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PRESTORAGE LEUKOREDUCTION ABROGATES THE DETRIMENTAL EFFECT OF AGING ON PACKED RED CELLS TRANSFUSED AFTER TRAUMA: A PROSPECTIVE COHORT STUDY

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Abstract

Background—We sought to prospectively duplicate our retrospective findings showing prestorage leukoreduction (PS-LR) blunts the detrimental effect of aging on banked packed red blood cells (PRBCs) transfused after injury.

Methods—Over 19 months, trauma patients transfused > 4 units PRBCs and surviving at least 24 hours were followed. The age of each unit was collected.

Results—The cohort consisted of 153 patients. All models showed no association between advancing blood age and the likelihood of developing multiorgan dysfunction syndrome (MODS) or infections regardless of whether mean age of blood was analyzed as a continuous variable, as a percentage of blood received which was <14 days old, or as a dichotomized value above or below 14 days old.

Conclusions—This prospective study duplicates our retrospective findings of an abrogation of the detrimental effects of advancing mean PRBC age on outcomes after trauma by performing PS-LR.

WORDS FOR INDEXING

Trauma; leukoreduction; outcomes; transfusion

INTRODUCTION

The decision to transfuse a patient with packed red blood cells (PRBCs) should balance the beneficial effects of increasing oxygen carrying capacity against the well known immunomodulatory effects that accompany this intervention [1–8]. A strong body of evidence implicates the length of time that a given unit of blood sits in storage after donation as a cause of these immune-modulating properties. Purdy et al demonstrated that septic patients who died had received blood which was a median of 8 days “older” (ie, PRBC units that had in the blood bank for 8 days longer) than a comparison cohort of survivors [9]. Further, Zalen and colleagues showed that trauma patients who developed multiple organ failure received blood that was an average of 6 days older than similarly injured patients in whom the syndrome was not seen [10]. Finally, Offner and colleagues demonstrated that each unit of blood greater than 14 days old received increased the odds of an infectious complication by 12% [11].

One hypothesis for the mechanism behind this storage lesion centers on the role of leukocytes in the donor units. Previous work has suggested that these leukocytes exert a variety of immunomodulatory effects on the recipient in a magnitude that is proportional to the length of time the donor unit is stored [12–16]. The process of prestorage leukoreduction (PS-LR) removes 99.9% of donor white blood cells, and would presumably abrogate any immunomodulatory effect resulting from donor leukocyte storage and transfusion. Earlier efforts by our group demonstrated that PS-LR did not impact mortality rates in trauma patients, but it and others examining the effects of PS-LR on outcomes in transfused trauma patients did not control for the age of the units transfused [17–19]. Given the importance of this confounder, our group subsequently examined the relationship between PS-LR and the age effect of transfused blood in trauma patients in a retrospective fashion [20]. We found that PS-LR blunted the detrimental effect of aging on banked PRBCs, and that the receipt of

PS-LR blood with an older mean age was associated with a protective effect on survival in some analyses. These results were at odds with another retrospective study of this question in which the effect of older blood was examined on a unit-by-unit basis [21]. We therefore sought to duplicate our results with a prospective cohort study in which we would perform both analyses. To our knowledge, this effort is the first prospective investigation in trauma patients to examine this issue.

METHODS

Study Design and Patients

This prospective cohort study was approved by the Institutional Review Board, and due to its observational nature a waiver of consent was granted. Our institution practiced universal PS-LR on all blood products throughout the time period of the study. Patient accrual took place at our urban Level I trauma center for a total of 19 months. Inclusion criteria were all trauma patients who: 1) were transfused at least four units packed red blood cells (PRBCs) within their first 24 hours in the hospital, 2) survived 24 hrs post-injury, and 3) were >18 yrs old. Pregnant patients and prisoners were excluded as they constituted vulnerable populations. Demographic and physiologic data were collected, as were the total amount of PRBCs transfused in the first 24 hrs, age in days of each unit transfused, and outcomes.

Dependent Variables

The primary outcomes were development of multiple organ dysfunction syndrome (MODS) and infectious complications. Each outcome was a binomial variable operationally defined as the presence or absence of the condition. In this study, we modeled the probability of the presence of the outcome (death, MODS, and infectious complications, respectively).

A modified Marshall score [22] identical to that used by the National Institute of General Medical Science's "Inflammation and the Host Response to Injury" project (the "Glue Grant") was used to calculate the rate of MODS. This modification consists of dropping the neurologic component of the score, starting to calculate scores 48 hours post-injury, and using a score of six or greater as diagnostic of MODS.

Infectious complications were defined as follows: ventilator associated pneumonia (VAP) was diagnosed using quantitative bronchoalveolar lavage specimens of $\geq 10^4$ colony forming units (CFU) and urinary tract infection (UTI) was diagnosed with a positive culture of $\geq 10^5$ CFU. Wound infections were defined as cellulitis, erythema, or drainage requiring opening of a skin incision and/or the initiation of antibiotic therapy. Cavitary abscess, empyema, and mediastinitis were diagnosed after radiographic findings were clinically correlated with reoperative findings or percutaneous drainage. Catheter-related blood stream infections were diagnosed by peripheral blood cultures and a catheter tip growing an identical organism, while bacteremia was diagnosed by a non-*S. epidermidis* positive peripheral blood culture.

Independent Variables and Covariates

The primary independent variables were measured in four ways. First, mean age of blood was measured in days as a continuous variable. Second, the absolute number of PRBC units <14 days old as well as the total number of PRBC units transfused were counted for each patient. The percentage of blood transfused which was <14 days old was entered into the model as a continuous independent variable for each patient. Mean age of blood was also dichotomized as \geq or < 14 days old (with <14 days as the reference group). Finally, mean age of blood for each patient was dichotomized as \geq or < 21 days old (with <21 days as the reference group). Prospectively maintained covariates included total units of PRBCs

transfused in the first 24 hours, patient age, Injury Severity Score (ISS) and Head Abbreviated Injury Score (AIS).

Data Analysis

Multiple logistic regression was used to estimate the adjusted odds of each outcome (MODS and infectious complications, respectively) with all covariates included in each model along with each respective independent variable. In model 1, mean age of blood was entered as a continuous independent variable. In model 2, the percentage of all PRBC units transfused which were <14 days old was entered as a continuous independent variable. In model 3, mean age of blood was entered after being dichotomized at 14 days as per the conventions of the field. The MODS and infectious complications analyses were also run with an additional analysis in which the age of blood was entered after dichotomization at 21 days. Models 2 and 3 were also repeated using mean age of blood as a binary indicator dichotomized at 21 days. Models 1–3 were conducted separately for each outcome and the 95% profile likelihood ratio confidence intervals (CI) were calculated for the Odds Ratios (OR). The likelihood ratio Chi-square statistic was used to test for a significant association between each independent variable/risk factor and each outcome. The area under the curve (AUC) for each multiple logistic regression model was calculated.

The Kaplan-Meier method of survival analysis was used to compare the time-to-first infection for patients with MODS vs. those without MODS. The hazard ratio was also estimated. The Logrank test was used to compare the two curves. As part of the Kaplan-Meier analysis, right-censoring was used in the current study. Right-censoring occurred when a patient completed the study by dying or being discharged without an infection.

We performed all statistical analyses using SAS 9.2 (SAS Institute, Inc., Cary, NC). The level of significance for all tests was set at $\alpha = .05$ (two-tailed) and p values were left unadjusted for multiple testing.

RESULTS

Table 1 demonstrates the demographic characteristics for the 153 patient cohort. The cohort was severely injured with a mean ISS of 25.9 ± 15.4 and a mean transfusion burden of 9.9 ± 9.0 units of PRBCs. Patients in whom MODS developed were found to be significantly more severely injured, had longer ICU and hospital stays, required higher volumes of transfusion in the first 24 hours, and had higher mortality (Table 2). Similarly, patients who developed at least one infectious complication were found to be more severely injured with longer ICU and hospital stays (Table 3). Of the 57 patients developing an infectious complication, 40.4% developed more than one. VAP and UTI were the most common infectious complication seen (Table 4).

Overall, 63.4% of the patients in the current study were right-censored. About 87.6% of the patients without MODS were right-censored, whereas about 12.4% of those with MODS were right-censored.

The Kaplan-Meier analysis revealed that the two curves of time-to-infection differed significantly between patients with MODS vs. those without MODS [$\chi^2(1) = 6.35, p=.0118$]. Figure 1 displays the survival curves and indicated that the probability of no infection was greater across the study for patients without MODS than for those with MODS. The median time to first infection was 28 days for patients without MODS and 9 days for those with MODS.

The Hazard Ratio indicated that patients with MODS had a significantly greater risk of infection than those without MODS (hazard ratio = 2.04, 95% CI = 1.00 to 4.13, $p < .05$). The hazard of infection for those with MODS was about 2 times greater than the hazard of infection for those without MODS.

For the MODS analysis, increasing ISS was found to be significantly associated with a higher likelihood of developing MODS through all analyses, as was increasing total amount of blood transfused in the analysis of dichotomization at 14 days and the analysis of the percentage of transfused blood <14 days old was (Table 5). Similarly, when conducting the analysis for infectious complications increasing ISS was found to be significantly associated with higher rates of infectious complications through all analyses (Table 6).

No significant relationship between age of blood and the development of MODS or infectious complications were seen in any of the analyses (Figure 2). The AUCs were 0.75 for the MODS model, and 0.72 for the infectious complications model.

DISCUSSION

Our results suggest that PS-LR seems to blunt the detrimental effects of the known PRBC storage lesion on MODS and infectious complications in transfused trauma patients. Further, the direction of most of the signals implies that the transfusion of older PS-LR products may actually be protective for these end points.

Of the many confounders that have muddled efforts to ascertain the true interaction between the process of PS-LR and the effects of aging on transfused blood, two have been the most problematic: whether there is a threshold for an effect, and if so how to separate that threshold from the overall transfusion burden[21]. The following example will illustrate this point. Let us suppose that PS-LR has no impact on the detrimental effects of storage time on banked PRBCs. If two injured patients are simultaneously transfused, and one patient received 10 units of younger, fresher PS-LR blood while the other received 9 units of young blood and 1 unit of older blood, would the age effect manifest itself? Skeptics of PS-LR's effects would argue that single unit of older blood "primes" the immune system, and exerts an effect that would independently contribute to a poorer outcome than the patient who received 10 units of all younger, fresher blood. Further, they would argue that using the mean age of blood is inappropriate because it diminishes the importance of this one outlier unit, and that the analysis should be conducted looking at the absolute number of older units that are transfused. What makes this method of analysis problematic in its own right is that it in turn discounts the importance of the overall transfusion burden since it treats a patient who received three units of blood, all of which were old, no differently from a patient who received three older units out of a total of 10. Our investigation sought to address this conundrum by performing an analysis in which the number of older units was expressed as a percent of the total transfusion burden, and then entering this value into the logistic regression model as a continuous variable (maintaining its continuous metric properties). By doing so, we feel that we have optimally controlled for any potential threshold effect as well as the overall transfusion burden in the best manner possible short of a randomized controlled trial. Unfortunately, neither our study nor the other large investigation dealing with this question [21] had large enough numbers of patients who received transfusions of exclusively young or old blood to be able to draw meaningful conclusions about the presence or absence of a threshold effect. Given blood bank practices of releasing older blood first to prevent wastage, it is unlikely that these studies will be done outside the auspices of a large, funded, multi-institutional endeavor. Short of that strength of evidence, however, we feel that investigations centered around a unit-by-unit analysis must be buttressed by some effort to control for the effect of the overall transfusion burden.

The mechanism behind an abrogation of the detrimental effect of aging by the process of PS-LR is straightforward if true. Given the evidence supporting the harmful effects of donor leukocytes that have been allowed to age [12–15], their removal followed by a resultant *decline in risk to baseline* makes intuitive mechanistic sense. Interestingly, the direction of most of the signals point to that of a protective effect to older blood after the process of PS-LR (albeit in a nonsignificant manner). This direction was also seen in our retrospective study of this same topic, and the previously stated explanation would not account for PS-LR conferring a protective effect on outcomes rather than simply bringing an increased risk back down to baseline. It is possible that the process of PS-LR causes an activation of donor leukocytes or other cellular elements exposed to the filter which in turn causes a release of inflammatory mediators into the donor unit. If these elements were to degrade over time, one would theoretically see patients transfused with fresher PS-LR blood be exposed to higher concentrations of these immunomodulatory mediators and consequently have higher rates of immune-based complications. Patients transfused with older blood in which these mediators have denatured in a time-dependent manner would be transfused with lower concentrations of these agents and consequently have better outcomes. If true, the corollary to this mechanism is that the optimal transfusion product would be fresh, non-leukoreduced blood as this would avoid the known problems of prolonged storage on donor leukocytes as well as our hypothesized proinflammatory effect of filtration.

This study is not without its limitations. First, transfusions of fresh frozen plasma (FFP) and platelets were not tracked. The ability of these products to have their own immunomodulatory properties is coming to be appreciated, and this is a potential confounder. Further, we chose not to analyze all-cause deaths. This was felt to be too problematic methodologically as neurologic deaths lie outside the putative immunologic pathways that PSLR and the age effect exert their influence. Finally, our limited sample size precluded us from being able to analyze patients who received exclusively young blood in order to further investigate the threshold effect more rigorously.

CONCLUSION

This prospective study duplicates our group's retrospective findings of an abrogation of the detrimental effects of advancing mean PRBC age on MODS and infectious complications. Given that the direction of the signal across most analyses suggests that a small protective effect may be conferred on advancing mean PRBC age by PS-LR as well, further studies are justified.

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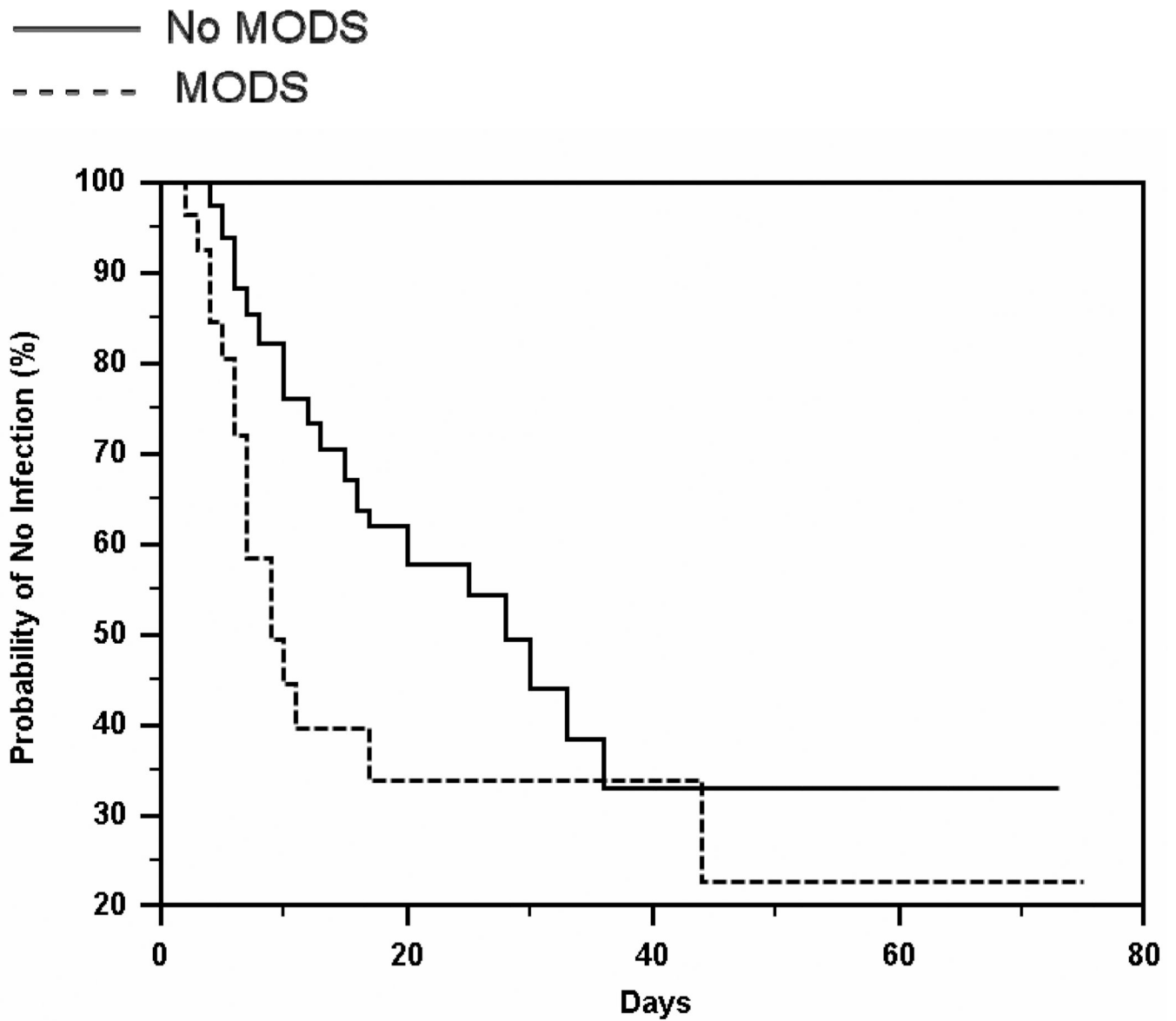


Fig 1. Time to infection for patients with and without MODS
 MODS patients had a significantly higher probability of infection ($p=0.012$) with a risk of slightly more than twice that of patients without MODS.

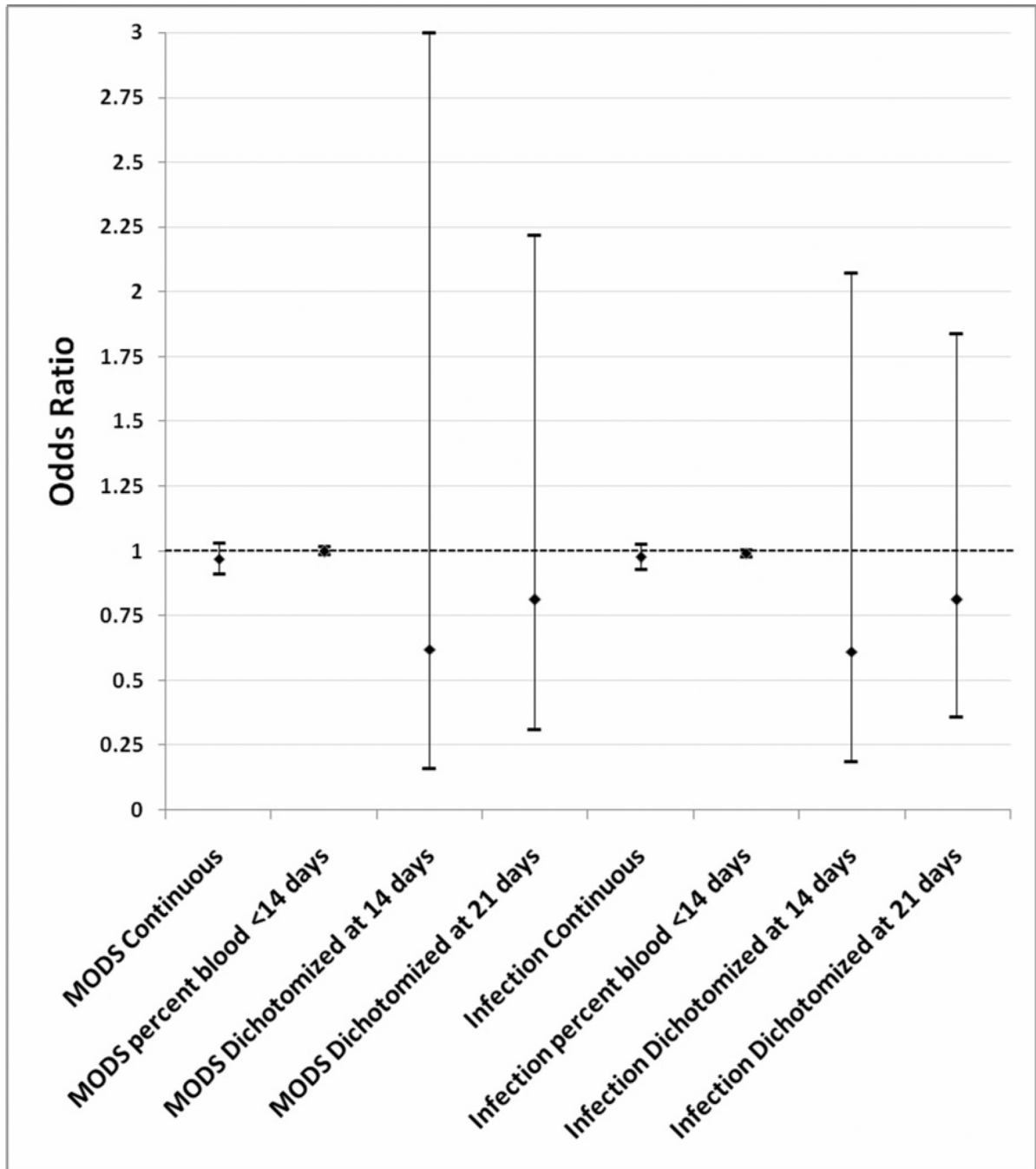


Fig 2. Odds ratios of MODS and infectious complications with 95% Confidence Intervals in the logistic regression models

PRBC= Packed Red Blood; ISS= Injury Severity Score; AIS= Abbreviated Injury Score

Table 1

Demographic characteristics of the cohort.

n	153
Age (years)	40.0 ± 16.4
Male/female (%)	78.4/21.6
Blunt/penetrating (%)	69.9/30.1
ISS	25.9 ± 15.4
PRBC (units)	9.9 ± 9.0
Mortality	11%
MODS	18%
Infectious complications	37%

ISS= Injury Severity Score; PRBC= Packed Red Blood Cell; AIS= Abbreviated Injury Score; MODS= Multiple Organ Dysfunction Score. All values are means ± SD

Table 2

Demographic characteristics of patients with and without MODS.

	MODS (n=28)	No MODS (n=125)	p value
Age	44.7 ± 17.1	39.1 ± 15.8	0.10
Blunt/penetrating (%)	85.7/14.3	67.9/32.1	0.06
Male/Female (%)	78.6/21.4	79.4/20.6	0.92
Injury severity score	32.9 ± 14.6	25.1 ± 15.1	0.01
Head AIS	1.4 ± 1.9	1.5 ± 1.9	0.81
Chest AIS	3.1 ± 1.5	2.1 ± 1.9	0.01
Abdominal AIS	2.2 ± 1.4	1.8 ± 1.6	0.22
First base excess	-9.7 ± 5.4	-8.2 ± 5.4	0.19
First lactate	4.4 ± 1.9	4.0 ± 2.5	0.44
ICU Length of stay	14.8 ± 9.6	8.1 ± 11.0	0.003
Hospital Length of stay	37.5 ± 43.7	21.9 ± 20.4	0.005
Mortality (%)	32.1	8.4	0.0003
PRBCs in first 24 hrs	13.5 ± 8.5	9.4 ± 9.0	0.03

AIS=Abbreviated Injury Score; ICU=Intensive Care Unit; PRBCs=Packed Red Blood Cells

Table 3

Demographic characteristics of patients with and without infectious complications.

	Infection (n=57)	No Infection (n=96)	p value
Age	41.5 ± 15.8	39.6 ± 17.1	0.50
Blunt/penetrating (%)	82.5/17.5	63.5/36.5	0.01
Male/Female (%)	75.4/24.6	80.2/19.8	0.49
Injury severity score	32.3 ± 14.3	22.7 ± 14.9	0.0003
Head AIS	1.9 ± 2.0	1.1 ± 1.8	0.002
Chest AIS	2.7 ± 1.7	1.9 ± 1.9	0.002
Abd AIS	2.3 ± 1.6	1.6 ± 1.5	0.01
First base excess	-7.6 ± 4.3	-9.0 ± 6.1	0.13
First lactate	3.9 ± 1.7	4.2 ± 2.8	0.55
ICU Length of stay	16.2 ± 14.7	5.1 ± 5.0	<0.0001
Hosp Length of stay	40.5 ± 34.5	15.2 ± 14.7	<0.0001
Mortality (%)	8.8	13.5	0.38
PRBCs in first 24 hrs	9.6 ± 6.8	10.1 ± 9.9	0.72

AIS=Abbreviated Injury Score; ICU=Intensive Care Unit; PRBCs=Packed Red Blood Cells

Table 4

Type and frequency of infectious complications.

Infection type	Infectious episode								
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Ventilator associated pneumonia	24	5	5	2	2	1	1	-	-
Urinary tract infection	19	9	5	2	1	1	1	2	-
Wound infection	9	6	2	1	2	1	1	-	-
intraabdominal abscess	-	1	1	-	-	-	-	-	-
Line infection	1	1	-	-	-	-	-	-	1
Other soft tissue	2	-	1	-	-	-	-	-	-
Sepsis	2	2	-	1	-	-	-	-	-
Other	-	1	1	-	-	-	-	-	-

Table 5

MODS analysis by model type.

Variable	Odds ratio	95% Confidence Interval
Mean PRBC age as a continuous variable	0.969	0.910 – 1.030
Number of transfused PRBC units	1.044	0.997 – 1.095
Patient age	1.028	0.999 – 1.058
ISS	1.046	1.011 – 1.085
Head AIS	0.868	0.644 – 1.147
Percentage of PRBC units <14 days old	0.999	0.984 – 1.017
Number of transfused PRBC units	1.048	1.001 – 1.100
Patient age	1.026	0.998 – 1.056
ISS	1.044	1.010 – 1.083
Head AIS	0.863	0.643 – 1.137
Percentage of PRBC units <21 days old	0.997	0.985 – 1.008
Number of transfused PRBC units	1.046	0.999 – 1.097
Patient age	1.027	0.999 – 1.057
ISS	1.045	1.010 – 1.083
Head AIS	0.869	0.645 – 1.146
PRBC age dichotomized at 14 days old	0.621	0.159 – 3.076
Number of transfused PRBC units	1.048	1.002 – 1.099
Patient age	1.027	0.998 – 1.057
ISS	1.046	1.011 – 1.085
Head AIS	0.858	0.639 – 1.131

ISS= Injury Severity Score; PRBC= Packed Red Blood Cell; AIS= Abbreviated Injury Score; MODS= Multiple Organ Dysfunction Score.

Table 6

Infectious complications analysis by model type.

Variable	Odds ratio	95% Confidence Interval
Mean PRBC age as a continuous variable	0.976	0.927 – 1.026
Number of transfused PRBC units	0.981	0.932 – 1.025
Patient age	1.013	0.990 – 1.038
ISS	1.043	1.013 – 1.077
Head AIS	1.087	0.864 – 1.361
Percentage of PRBC units <14 days old	0.992	0.979 – 1.006
Number of transfused PRBC units	0.981	0.933 – 1.024
Patient age	1.012	0.989 – 1.036
ISS	1.044	1.014 – 1.077
Head AIS	1.086	0.865 – 1.358
Percentage of PRBC units <21 days old	0.995	0.986 – 1.005
Number of transfused PRBC units	0.980	0.931 – 1.024
Patient age	1.013	0.990 – 1.038
ISS	1.043	1.013 – 1.077
Head AIS	1.092	0.867 – 1.368
PRBC age dichotomized at 14 days old	0.612	0.189 – 2.070
Number of transfused PRBC units	0.984	0.935 – 1.027
Patient age	1.012	0.989 – 1.036
ISS	1.043	1.013 – 1.076
Head AIS	1.076	0.855 – 1.345

ISS= Injury Severity Score; PRBC= Packed Red Blood Cell; AIS= Abbreviated Injury Score; MODS= Multiple Organ Dysfunction Score.