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Recurrent event frailty models reduced time-varying and other biases in evaluating transfusion protocols for traumatic hemorrhage

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Abstract

Objective—Transfusion research seeks to improve survival for severely injured and hemorrhaging patients using optimal plasma and platelet ratios over red blood cells (RBC). However, most published studies comparing different ratios are plagued with serious bias and ignore time-varying effects. We applied joint recurrent event frailty models to increase validity and clinical utility.

Study Design and Setting—Using the PROspective Observational Multicenter Major Trauma Transfusion (PROMMTT) study data, our joint random effects models estimated the association of 1) clinical covariates with transfusion rate intensities, and 2) varying plasma:RBC and platelet:RBC ratios with survival over the 24 hours after hospital admission. Along with survival time, baseline patient vital signs, laboratory values and longitudinal data on types and volumes of transfusions were included.

Results—Baseline systolic blood pressure, heart rate, pH and hemoglobin were significantly associated with RBC transfusion rates. Increased transfusion rates (per hour) of plasma ($p=0.05$),

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platelets ($p<0.001$) or RBCs were associated with increased 24-hour mortality. Higher ratios of plasma:RBC ($p=0.107$) and platelet:RBC ($p<0.001$) were associated with reduced mortality in a time-varying pattern ($p<0.001$).

Conclusions—The proposed joint analysis of transfusion rates and ratios offers a more valid statistical approach to evaluate survival effects in the presence of informative censoring by early death.

Keywords

Hemorrhage; Joint modeling; Multivariate recurrent events; Survival analysis; Transfusion ratio; Trauma

1. Introduction

In the United States, uncontrolled hemorrhage is the most common cause of preventable death for those who reach a hospital alive after injury. Death from hemorrhage generally occurs within the first three to six hours after hospital admission [1–3]. The high mortality risk following injury occurrence creates urgency in identifying the patients who are massively bleeding and providing optimal treatment in time. The treatment for hemorrhagic shock is resuscitation, preferably with whole blood or blood products, and operative intervention. However, no universally accepted transfusion protocol exists for the treatment of hemorrhagic shock. While early transfusion of plasma and platelets has been associated with improved outcomes [2,4–6], findings among observational studies seeking to identify optimum trauma transfusion protocols have been conflicting and difficult to interpret [7,8]. In earlier works [9,10], our group has identified major challenges in the design and statistical analysis of trauma transfusion studies.

The treatment of hemorrhagic shock is complex and highly dynamic. First, trauma patients receive multiple blood products, namely red blood cells (RBCs), plasma and platelets. Secondly, these blood products are usually administered in different orders depending upon their availability and the patient's condition. Therefore, traditional data analysis strategies, in which correlations among multiple blood transfusion processes are ignored and cumulative blood transfusion sums and/or ratios are computed at pre-defined time points (e.g., 6 or 24 hours), may misrepresent the patient's actual transfusion experience and response. These approaches cannot distinguish between rapid successive transfusions and intermittent transfusions over an extended 24-hour period. Third, many hemorrhaging patients die before achieving hemostasis, and transfusion studies with traditional statistical methodologies have been susceptible to survival bias and the unrealistic assumption that censoring due to death is ignorable. To reduce survival bias, many studies [5,6,11] have enlisted different approaches including the incorporation of blood product ratios cumulated hourly as time-dependent covariates in Cox proportional hazards (PH) regression models. However, the time-dependent covariate Cox model must be used cautiously [12], because initial transfusions can influence patients' need for subsequent transfusion of specific blood components and thereby introduce time-dependent confounding. In general, the presence of time-dependent confounding renders causal interpretation difficult with conventional Cox

PH modeling, and the inclusion of time-dependent covariates can actually introduce rather than reduce bias.

The PROspective Observational Multicenter Major Trauma Transfusion (PROMMTT) study collected event time, transfusion, and clinical patient data across 10 US Level-1 Trauma centers. PROMMTT applied several different data analysis strategies [2,13,14] and reported that most trauma patients eventually received blood product transfusions in the ratio of 1:1:1 or 1:1:2 in plasma:platelet:RBC. Using the PROMMTT data, in this article, we propose an advanced random-effect modeling approach, which models multi-type repeated blood transfusions as correlated recurrent events and defines death as a dependent censoring event that prevents subsequent treatment with blood transfusion [15–20]. The study objectives were to (i) accurately describe when RBCs, plasma and platelets were infused and (ii) assess the effect of transfused blood product ratios on in-hospital mortality. Using the proposed random-effect model, we jointly assess recurrence intensities for RBC and plasma (or platelet) transfusions and also include hazard rate analysis to evaluate the effects of multiple blood transfusions on early trauma mortality. A particular advantage of our model is to introduce a common baseline recurrence intensity function for multiple types of blood transfusion to better estimate changing transfusion ratios (plasma and platelets) relative to RBCs. Our earlier work [21] also investigated a flexible random-effect modeling approach to evaluate blood transfusion ratios. The present work will further provide a means of assessing the effect of transfusion ratio on patients' survival, which is of primary clinical interest.

2. Methods

2.1. PROMMTT study

PROMMTT was a prospective, multicenter observational cohort study that enrolled 1,245 adult trauma patients requiring the highest level of trauma activation from July 2009 through October 2010. Severely injured patients were eligible if they were age 16 years or older and received at least one unit of RBCs within the first 6 hours after admission. Exclusions included hospital transfers, patients receiving >5 minutes of cardiopulmonary resuscitation within 30 minutes of admission, pregnant females, inhalation injuries, burns to 20% or more of body surface, prisoners, and deaths within 30 minutes of admission. Real-time data collection on transfusions and other interventions, their indications and their administration times, was initiated on patients until active resuscitation ended. Information on in-hospital mortality, complications, and later treatment were recorded daily from the medical record until death or discharge. Additional details regarding the design and main results of PROMMTT have been previously published [2,13,14,22].

2.2. Analysis cohort

Earlier trauma studies with retrospective transfusion data [4–6] have mostly focused on the subgroup of massive transfusion (MT) patients, defined as receiving at least 10 units of RBCs within 24 hours of hospital admission. However, in addition to introducing collider bias [10], this approach misclassifies and effectively excludes bleeding patients who do not survive long enough to receive a 10th unit of RBCs. Instead, we considered all 919 PROMMTT study patients who had survived long enough to receive at least 3 blood product

units and had complete observations for the following baseline variables: systolic blood pressure (SBP), heart rate (HR), hemoglobin concentration (Hgb) and pH. The rationale for setting a minimum of 3 blood product transfusions as an eligibility criterion was that only after the third transfusion would PROMMTT patients have had the chance to receive plasma and platelets in addition to RBCs. PROMMTT's exclusion of patients dying within the first 30 minutes precluded a valid assessment of the association between early mortality and the earliest possible transfusion of plasma or platelets. The primary outcomes of interest include in-hospital mortality at 6, 24 hours and 30 days post admission. We coded the following covariates as binary variables: SBP less than 90 mm Hg (29.6%), HR greater than or equal to 120 bpm (32.7%), Hgb less than 11 (37.3%), pH less than 7.25 (39.7%).

2.3. Statistical models

Our statistical strategy for modeling blood product transfusions with RBCs, plasma and platelet is to regard them as multiple-type recurrent events. However, existing methods [23–25] on recurrent events that are valid only under a non-informative censoring assumption may yield misleading results if applied to trauma transfusion studies, in which the censoring times (due to death or successful hemorrhage control) are associated with the recurrent events (i.e., successive transfusions). In the PROMMTT study, death or discontinuation of transfusions due to hemostatic interventions (e.g., surgery or endovascular procedures) cannot necessarily be treated as non-informative censoring because each may be correlated with the timing and amount of blood transfusion.

Our approach for analysis of the PROMMTT data assumes two recurrence intensity functions for RBCs and plasma (or platelet) and a hazard function for death, which are assumed to be independent, conditioning on covariates and event-specific random-effects. We focused on accurately evaluating the effects of blood transfusion ratios (plasma:RBC and platelet:RBC) on in-hospital mortality, in addition to assessing baseline covariate effects on recurrent blood product transfusions. This requires modeling separately rate functions of multiple-type recurrent events as well as the hazard of death. However, simultaneous estimations of event ratios for two recurrent event processes (e.g., plasma:RBC and platelet:RBC ratios) are intrinsically difficult because the changes in each do not occur at the same time. To model such a complicated phenomenon, we propose a joint random-effect model that includes three submodels: (a) an intensity model for RBC transfusion, (b) an intensity model for transfusion of plasma or platelet, and (c) a hazard model for death. We allow an event-specific frailty to account for the within-event dependence and explore potential collinearities between multiple blood product transfusions (i.e., between RBC and either plasma or platelet), while adopting another common frailty to be shared by all recurrent events and informative death times to estimate the transfusion rates (of RBC and either plasma or platelet) and the effect of each ratio (plasma:RBC or platelet:RBC) on survival. Our separate models for plasma and platelets assume that the transfusion ratio for each (e.g., plasma:RBC) has an effect on survival independent of that of the alternate ratio (e.g., platelet:RBC). Specific model formulation and statistical inferential procedures are presented in Appendix 1 and 2, respectively.

The joint distribution of multiple event times and time-varying outcomes are modeled through a set of random-effects that account for the associations between these outcomes, which helps reduce potential bias in making various statistical inferences when the terminal event (such as death) is likely to be correlated with time-informative blood transfusions. This approach is useful in solving difficulties in Cox PH models with time-dependent covariates that could be affected by multicollinearity due to high correlation between multiple blood products transfused and providing estimates of the independent effect of each transfusion ratio adjusted for the effects of other covariates. We conducted joint analysis to evaluate the effects of plasma:RBC and platelet:RBC ratios on survival, based on cumulative observations up to 24 hours and adjusting for baseline covariates. The null hypotheses of time-varying effects of transfusion ratios or covariates can be tested by Likelihood Ratio (LR) methods. Using empirical Bayes estimates for the random-effects, obtained by the SAS Proc NLMIXED procedure, we estimated the averaged blood transfusion ratios at death or censoring time.

3. Results

3.1. Patient characteristics

The mean follow-up time was 17.7 days (SD: 18.6) for the analysis cohort. A total of 33 (3.6%), 59 (6.4%) and 94 (10.2%) patients died during the first 3, 6 and 24 hours, respectively, others were censored. The 919 study patients received a total of 5868 units of RBCs, while 635 (69.2%) received a total of 4157 units of plasma and 262 (28.1%) received a total of 3045 units of platelets within 24 hours. Since not all 919 patients had received plasma or platelets, we also performed subgroup analyses that focused on the subsets of 635 patients for the analysis of plasma:RBC and 262 patients for the analysis of platelet:RBC, in which patients were transfused at least 1 unit of plasma or platelets, respectively. In each subgroup, there were 78 (12.3%) and 44 (16.8%) deaths within 24 hours. Figure 1 illustrates the observed ratios of (a) plasma:RBC and (b) platelet:RBC during the first 12 hours of admission. Overall, the PROMMTT patients received more early plasma than platelet transfusions, with greater variation in the platelet:RBC ratio.

3.2. Blood transfusion rates

Displayed in Figure 2 are the nonparametric estimators of the cumulative rates for blood products during the first 12 hours of ED admission, based on (A) 919 patients, (B) 635 patients who received plasma transfusion and (C) 262 patients who received platelet transfusion within 24 hours of admission. Figure 2(a) shows that the overall amount of blood products transfused gradually increases within the first 6 hours of admission and thereafter become stabilized. Compared to the entire analysis cohort in (A), patients in (B) and (C) on average showed higher rates of RBC transfusion. Patients receiving multiple units of RBCs were likely to receive at least one unit of plasma and platelets as well. Interestingly, the platelet:RBC ratio among subgroup (C) maintained nearly a 1:1 ratio up to 12 hours of admission. It is also noteworthy that overall transfusion of platelets began later compared to other blood components.

3.3. Model interpretation

The results in Table 1(a) and 2(a) for 919 patients show that (1) all covariates were significantly associated with the RBC transfusion rate, (2) the difference in coefficients between RBC and plasma rates seemed relatively negligible for all covariates, but the difference in coefficients between RBC and platelets was significant for pH ($p = 0.022$) and Hgb ($p < 0.001$), and (3) the association of pH level with survival was significant ($p < 0.001$); patients with lower pH level (< 7.25) were likely to die earlier. The estimated plasma:RBC and platelet:RBC transfusion ratios for the entire study cohort of $n=919$ were 0.38 (95% CI: 0.24–0.59) and 0.30 (95% CI: 0.09–0.95), respectively, which is consistent with transfusion rates shown in Figure 2(a). For random-effects, heterogeneity (over time) exists; $\hat{\theta}_1=0.615, p<0.001$ for the model for plasma:RBC, and $\hat{\theta}_1=0.586, p<0.001$ for the model for platelet:RBC. Overall, transfusion of a high total number of blood products was associated with increased 24-hour mortality, including transfusion of both plasma ($\hat{\phi}_1=1.135, p=0.051$) and platelets ($\hat{\phi}_2=0.964, p=0.037$), in addition to RBCs. For the association between transfusion ratio and mortality, we note that $\hat{\phi}_2 = -0.392 (p=0.107)$ for plasma:RBC and $\hat{\phi}_2 = -0.529 (p<0.001)$ for platelet:RBC. The results, based on the subset of patients who had at least one unit of plasma or platelet, were shown in Tables 1(b) and 2(b), were generally similar to those in Tables 1(a) and 2(a), respectively. In plasma transfusion (Table 1), there were no significant differences between the covariate coefficient with transfusion rates of RBCs and those of plasma (i.e., $\beta_p \approx 0$ for $p = 1, \dots, 4$). In contrast, the differential covariate coefficient of Hgb has a significant impact on platelet transfusion (Table 2); patients with Hgb < 11 received a larger amount of platelets ($p < 0.0001$). Patients' pH level appeared to be an important factor associated with mortality in all analyses.

3.4. Estimated transfusion ratios

Averaged Bayes-estimated transfusion ratios were 0.564 for plasma:RBC and 0.323 for platelet:RBC for the entire study cohort of 919 PROMMTT patients. For the subsets of 635 and 262 patients, the average transfusion ratios were 0.691 for plasma:RBC and 0.606 for platelet:RBC, respectively. Estimated blood transfusion ratios for plasma:RBC and platelet:RBC, based on the empirical Bayes estimates for the random-effects from the proposed model, are presented in Figures 3(a) and 3(b), respectively.

4. Discussion

In this article, we considered a joint random-effects model for multiple-type recurrent transfusion rates of blood products and hazard of death with applications to data from the PROMMTT study. Our proposed model permits estimating (i) recurrence intensity functions for transfusion of multiple types of blood products, (ii) changes over time in the ratios (i.e., plasma:RBC and platelet:RBC) and their effects on patient survival, and (iii) the covariates' effect on the intensity of each successive transfusions as well as the hazard of death. Joint estimation of all parameters facilitates comparison between effects associated with different types of blood products transfusions. Further, we used cubic regression splines for modeling time-dependent transfusion ratios, which provide a versatile tool for modeling complex associations in many medical studies where the shapes of different functions of interest are

not known *a priori*. Our analysis of the PROMMTT data demonstrates that detecting and modeling such time-dependent effects could yield important new insights in real-life prognostic studies in trauma transfusion research.

In our study sample of 919 trauma patients, the results suggest that increased plasma:RBC and platelet:RBC ratios may lead to improved survival, although only the platelet:RBC association was statistically significant. However, these findings should be interpreted with caution, because the associated variance of the random effect in platelet transfusion rate was very large ($\hat{\theta}_2=7.385, p=0.001$). We interpret the data as suggestive but inconclusive for an independent protective association between higher plasma:RBC and platelet:RBC transfusion ratios and injury mortality. Transfusion ratios for both plasma and platelet showed statistically significant time-varying patterns especially in the early phase of resuscitation. This complicates the identification of optimal blood transfusion ratios, and warrants further research to confirm or refute the potential benefit of a transfusion protocol that initiates early plasma and platelet transfusion and sustains balanced ratios of 1:1:1 (plasma:platelet:RBC).

Strengths of this study include its prospective design and availability of timing of transfusion data from PROMMTT. Rather than directly calculating transfusion ratios with interpolation or summing them within an arbitrary time window, we applied joint recurrent event models that enabled blood transfusion to be estimated as an outcome. However, the proposed joint model assumes that the submodels for recurrent and terminal events operate independently, given the random-effects, which may be too strict for highly dynamic real-life resuscitation strategies. Only a well-designed, conducted and analyzed randomized trial could possibly overcome the many threats to validity in observational trauma transfusion research. More recently, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial reported that early administration of plasma, platelet and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in overall mortality at 24 hours, but more patients in the 1:1:1 group achieved hemostasis and fewer died from exsanguination[3]. Given that most of the hemorrhage-related deaths occurred within the first few hours after admission, our findings of significantly time-varying effects of plasma and platelet transfusion ratios on mortality in PROMMTT are consistent with those of PROPPR [3].

Yet other situations requiring joint models include analysis of longitudinal measurements with survival as the ultimate endpoint [26–30]. Joint analysis will enable appropriate examination of the underlying interrelations among multiple recurrent events in the same patient. In the trauma setting, novel design and analysis approaches (e.g., adaptive trial design, artificial censoring and inverse probability weighting, sequential Cox analysis) that have been motivated by conceptually similar challenges in other clinical research contexts could be adapted or extended to promote a better integrated system of transfusion research and clinical practice [31–36].

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Appendix 1: Model formulation

Suppose there are n patients in the study indexed by $i = 1, \dots, n$, who may experience recurrent transfusions of RBC ($k = 1$), plasma or platelets ($k = 2$), which will be viewed as recurrent events in our analysis. For each pair (k, i) , let $N_{ki}^{R*}(t)$ denote the number of type- k recurrent events that have occurred up to time t and $\mathbf{x}_i$ be the P -vector of explanatory variables measured at baseline in patient i . Let $Y_i = \min(C_i, T_i)$, the minimum of an independent censoring time C_i and a dependent death time T_i , respectively, and define the censoring indicator as $\delta_i = I(T_i \leq C_i)$. Define $N_{ki}^R(t) = N_{ki}^{R*}(t \wedge Y_i)$ as the actual number of recurrent events $(0, t]$ in for the type- k recurrent event in the i th individual. Similarly, denote by $N_i^D(t) = I(T_i \leq t, \Delta_i = 1)$ the observed counting process for death. Three normally distributed random-effects of (u_i, v_i) are considered to relate correlated recurrent and terminal events. Given random-effects, covariates and the condition $T_i > t$ (being alive just before time t), we let $r_{1i}(t, \mathbf{x})$ and $r_{2i}(t, \mathbf{x})$ denote the intensity functions of recurrent event processes for transfusion of RBCs and plasma (or platelets) at time t , respectively, which correspond to $N_{1i}^R(t)$ and $N_{2i}^R(t)$. Also, let us denote mortality hazard function by $\lambda_i(t, \mathbf{x})$ for the process $N_i^D(t)$. Specifically, we model recurrence intensity functions and hazard function as

$$r_{1i}(t, \mathbf{x}) = r_0(t) \exp \left(\sum_{p=1}^P \alpha_p x_{ip} + u_i \right), \quad (1)$$

$$r_{2i}(t, \mathbf{x}) = r_0(t) \exp \left(b_0 + \sum_{p=1}^P (\alpha_p + \beta_p) x_{ip} + u_i + v_i \right), \quad (2)$$

$$\lambda_i(t, \mathbf{x}) = \lambda_0(t) \exp \left(\sum_{p=1}^P \gamma_p x_{ip} + \phi_1 u_i + \phi_2 v_i \right). \quad (3)$$

The function $r_0(t)$ in model (1) represents the baseline intensity function for the ‘reference’ event ($k = 1$). Notice that $r_0(t)$ is also present in model (2) and that the baseline intensity function for model (2) can be expressed simply as $r_0(t) \exp(b_0)$. The effects of the

explanatory variables are assumed to be different for multiple recurrent event and death times. The effect of a covariate $x_p, p = 1, \dots, P$, in model (2) is split into a common effect through the regression parameter α_p (corresponding to the effect on the event $k = 1$), and into a differential effect through the regression parameter β_p (corresponding to the additional effect on the event $k = 2$). In the proposed model, we consider that two recurrence intensity functions in expressions (1) – (3) depend on repeated blood transfusions through the random effect $u_i \sim N(0, \theta_1)$, as patients who received RBCs are more likely to receive plasma or platelet transfusion. The random effect $v_i \sim N(0, \theta_2)$ in models (2) and (3) is assumed to relate the intensity for the type-2 recurrent event with the hazard of death. We here assume that two random-effects are independent of each other. Given this model specification, the ratio of two baseline recurrence intensity functions for plasma (or platelet) to RBCs is represented by $\exp(b_0 + v_i)$ upon inclusion of random-effects, therefore the effect on survival of transfusion ratio can be estimated through the association parameter ϕ_2 . Also, the overall common random effect in blood transfusions may be evaluated through ϕ_1 . In our application, it may be too strict to assume that the transfusion ratio is invariant over the entire study time window. To complement the time-dependent logarithm of the ratio between RBC and plasma or platelets, we may replace the constant b_0 in (2) with a flexible function of time, say $b_0(t)$. We use cubic B-splines [27], and for each B-spline we choose the support interval $[0, U]$, where U has to be equal to or slightly higher than the maximum time (representing either an event or a censored observation, whichever occurred first) observed in a given data set. This method may also be extended to facilitate $\alpha_p(t)$, $\beta_p(t)$ and $\gamma_p(t)$, replacing α_p , β_p , and γ_p to accommodate time-varying covariate effects.

Appendix 2: Estimation procedure

The likelihood function for the proposed joint models in (1) – (3) can be formulated following the general theory of counting processes, which involves an integral with respect to random-effects (u , v), but this integral cannot be evaluated analytically. For the estimating procedure we adopted adaptive Gaussian quadrature to approximate the integral in joint models[1]. In numerical analysis, a quadrature rule is an approximation of the likelihood in integral by a weighted sum of function values at specified points within the domain of integration. In addition to accurate parameter estimates and available standard error (SE) estimates, this estimation approach possesses the advantage of easy implementation because SAS procedure NLMIXED requires inputting the likelihood (conditional on random-effects) explicitly and the approximation of the marginal likelihood can be directly maximized. For the Gaussian quadrature estimation, we assumed two separate 5-step piecewise constant functions for the intensity of blood transfusion and the hazard of death. To accommodate time-varying patterns of the transfusion ratios, we included B-splines for natural cubic splines for $b_k(t)$ with four degrees-of-freedom (df) that place the interior knot location at quartiles of recurrence event times.

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Figure 1.
Observed blood product ratios of (a) plasma:RBC and (b) platelet:RBC. Solid line represents simple averaged ratios and dashed line represents the spline smoothed version

Figure 2.

Nonparametric estimates of cumulative rate functions of blood product transfusions based on data from PROMMTT study for (a) all 919 patients who had at least three units of blood transfusion during the first 6 hours, (b) 635 patients who had at least one unit of plasma transfusion, and (c) 262 patients who had at least one unit of platelet transfusion

Figure 3.
Estimated blood transfusion ratios for (a) plasma:RBC and (b) platelet:RBC using the empirical Bayes estimates for the random-effects from the proposed model

Joint analysis of transfusion rates/ratios of plasma and RBCs and 24-hour survival in (a) the study cohort with 919 PROMMTT patients and (b) 635 patients who received at least one unit of plasma transfusion

Table 1

Parameter	(a) Analysis cohort (n = 919)		(b) Subset cohort (n = 635)	
	Point estimate	SE	P-value	P-value
<i>Recurrent RBC transfusion</i>				
SBP<90 (α_1)	0.288	0.056	<0.001	0.318 0.094 0.001
HR 120 (α_2)	0.124	0.055	0.021	0.096 0.092 0.296
pH<7.25 (α_3)	0.445	0.054	<0.001	0.352 0.090 0.001
Hgb<11 (α_4)	0.316	0.053	<0.001	0.343 0.089 0.001
<i>Recurrent plasma transfusion (differential effect)</i>				
SBP<90 (β_1)	-0.014	0.043	0.738	-0.033 0.101 0.741
HR 120 (β_2)	-0.058	0.043	0.179	-0.054 0.099 0.589
pH<7.25 (β_3)	0.036	0.044	0.412	0.117 0.098 0.229
Hgb<11 (β_4)	-0.041	0.042	0.327	-0.089 0.097 0.358
<i>Death</i>				
SBP<90 (γ_1)	-0.334	0.651	0.608	-0.584 0.601 0.332
HR 120 (γ_2)	0.055	0.615	0.928	-0.053 0.577 0.927
pH<7.25 (γ_3)	1.322	0.615	0.032	2.391 0.623 0.001
Hgb<11 (γ_4)	0.680	0.586	0.246	1.427 0.567 0.012
<i>Model association</i>				
b_0	-1.404	0.193	<0.001	-1.241 0.101 <0.001
ϕ_1	1.135	0.581	0.051	1.501 0.623 0.016
ϕ_2	-0.392	0.243	0.107	-0.453 0.308 0.141
<i>Covariance matrix</i>				

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(a) Analysis cohort (n = 919)						(b) Subset cohort (n = 635)					
Parameter	Point estimate	SE	P-value	Point estimate	SE	P-value	Point estimate	SE	P-value	Point estimate	SE
θ_1	0.615	0.020	<0.001	0.611	0.022	<0.001	0.611	0.022	<0.001	0.611	0.022
θ_2	0.480	0.024	<0.001	0.370	0.023	<0.001	0.370	0.023	<0.001	0.370	0.023

Joint analysis of transfusion rates/ratios of platelets and RBCs and 24-hour survival in (a) the study cohort with 91a9 PROMMTT patients and (b) 262 patients who received at least one unit of platelet transfusion

Table 2

(a) Analysis cohort (n = 919)				(b) Subset cohort (n = 262)			
Parameter	Point estimate	SE	P-value	Point estimate	SE	P-value	
<i>Recurrent RBC transfusion</i>							
SBP<90 (α_1)	0.271	0.055	<0.001	0.177	0.087	0.042	
HR 120 (α_2)	0.124	0.054	0.023	0.072	0.085	0.398	
pH<7.25 (α_3)	0.453	0.053	<0.001	0.435	0.085	<0.001	
Hgb<11 (α_4)	0.323	0.052	<0.001	0.204	0.083	0.015	
<i>Recurrent platelets transfusion (differential effect)</i>							
SBP<90 (β_1)	-0.012	0.262	0.962	2.033	0.915	0.027	
HR 120 (β_2)	0.106	0.256	0.678	0.500	0.894	0.576	
pH<7.25 (β_3)	0.579	0.252	0.022	-0.592	0.882	0.503	
Hgb<11c (β_4)	1.385	0.252	<0.001	2.932	0.868	0.001	
<i>Death</i>							
SBP<90 (γ_1)	-0.342	0.347	0.325	-1.161	0.451	0.107	
HR 120 (γ_2)	0.038	0.333	0.908	-0.111	0.409	0.786	
pH<7.25 (γ_3)	1.405	0.328	<0.001	1.223	0.424	0.004	
Hgb<11 (γ_4)	0.746	0.318	0.019	0.669	0.407	0.102	
<i>Model association</i>							
h_0	-0.187	0.165	0.257	-0.150	0.171	0.366	
ϕ_1	0.964	0.461	0.037	1.059	0.407	<0.001	
ϕ_2	-0.529	0.050	<0.001	-0.186	0.037	<0.001	
<i>Covariance matrix</i>							

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(a) Analysis cohort (n = 919)						(b) Subset cohort (n = 262)					
Parameter	Point estimate	SE	P-value	Point estimate	SE	P-value	Point estimate	SE	P-value	Point estimate	SE
θ_1	0.586	0.020	<0.001	0.568	0.032	<0.001	0.568	0.032	<0.001	0.568	0.032
θ_2	7.385	0.327	<0.001	6.855	0.304	<0.001	6.855	0.304	<0.001	6.855	0.304