrospective study, it is subject to many forms of bias. Collection of data was not specific for this study and may have been missing or misclassified. However, to minimize this, other databases were searched to reconcile missing or discrepant data. Second, we did not assess if the use of RBCs contributed to the progression to lung injury and, therefore, did not control for the effects of transfusion-related ALI (TRALI) as a potential cause for ALI. The incidence of TRALI is approximately 1 in every 5000 blood components transfused [15]. Given the number of blood and blood products transfused in this cohort, TRALI probably did not significantly contribute as a cause for ALI. The incidence of TRALI would be low and would not have affected our analysis. Third, the diagnosis of ALI was based on discharge *ICD-9* coding, which is therefore dependent on the physician's astuteness at diagnosing this disease process. As a result, misclassification bias could have occurred. In fact, prior evidence suggests that 8% to 40% of cases are misdiagnosed based on *ICD-9* coding, depending on the diagnosis [27-29]. However, for ALI specifically, systematically auditing charts to determine the ability of *ICD-9* coding to identify the true incidence of ALI yields a sensitivity ranging from 79% to 88% and a specificity of 98% to 99% [30]. Fourth, the diagnosis of ALI was relatively uncommon, occurring in only 11.2% of the entire cohort. Thus, this study may be underpowered to truly assess risk factors associated with ALI. This small sample size further limits our ability to determine whether the development of ALI in this population has any affect on mortality or if increasing exposure of WFWB truly affected the development of ALI. Finally, most subjects were young men who underwent penetrating trauma injuries. As such, the results of this study may not be generalizable to other patients with trauma who need massive transfusion. However, the subjects were relatively young and healthy when they acquired their trauma-induced injuries, and the diagnosis of ALI was presumably less confounded by other comorbid conditions or disease processes, which would only exaggerate this correlation.

5. Conclusion

Fresh whole blood may be associated with an increased risk of ALI in those who have traumatic injuries requiring massive transfusion, but this is confounded by increased injury and crystalloid use in patients receiving WFWB. The risk/benefit ratio of WFWB must be carefully weighed before its administration. Although the use of WFWB is lifesaving when other components are not available, its potential to increase morbidity must also be considered. Findings from this hypothesis-generating study can be used to facilitate further research in this field. To clarify the relationship between WFWB and the development of ALI, a larger prospective study to examine whether increasing exposure to WFWB affects the risk for ALI would be warranted. Unfortunately, a randomized controlled trial would not be feasible because limiting such therapy to critically ill patients with trauma would violate equipoise. In addition, diagnosing ALI prospectively would decrease potential confounding from misclassification bias. Certainly, given the importance of this lifesaving therapy, research elucidating the potential harms associated with WFWB administration must be prioritized to adequately prevent and treat potential complications.

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