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Estimating the Ratio of Multivariate Recurrent Event Rates with Application to a Blood Transfusion Study

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Abstract

In comparative effectiveness studies of multi-component, sequential interventions like blood product transfusion (plasma, platelets, red blood cells (RBCs)) for trauma and critical care patients, the timing and dynamics of treatment relative to the fragility of a patients condition is often overlooked and underappreciated. While many hospitals have established massive transfusion (MT) protocols to ensure that physiologically optimal combinations of blood products are rapidly available, the period of time required to achieve a specified MT standard (e.g., a 1:1 or 1:2 ratio of plasma or platelets:RBCs) has been ignored. To account for the time-varying characteristics of transfusions, we use semi-parametric rate models for multivariate recurrent events to estimate blood product ratios. We use latent variables to account for multiple sources of informative censoring (early surgical or endovascular hemorrhage control procedures or death). The major advantage is that the distributions of latent variables and the dependence structure between the multivariate recurrent events and informative censoring need not be specified. Thus, our approach is robust to complex model assumptions. We establish asymptotic properties and evaluate finite sample performance through simulations, and apply the method to data from the PROspective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study.

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Keywords

Informative censoring; Multivariate recurrent event; Rate ratio; Transfusion medicine

1 Introduction

In studies of the comparative effectiveness of trauma resuscitation and critical care interventions like multi-component blood product transfusion (i.e., red blood cells (RBCs), plasma and platelets), the influence of the timing and dynamics of complex, sequential treatments relative to the fragility of a patients condition is often overlooked and underappreciated. While many hospital blood banks and Level One trauma centers have established massive transfusion (MT) protocols to ensure that physiologically optimal combinations of blood products are rapidly available, the patient survival time required to diagnose potentially life-threatening hemodynamic instability and to achieve the specified transfusion standard (e.g., a 1:1 or 1:2 ratio of plasma or platelets:RBCs) has been ignored. Systematic reviews have reported significant heterogeneity among the findings of published studies assessing the effects of different MT protocols on trauma outcomes.^{1,2} The use of conventional analysis strategies in these high-risk, time-urgent clinical research settings have failed to adequately adjust for serious confounding (due to indication bias, survival bias, collider bias, and informative censoring)^{3,4,5,6} yielding irreproducible and uninterpretable findings. Meaningful evaluation of the effects of different MT protocols on patient outcomes will first require accurate representation of the timing and dynamics of transfusion.

Research in this area has been hindered by both the difficulty of collecting data on the timing of each blood product transfusion and the lack of appropriate statistical analysis tools that can handle informative censoring. Our work was motivated by the PROspective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, which was a 10-center prospective observational study of trauma patients admitted directly from the scene of injury to a Level 1 trauma center in the US.^{7,8} The study enrolled 1245 adult trauma patients between July 2010 and October 2011, who survived for at least 30 minutes after emergency department (ED) admission and received a transfusion of at least 1 unit of RBCs within 6 hours of admission. The study collected minute-to-minute transfusion times for RBCs, plasma and platelets. The key feature of the recurrent blood transfusion data is that the transfusion times of different blood products within a patient are typically correlated and stochastically ordered. In addition, there are several potential informative censoring mechanisms that preclude any further blood transfusions. For example, Holcomb *et al.*⁷ demonstrated time-varying plasma:RBC and platelet:RBC ratios. In their method, the cumulative ratios of plasma:RBCs and platelet:RBCs were computed at the time of study enrollment and for as many of 14 consecutive time intervals as study patients survived. In a similar approach, Snyder *et al.*⁹ divided the first 24 hours into 12 time intervals and calculated the aforementioned ratios within each interval. Both methods computed cumulative transfusion ratios within subjective discrete time intervals, and hence did not fully capture the time-varying property of transfusion ratios. Further, such methods ignored the fact that blood products transfusions are subject to informative censoring, which could result in biased estimates for the transfusion ratios.

Multivariate recurrent event data are commonly encountered and have been well-studied in applications to epidemiological and medical studies. For example, in an asthma study, Cai *et al.*¹⁰ considered physician office visits and hospitalization attributable to asthma as two recurrent events of interest. Similarly, in an acute myeloid leukemia study, bacterial infection and fungal or viral infection were considered as two recurrent events of interest.¹¹ Several statistical methodologies have been proposed in the literature for the study of multivariate recurrent event data using multivariate point processes.^{10,11,12,13,14,15} However, these methods are not tailored to the analysis of the ratios of multivariate recurrent blood transfusions. Another challenge is that the critical assumption of non-informative censoring is violated in comparative effectiveness studies of trauma and transfusion medicine. Patients may be unable to complete their intended MT protocol because the initial transfusions precipitate either successful early hemorrhage control (through surgery, endovascular or other procedures) or early death. Thus, informative censoring in these transfusion studies is caused not by differential drop-out or loss to follow-up, but by differential early hemorrhage control or death. Stated another way, the amount of blood products that can be given to achieve transfusions specified by a MT protocol is dependent upon the duration of hemodynamically unstable survival, which in turn can be influenced by the order and number of initial blood product transfusions. One possible strategy is to use a shared frailty model to jointly model the recurrent events and censoring mechanisms. By imposing some distributional assumptions on the shared random effects, one can produce unbiased estimators.^{16,17} However, as mentioned previously, there exist different kinds of informative censoring in studies of MT protocols, thus it is computationally intensive to model all the censoring mechanisms. Our strategy is to extend the model of Wang *et al.*¹⁸ for single recurrent event data with informative censoring, in which multiple informative censoring is treated as a nuisance parameter; hence, there is no need to specify its distribution.

The objective of this paper is to improve the validity and efficiency of estimating transfusion ratios of blood products (plasma:RBCs and platelet:RBCs) that are subject to multiple informative censoring. To achieve this objective, we extend the framework of Wang *et al.* to accommodate multiple recurrent event data taking into account informative censoring.¹⁸ Then, we evaluate the ratio of multiple recurrent event rates. Further, we estimate the degree of dependence between different blood product transfusions by using the rate ratio proposed by Ning *et al.*¹⁹ To our knowledge, this is the first attempt to accurately and precisely estimate the time-varying ratio of blood product transfusion rates. In our method, both the distributions of the latent variables and the dependence structure between the multivariate recurrent events and informative censoring do not need to be specified, and multiple sources of censoring can be easily accommodated. The remainder of this paper is organized as follows. In Section 2, we introduce the notations, models, and estimating procedures. In Section 3, we report the simulation results. We provide a real data application to PROMMTT in Section 4, followed by a discussion in Section 5. We provide the proofs and other details in the Appendix.

2 Notation and models

Without loss of generality, we use the data from PROMMTT as an example to introduce the notations and models. For patient i , let $N_{ik}(t)$ denote the cumulative number of transfusions

of type k blood product up to time t , where $k = 1$ for plasma, 2 for platelets and 3 for RBCs. Let C_{ik} be the censoring time, τ be the maximum follow-up time and m_{ik} be the observed total number of events before censoring time C_{ik} for patient i of type k recurrent event. Note that the model allows for multiple sources of censoring, including informative censoring (e.g., death or surgical intervention) and non informative censoring (e.g., the end of the study). The observed event times of type k for the i th patient are $0 < t_{ik1} < \dots < t_{ikm_{ik}} < \tau$. Let X_i be a $p \times 1$ vector of the time-independent covariates, where p is the dimension of covariates.

2.1 Regression models

We first model three transfusion rate functions (plasma, platelets and RBCs) simultaneously by using subject-specific and type-specific latent variables. Specifically, for patient i , we assume that there exists a non-negative latent variable ξ_{ik} . With $E(\xi_{ik} | x_i) = E(\xi_{ik})$ and given ξ_{ik} and x_i , $N_{ik}(t)$ is a non-stationary Poisson process with intensity

$$\lambda_{ik}(t; \xi_{ik}, x_i) = \xi_{ik} \lambda_{0k}(t) \exp\left(x_i^T \alpha_k\right) \quad k=1, 2, 3, \quad (1)$$

where α_k is a $p \times 1$ vector of regression parameters, and $\lambda_{0k}(t)$ is the type-specific continuous function with $\Lambda_{0k}(\tau) = \int_0^\tau \lambda_{0k}(u) du = 1$.

The subject-specific and type-specific latent variable ξ_{ik} is used to characterize the heterogeneity among patients. For the i th patient, a large value of ξ_{ik} implies more frequent occurrences and a small value of ξ_{ik} implies less frequent occurrences of type k blood transfusions. Notice that model (1) is quite flexible, in which three latent variables from the same patient are potentially correlated and three unspecified rate functions are allowed to be different. We further assume that conditioning on covariates X_i and latent variables (ξ_{ik}), $\{N_{ik}(\cdot), C_{ik}\}$ ($k=1, 2$ and 3) are mutually independent. From this assumption, model (1) allows the censoring time to be dependent on the recurrent events through the latent variables and covariates, which relaxes the usual independent censoring assumption. Unlike the standard joint modeling approach of Liu *et al.*¹⁶, our method does not specify the role of latent variables in the distribution of informative censoring.

Our interest is to estimate the time-varying plasma:RBC and platelet:RBC ratios for patient i , denoted as $r_{12}(t)$ and $r_{23}(t)$, respectively. The transfusion rate models in equation (1) imply a multiplicative ratio model. Specifically, we have

$$r_{ik}(t; \zeta_{ik}, x_i) = \frac{\lambda_{ik}(t; \xi_{ik}, x_i)}{\lambda_{i3}(t; \xi_{i3}, x_i)} = \zeta_{ik} r_{0k}(t) \exp\left(x_i^T \beta_k\right) \quad k=1, 2, \quad (2)$$

where β_k is a $p \times 1$ vector of the regression parameters on the ratio, $r_{0k}(t)$ is an unspecified baseline ratio function, and ζ_{ik} is the latent variable that characterizes the heterogeneity among patients.

2.2 Dependence measure

It is also of interest to explore the dependence structure between the transfusion of different blood products under model (1). Ning *et al.*¹⁹ recently proposed the rate ratio, a measure used to assess the degree of dependence between two types of recurrent event processes. It is the ratio of the conditional rate $\lambda_{k_1|k_2}(\cdot)$ to the marginal rate $\lambda_{k_1}(\cdot)$,

$$\rho_{k_1 k_2}(s, t) = \frac{\lambda_{k_1|k_2}(s|t)}{\lambda_{k_1}(s)}, \quad s, t \geq 0; k_1, k_2 = 1, 2, 3 \quad (3)$$

where $\lambda_{k_1|k_2}$ is a conditional rate function defined as

$$\lambda_{k_1|k_2}(s|t) = \lim_{\Delta \rightarrow 0^+} Pr \{N_{k_1}(s+\Delta) - N_{k_1}(s) > 0 | N_{k_2}(t+\Delta) - N_{k_2}(t) > 0\} / \Delta. \quad (4)$$

In our motivating study, the rate ratio can be interpreted as the factor of an additional probability for receiving at least one k_1 type of blood product transfusion at time s due to the k_2 type of blood product transfusion at time t . A limitation of the estimating procedure of Ning *et al.* is the assumption of non-informative censoring, which is not valid in our case. To relax the non-informative censoring assumption, we further explore the relationship between the rate ratio and our model to estimate the degree of dependence in the presence of informative censoring.

By the definition of the rate ratio, $\rho_{k_1 k_2}(s, t)$, we find that the rate ratio depends on s and t through the covariance and means of the latent variables,

$$\rho_{k_1 k_2}(s, t) = 1 + cov(\xi_{k_1}, \xi_{k_2}) / (\mu_{\xi_{k_1}} \mu_{\xi_{k_2}}), \quad s, t \geq 0; k_1, k_2 = 1, 2, 3 \quad (5)$$

where μ_{ξ_k} is the mean of ξ_{ik} . By definition, $0 < \rho_{k_1 k_2}(s, t) < \infty$, and the magnitude of dependence is reflected by the value of $\rho_{k_1 k_2}(s, t)$. Equation (5) indicates that the dependence between two recurrent event processes is determined by the dependence between the two latent variables under model (1). For example, if ξ_{k_1} and ξ_{k_2} are positively correlated, the two recurrent event processes are positively correlated and the degree of dependence is constant over time and determined by the standardized covariance between ξ_{k_1} and ξ_{k_2} .

3 Estimation Procedure and Asymptotic Property

First, we simultaneously estimate the multiple recurrent event rates subject to informative censoring. As pointed out by Wang *et al.*¹⁸, the observed k th-type recurrent event times $(t_{ik1}, t_{ik2}, \dots, t_{ikm_{ik}})$ given $(\xi_{ik}, x_i, C_{ik}, m_{ik})$ are the order statistics of a set of independent, identically distributed (i.i.d) random variables, with density function

$$f_k(t) = \frac{\xi_{ik} \lambda_{0k}(t) \exp(x_i^T \alpha_k)}{\xi_{ik} \Lambda_{0k}(C_{ik}) \exp(x_i^T \alpha_k)} = \frac{\lambda_{0k}(t)}{\Lambda_{0k}(C_{ik})}, \quad 0 \leq t \leq C_{ik}, \quad (6)$$

where $\Lambda_{0k}(t) = \int_0^t \lambda_{0k}(s) ds$. Then the conditional likelihood of the observed data given $(\xi_{ik}, x_i, C_{ik}, m_{ik})$ is proportional to

$$L_c \propto \prod_{i=1}^n \prod_{k=1}^3 \prod_{j=1}^{m_{ik}} \frac{\lambda_{0k}(t_{ikj})}{\Lambda_{0k}(C_{ik})}. \quad (7)$$

Although the data are correlated, computationally the conditional likelihood has the form of likelihood of independently right truncated data. The nonparametric maximum likelihood estimator (MLE) of $\Lambda_{0k}(\cdot)$, denoted as $\hat{\Lambda}_{0k}(\cdot)$, based on independently right truncated data, is known to have a product-limit representation,

$$\hat{\Lambda}_{0k}(t) = \prod_{s_{k(l)} > t} \left(1 - \frac{d_{k(l)}}{R_{k(l)}} \right), \quad (8)$$

where $\{s_{k(l)}, l=1, \dots, L\}$ are the ordered and distinct values of the event times $\{t_{ikj}, j=1, \dots, m_{ik}\}$ of the k th type, $d_{k(l)}$ is the number of events occurring at $s_{k(l)}$, and $R_{k(l)}$ is the total number of events satisfying $\{t_{ikj} \leq s_{k(l)} \leq C_{ik}\}$.

The unbiased estimating equations for regression coefficients α_k are defined as

$$U(\alpha_k) = \frac{1}{n} \sum_{i=1}^n \bar{X}_i^T \left\{ m_{ik} \Lambda_{0k}(C_{ik})^{-1} - \exp(\bar{X}_i^T \gamma_k) \right\} = 0 \quad k=1, 2, 3 \quad (9)$$

where $\bar{X}_i = (1, X_i)$ and $\gamma_k = (\ln(\mu_{\xi_k}), \alpha_k)^T$. Then, α_k can be estimated by solving equation (9) by replacing $\Lambda_{0k}(C_{ik})$ with its estimator $\hat{\Lambda}_{0k}(C_{ik})$. After that, we have the estimates of the baseline ratio function and the regression parameters in equation (2),

$$\hat{R}_{01}(t) = \int_0^t \hat{r}_{01}(s) ds = \frac{\hat{\Lambda}_{01}(t)}{\hat{\Lambda}_{03}(t)}, \quad \hat{R}_{02}(t) = \int_0^t \hat{r}_{02}(s) ds = \frac{\hat{\Lambda}_{02}(t)}{\hat{\Lambda}_{03}(t)}, \quad (10)$$

$$\hat{\beta}_1 = \hat{\alpha}_1 - \hat{\alpha}_3, \quad \hat{\beta}_2 = \hat{\alpha}_2 - \hat{\alpha}_3. \quad (11)$$

Although we cannot observe the values of the latent variables for each patient, we can estimate the subject-specific and type-specific latent variable by

$$\hat{\xi}_{ik} = \frac{m_{ik}}{\hat{\Lambda}_{0k}(C_{ik}) \exp(x_i^T \hat{\alpha}_k)}, \quad \hat{\xi}_{i1} = \frac{\hat{\xi}_{i1}}{\hat{\xi}_{i3}}, \quad \hat{\xi}_{i2} = \frac{\hat{\xi}_{i2}}{\hat{\xi}_{i3}}. \quad (12)$$

Given equation (12), the moments of the latent variables and the rate ratio can be naturally estimated by

$$\hat{\mu}_{\xi_k} = \sum_{i=1}^n \hat{\xi}_{ik} / n, \quad \hat{cov}(\xi_{k_1}, \xi_{k_2}) = \sum_{i=1}^n \hat{\xi}_{ik_1} \hat{\xi}_{ik_2} / n - \hat{\mu}_{\xi_{k_1}} \hat{\mu}_{\xi_{k_2}}, \quad \hat{\rho}_{k_1 k_2} = 1 + \hat{cov}(\xi_{k_1}, \xi_{k_2}) / (\hat{\mu}_{\xi_{k_1}} \hat{\mu}_{\xi_{k_2}}). \quad (13)$$

The large sample properties of the estimators in model (1) have been well studied by Wang *et al.*^{18,20} We further establish the asymptotic properties of the estimators in Model (2) and the estimated rate ratio. Let $\theta = (\beta_k, R_{0k})$, $k=1,2$ and denote θ_0 and $\hat{\theta}_n$ as its true value and estimators, respectively. Under the regularity conditions specified in the Appendix, we show that the consistency and weak convergence of $\hat{\theta}_n$, as summarized in Theorem 1.

Theorem 1 Under the regularity conditions (A1-A3) specified in the Appendix, the estimator $\hat{\theta}_n$ is consistent, as defined by

$$\sum_{k=1}^2 |\hat{\beta}_k - \beta_k| + \sum_{k=1}^2 \sup_{t \in [0, \tau]} |\hat{R}_{0k}(t) - R_{0k}(t)|, \quad (14)$$

and converges to 0 almost surely and uniformly as $n \rightarrow \infty$. Further, $n^{1/2}(\hat{\theta}_n - \theta)$ converges weakly to a tight zero-mean Gaussian process as $n \rightarrow \infty$.

Theorem 2 Under the regularity conditions (A1-A3) specified in the Appendix, the estimator $\hat{\rho}_{k_1 k_2}$ is consistent, as defined by

$$\sum_{k_1 \neq k_2=1}^3 |\hat{\rho}_{k_1 k_2} - \rho_{k_1 k_2}|, \quad (15)$$

and converges to 0 almost surely as $n \rightarrow \infty$. Further, $n^{1/2}(\hat{\rho}_{k_1 k_2} - \rho_{k_1 k_2})$ converges to a normal distribution as $n \rightarrow \infty$.

The asymptotic variance-covariance matrices and details of the proofs for Theorems 1 and 2 are provided in the Appendix. The estimation of the variance-covariance matrix is not

straightforward because of the unknown baseline rate functions. Given the aforementioned weak convergence, we use a bootstrap resampling technique to approximate the variance-covariance matrices for the estimated parameters.

4 Simulation Studies

To evaluate the finite-sample performance of the proposed methods, we conducted a series of Monte -Carlo simulations. We generated bivariate recurrent event data from n patients, with a maximum follow-up time of 10 hours. We introduced dependence between the bivariate recurrent event data by a pair of latent variables generated from either a uniform distribution or a gamma distribution. Specifically, for patient i we first generated three independent latent variables $(\xi_i, \xi_{i1}^*, \xi_{i2}^*)$, and then let the two correlated subject-specific latent variables be $\xi_{i1} = 0.9\xi_i + 0.1\xi_{i1}^*$ and $\xi_{i2} = 0.9\xi_i + 0.1\xi_{i2}^*$. For the uniform setting (scenario 1-2), we chose the distribution to be uniform on the interval (0.2, 3) such that the degree of dependence is relatively weak $\rho = 1.20$, and for the gamma setting (scenario 3-4), we chose the distribution to be gamma(1, 0.2), yielding a relatively strong dependence, $\rho = 1.80$. For patient i , we included two covariates: x_{i1} from a Bernoulli distribution, Bernoulli(0.5), and x_{i2} from the standard normal distribution. Given the latent variable (ξ_{i1}, ξ_{i2}) and covariate x_i , the bivariate process $\{N_{i1}(t), N_{i2}(t)\}$ was generated from a pair of non-stationary Poisson processes with the rate functions as

$$\lambda_{i1}(t) = \xi_{i1} \lambda_{01}(t) \exp(x_i^T \alpha_1) = \xi_{i1} (0.05 + 0.01t) \exp(x_i^T \alpha_1) \quad (16)$$

and

$$\lambda_{i2}(t) = \xi_{i2} \lambda_{02}(t) \exp(x_i^T \alpha_2) = \xi_{i2} (0.06 + 0.008t) \exp(x_i^T \alpha_2). \quad (17)$$

It should be noted that we have $\int_0^T \lambda_{01}(s) ds = 1$ and $\int_0^T \lambda_{02}(s) ds = 1$ for the identifiability issue. To complete the data generation, we generated two types of censoring: non-informative censoring from the uniform distribution, $U(0,30)$, and informative censoring from the following hazard function:

$$h_k(t; x_i) = \xi_{ik} h_0(t) \exp(x_i^T \gamma),$$

where $h_0(t) = t/400$ and $\gamma = (1, -0.5)$. For each scenario, we considered two sample sizes ($n=250$ and $n=500$) with 1000 replications or resamples.

Table 1 summarizes the average of the estimates, empirical standard errors and bootstrap standard errors based on 200 resamples. The average number of recurrent events per patient was approximately 2.59 and 2.45 for the two types of recurrent events in scenario 1, and approximately 4.41 and 6.36 for scenario 2. All model parameters, including the degree of the dependence, were estimated very well by the proposed method in all scenarios: the

biases were small and the bootstrap standard errors were close to the empirical deviation. As expected, the standard errors of all estimates decreased by 23.3% to 34.5% with increasing sample size.

The empirical averaged estimates of the cumulative ratio of the two recurrent rate functions, $R_{01}(t) = \Lambda_{01}(t)/\Lambda_{02}(t)$, are plotted in Figure 1. The estimated curves were very close to the true curves with indistinguishable biases. Note that the estimated curves had relatively large biases and variation at the very beginning of the study due to the limited observed information. Then by using the cumulative information over time, the estimated curves better approximated the true curves.

We have also compared the performance of the proposed method to that of the naive method, in which the cumulative rate functions are estimated by the observed numbers of the recurrent events and the ratio is estimated by the proportion of the observed numbers of two recurrent events. The simulation results are summarized in the Supplementary Material. In summary, the proposed method was empirically unbiased, while the naive method produced biased results. In particular, the naive method underestimated the ratio curves heavily at the tail.

5 Applications to Trauma Transfusion Data

We applied our proposed method to data from the motivating study, PROMMTT, to study the time pattern of the blood product rate ratios (i.e. plasma:RBCs and platelet:RBCs) and evaluate factors associated with the rate ratios. The PROMMTT study was the first large-scale, prospective study of trauma patients admitted directly from the injury scene to ten Level-1 trauma centers in the U.S. Among the total of 1245 enrolled trauma patients, only 919 patients had complete baseline covariate information, including systolic blood pressure (SBP), heart rate (HR), hemoglobin concentration (Hgb), and pH. We did not impute the missing covariate information and therefore included only 919 patients in our analysis dataset. In the study, all 919 patients received RBCs, with a total of 5868 units of RBC transfusions; 635 (69.2%) patients had received plasma, with a total of 4157 units of plasma transfusions; and 262 (28.1%) patients had received platelets, with a total of 3045 units of platelet transfusions. As mentioned before, possible reasons for censoring could be any hemorrhage control intervention (e.g., surgery, endovascular procedures), death, or the end of the study. Specifically, during the study, 94 out of 919 (10.2 %) patients died within 24 hours of hospital admission.

In Figure 2 (a), we display the estimated cumulative rate functions of RBCs, plasma and platelets. For comparison, we also plot the three naive curves by accounting for the total number of transfusions up to time t , ignoring the informative censoring. As shown, such a naive method will have biased results, leading to underestimation of blood products in our case. In Figure 2(b), we present the estimated blood product ratios (i.e. plasma:RBCs and platelet:RBCs). Overall, the two ratios were not constant over time, but the ratio curves had the similar shapes. The two curves increased within the first five hours after ED admission, and then remained stable. This can be partially explained by the fact that most blood product transfusions are administered within the first five hours of admission to the ED. The ratio of

plasma:RBC rates always stayed beyond the ratio of platelets:RBC rates. Specifically, after the first five hours, the ratio of plasma:RBC rates was around 0.7, and the ratio of platelets:RBC rates was around 0.5.

In addition to studying the time-varying pattern of the transfusion ratios, we were interested in evaluating the association with baseline covariates on blood transfusions. This assessment can be addressed by fitting models (1) and (2). Table 2 summarizes the analytic results for three rate models for RBCs, plasma and platelets. Moreover, Table 3 lists the analytic results for two rate ratio models for plasma:RBCs and platelets:RBCs. As shown in Table 2, patients with lower Hgb (< 11), lower pH (< 7.25), and bleeding sites involving the abdomen and pelvis tended to receive more transfusions of all three blood products. Also, patients with lower SBP (< 90) were more likely to receive more RBC and plasma transfusions. For example, on average, the number of RBC transfusions of patients with lower Hgb (< 11) was higher by a factor of 1.433 (95 % confidence interval [1.12, 1.71]) compared with patients having higher Hgb (≥ 11) after controlling for other baseline covariates. Interestingly, we found that the association of baseline covariates with the rate ratios of transfusions (plasma:RBCs and platelets:RBCs) were different from their association with the amounts of blood product transfusions. As shown in Table 3, for the ratio of plasma:RBC transfusion rates, the significant factor are pH and bleeding site involving the head and pelvis. Patients with pelvic hemorrhage tended to receive a higher ratio of plasma:RBCs by a factor of 1.170 (95 % confidence interval [1.08, 1.27]). For the ratio of platelets:RBC transfusion rates, the significant factor are Hgb and bleeding site involving the abdomen and pelvis. The ratio of platelets:RBC transfusion rates for patients with lower Hgb (< 11) is higher by a factor of 1.465 (95 % confidence interval [1.19, 1.80]) than those of patients with higher Hgb.

As expected, our analysis indicated that the three types of blood transfusions were positively inter-dependent. The degree of dependence between RBC and plasma transfusion rates was 2.86 with a 95% confidence interval of [2.58, 3.15]. Similarly, the degree of dependence between RBC and platelet transfusion rates was 3.21 with a 95% confidence interval of [2.84, 3.58], and between plasma and platelet transfusion rates, it was 3.54 with a 95% confidence interval of [3.14, 3.94]. Such strong positive inter-dependence suggests that the joint models of blood products rate ratios would gain statistical efficiency compared with separate models for each type of blood transfusion.

6 Discussion

Our methodology assesses models and estimation procedures for the ratio of rates for multivariate recurrent event data. The estimating procedure benefits from simplicity and flexibility relative to the alternative maximum likelihood estimator under the shared frailty models, which is subject to the parametric assumption of the shared frailty and the specified assumptions on the relationship between the multivariate recurrent event data and dependent censoring. Though the proposed model is presented in the context of three types of recurrent events, extensions to handle multivariate recurrent event data with $K \geq 3$ are straightforward because the estimation procedure does not rely on the dimension of the multivariate recurrent event data.

One limitation of the proposed estimation procedure is the assumption of non-time-dependent covariates. Although this assumption holds in our blood transfusion study, it may not hold in other applications. In this case, the estimation procedure proposed by Huang *et al.*²¹ can be generalized to accommodate the time-dependent covariates.

In this paper, our focus is the estimation of the ratios of transfusion rates of different blood products for trauma patients, and the evaluation of covariate effects on such ratios. It is also of interest to evaluate the effects of such time-dependent ratios on subsequent clinical outcomes, such as the ensuing survival time.^{7,9} Developing rigorous statistical tools to answer this question is beyond the scope of this paper, and is a worthy objective for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

To establish the large-sample properties of the proposed parameter estimators, we impose the following regularity conditions:

1. $\Lambda_{0k}(\tau) > 0$ and $P(C_k = \tau, \xi_k > 0) > 0$,
2. X is uniformly bounded,
3. $E[\xi_k^2] < \infty$, and $G_k(u) = E[\xi_k I(C_k \geq u)]$ is a continuous function for $u \in [0, \tau]$, $k = 1, 2, 3$.

Sketch of proof for Theorem 1. Denote t_{ikj} as the j th event time of the i th patient and k th process, and define the functions $G_k(t) = E[\xi_k I(C_k \geq t)]$, $R_k(t) = G_k(t) \Lambda_{0k}(t)$, $Q_k(t) = \int_0^t G_k(u) d\Lambda_{0k}(u)$. Let V_k be the joint probability measure of $(\bar{X}, m_k, C_k)$, $k = 1, 2, 3$. Following the method proposed by Wang *et al.*¹⁸, we can establish the independent and identically distributed (i.i.d.) representation of the estimated regression coefficients in model (1),

$$\sqrt{n}(\hat{\alpha}_k - \alpha_k) = n^{-1/2} \sum_{i=1}^n d_{ik}(\alpha_k) + o_p(1),$$

where

$$b_{ik}(t) = \sum_{j=1}^{m_{ik}} \left\{ \int_t^{\tau} \frac{I(t_{ikj} \leq u \leq c_{ik}) dQ_k(u)}{R_k^2(u)} - \frac{I(t < t_{ikj} \leq \tau)}{R_k(t_{ikj})} \right\}.$$

$$e_{ik} = \left\{ - \int \frac{\bar{x}^T m_k b_{ik}(c_k) dV_k(\bar{x}, m_k, c_k)}{\Lambda_{0k}(c_k)} \right\} + \bar{x}_i^T \left\{ \frac{m_{ik}}{\Lambda_{0k}(c_{ik})} - \exp(x_i^T \gamma_k) \right\},$$

and d_{ik} is the vector function $E[e_{1k}']^{-1} e_{ik}$ without first entry. Hence, $\sqrt{n}(\hat{\alpha}_k - \alpha_k)$ converges weakly to a normal distribution with mean zero and variance $E[d_{1k}^2]$ by the central limit theorem. Similarly, it is can be shown that

$$\sqrt{n} \{ \hat{\Lambda}_{0k}(t) - \Lambda_{0k}(t) \} = n^{-1/2} \sum_{i=1}^n \Lambda_{0k}(t) b_{ik}(t) + o_p(1)$$

for $\inf\{c_k : \Lambda_{0k}(c_k) > 0\} < t < \tau$. It implies that $\sqrt{n} \{ \hat{\Lambda}_{0k}(t) - \Lambda_{0k}(t) \}$ converges weakly to a normal distribution with mean zero and variance $\Lambda_{0k}(t)^2 E[b_1^2(t)]$.

Given the asymptotic properties of the estimated regression coefficients in model (1), it is straightforward to derive the asymptotic properties for the estimated regression coefficients

$\hat{\beta}_k$ in model (2). The i.i.d. representation of $\hat{\beta}_k$ is $\sqrt{n}(\hat{\beta}_k - \beta_k) = n^{-1/2} \sum_{i=1}^n f_{ik} + o_p(1)$,

where $f_{ik} = d_{ik}(a_k) + d_{11}(a_1)$, which implies that $\sqrt{n}(\hat{\beta}_k - \beta_k)$ converges weakly to a

normal distribution with mean zero and variance $E[f_{1k}^2]$. Further, by the functional delta method, we can derive the i.i.d. representation of the estimated cumulative baseline ratio

$\hat{R}_{0k}(t)$,

$$\begin{aligned} \sqrt{n} \{ \hat{R}_{0k}(t) - R_{0k}(t) \} &= - \sqrt{n} \frac{\Lambda_{0k}(t)^* \{ \hat{\Lambda}_{01}(t) - \Lambda_{01}(t) \}}{\Lambda_{01}(t)^2} + \sqrt{n} \frac{\hat{\Lambda}_{0k}(t) - \Lambda_{0k}(t)}{\Lambda_{01}(t)} \\ &= - \frac{1}{\sqrt{n}} \sum_{i=1}^n \frac{\Lambda_{0k}(t) b_{i1}(t)}{\Lambda_{01}(t)} + \frac{1}{\sqrt{n}} \sum_{i=1}^n \frac{\Lambda_{0k}(t) b_{ik}(t)}{\Lambda_{01}(t)} + o_p(1) \\ &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \frac{\Lambda_{0k}(t)^* \{ b_{ik}(t) - b_{i1}(t) \}}{\Lambda_{01}(t)} + o_p(1) \\ &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \phi_i(t) + o_p(1) \end{aligned}$$

where

$$\phi_i(t) = \sum_{j=1}^{m_i} \frac{\Lambda_{0k}(t)}{\Lambda_{01}(t)} \left[\left\{ \int_t^{\tau} \frac{I(t_{ij} \leq u \leq C_{ik}) dQ(u)}{R_k^2(u)} - \frac{I(t < t_{ij} < \tau)}{R_k(t_{ij})} \right\} - \left\{ \int_t^{\tau} \frac{I(t_{ij} \leq u \leq C_{ik}) dQ(u)}{R_1^2(u)} - \frac{I(t < t_{ij} < \tau)}{R_1(t_{ij})} \right\} \right]$$

Hence, $\sqrt{n} \left\{ \hat{R}_{0k}(t) - R_{0k}(t) \right\}$ converges weakly to a normal distribution with mean zero and variance $E \left[\phi_i^2(t) \right]$.

Sketch of proof for Theorem 2. We first established the asymptotic normality of the estimated mean for the latent variable, which relies on the normality of $\hat{\Lambda}_{0k}(t)$ and $\hat{\alpha}_k$. Using arguments similar to those in the proof for Theorem 1, we have

$$\begin{aligned} \sqrt{n} \left(\hat{\mu}_{\xi_k} - \mu_{\xi_k} \right) &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \left\{ \frac{m_{ik}}{\hat{\Lambda}_{0k}(c_{ik}) \exp(x_i^T \hat{\alpha}_k)} - \frac{m_{ik}}{\Lambda_{0k}(c_{ik}) \exp(x_i^T \alpha_k)} + \frac{m_{ik}}{\Lambda_{0k}(c_{ik}) \exp(x_i^T \alpha_k)} - \mu_{\xi_k} \right\} \\ &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \psi_i + o_p(1). \end{aligned}$$

As n goes to infinity, $\sqrt{n} \left(\hat{\mu}_{\xi_k} - \mu_{\xi_k} \right)$ converges to a normal distribution with variance $E \left[\psi_i^2 \right]$. Next, we established the asymptotic normality of the estimator for the second moment of the latent variables $\mu_{\xi_{k_1} \xi_{k_2}} = E(\xi_{k_1} \xi_{k_2})$. The second moment can be estimated by

$\hat{\mu}_{\xi_{k_1} \xi_{k_2}} = \frac{1}{n} \sum_{i=1}^n \hat{\xi}_{k_1} \hat{\xi}_{k_2}$. Let V be the joint probability measure of $(\bar{X}, m_{k_1}, m_{k_2}, C_{k_1}, C_{k_2})$. Then, we show that

$$\begin{aligned} \sqrt{n} \left(\hat{\mu}_{\xi_{k_1} \xi_{k_2}} - \mu_{\xi_{k_1} \xi_{k_2}} \right) &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \left\{ \frac{m_{ik_1}}{\hat{\Lambda}_{0k_1}(c_{ik_1}) \exp(x_i^T \hat{\alpha}_{k_1})} \frac{m_{ik_2}}{\hat{\Lambda}_{0k_2}(c_{ik_2}) \exp(x_i^T \hat{\alpha}_{k_2})} - \mu_{\xi_{k_1} \xi_{k_2}} \right\} \\ &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \left\{ \frac{m_{ik_1}}{\hat{\Lambda}_{0k_1}(c_{ik_1}) \exp(x_i^T \hat{\alpha}_{k_1})} \frac{m_{ik_2}}{\hat{\Lambda}_{0k_2}(c_{ik_2}) \exp(x_i^T \hat{\alpha}_{k_2})} - \frac{m_{ik_1}}{\Lambda_{0k_1}(c_{ik_1}) \exp(x_i^T \alpha_{k_1})} \frac{m_{ik_2}}{\Lambda_{0k_2}(c_{ik_2}) \exp(x_i^T \alpha_{k_2})} \right\} \\ &= - \frac{1}{\sqrt{n}} \sum_{i=1}^n \int \frac{m_{k_1} m_{k_2} b_{ik_1 k_2}(c_{k_1}, c_{k_2})}{\Lambda_{0k_1}(c_{k_1}) \exp(x_i^T \alpha_{k_1}) \Lambda_{0k_2}(c_{k_2}) \exp(x_i^T \alpha_{k_2})} dV(\bar{x}, m_{k_1}, m_{k_2}, c_{k_1}, c_{k_2}) \\ &\quad + \frac{1}{\sqrt{n}} \sum_{i=1}^n \left\{ \frac{m_{ik_1}}{\Lambda_{0k_1}(c_{ik_1}) \exp(x_i^T \alpha_{k_1})} \frac{m_{ik_2}}{\Lambda_{0k_2}(c_{ik_2}) \exp(x_i^T \alpha_{k_2})} - \mu_{\xi_{k_1} \xi_{k_2}} \right\} + o_p(1) \\ &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \varphi_i + o_p(1). \end{aligned}$$

where

$$\begin{aligned} \varphi_i &= \int \frac{m_{k_1} m_{k_2} b_{ik_1 k_2}(c_{k_1}, c_{k_2})}{\Lambda_{0k_1}(c_{k_1}) \exp(x_i^T \alpha_{k_1}) \Lambda_{0k_2}(c_{k_2}) \exp(x_i^T \alpha_{k_2})} dV(\bar{x}, m_{k_1}, m_{k_2}, c_{k_1}, c_{k_2}) \\ &\quad + \left\{ \frac{m_{ik_1}}{\Lambda_{0k_1}(c_{ik_1}) \exp(x_i^T \alpha_{k_1})} \frac{m_{ik_2}}{\Lambda_{0k_2}(c_{ik_2}) \exp(x_i^T \alpha_{k_2})} - \mu_{\xi_{k_1} \xi_{k_2}} \right\} \\ b_{ik_1 k_2}(t_1, t_2) &= \sum_{j=1}^{\tau} \sum_{l=1}^{\tau} \left\{ \int_{t_1}^{\tau} \int_{t_2}^{\tau} \frac{I(t_{ik_1 j} \leq u \leq c_{ik_1}, t_{ik_2 l} \leq v \leq c_{ik_2}) dQ_{k_1}(u) dQ_{k_2}(v)}{R_{k_1}^2(u) R_{k_2}^2(v)} - \frac{I(t_1 < t_{ik_1 j} \leq \tau, t_2 < t_{ik_2 l} \leq \tau)}{R_{k_1}(t_{ik_1 j}) R_{k_2}(t_{ik_2 l})} \right\}. \end{aligned}$$

It follows that $\sqrt{n} \left(\hat{\mu}_{\xi_{k_1} \xi_{k_2}} - \mu_{\xi_{k_1} \xi_{k_2}} \right)$ converges to a normal distribution with variance $E \left[\varphi_i^2 \right]$. Summarizing the previous arguments and using the multivariate Delta method, we have

$$\sqrt{n}(\hat{\rho}_{k_1 k_2} - \rho_{k_1 k_2}) : N(0, \nabla^T \Sigma \nabla)$$

where ∇ denotes the vector of the first derivatives of $\rho_{k_1 k_2}$ with respect to $\mu_{\xi_{k_1} \xi_{k_2}}$, $\mu_{\xi_{k_1}}$, and $\mu_{\xi_{k_2}}$, and Σ denotes the variance-covariance matrix of

$$\sqrt{n}(\hat{\mu}_{\xi_{k_1} \xi_{k_2}} - \mu_{\xi_{k_1} \xi_{k_2}}, \hat{\mu}_{\xi_{k_1}} - \mu_{\xi_{k_1}}, \hat{\mu}_{\xi_{k_2}} - \mu_{\xi_{k_2}})^T.$$

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Figure 1.

Cumulative baseline ratio of rates function for two recurrent events under four scenarios

Figure 2.

Estimated cumulative rates and ratios of the rates of blood product transfusions.

Table 1

Summary of simulation studies.

n	Para	TRUE	EST	SD	SE	n	Para	TRUE	EST	SD	SE
Uniform # of event = 2.59, 2.45											
250	μ_{ξ_1}	1.60	1.601	0.252	0.242	250	μ_{ξ_1}	5.00	5.005	0.876	0.817
	α_{11}	1.00	1.012	0.170	0.164		α_{11}	1.00	0.943	0.187	0.181
	α_{12}	1.00	0.991	0.090	0.089		α_{12}	1.00	0.935	0.109	0.099
	μ_{ξ_2}	1.60	1.588	0.244	0.230		μ_{ξ_2}	2.67	4.939	0.753	0.726
	α_{21}	1.50	1.511	0.168	0.161		α_{21}	2.00	1.995	0.171	0.162
	α_{22}	0.50	0.502	0.083	0.079		α_{22}	0.50	0.481	0.095	0.089
	β_1	-0.50	-0.499	0.213	0.206		β_1	-1.00	-1.052	0.162	0.160
	β_2	0.50	0.488	0.104	0.102		β_2	0.50	0.454	0.089	0.084
	ρ	1.20	1.180	0.173	0.163		ρ	1.80	1.743	0.207	0.198
500	Para	TRUE	EST	SD	SE	500	Para	TRUE	EST	SD	SE
	μ_{ξ_1}	1.60	1.618	0.178	0.175		μ_{ξ_1}	5.00	4.979	0.621	0.597
	α_{11}	1.00	0.995	0.117	0.116		α_{11}	1.00	0.936	0.137	0.131
	α_{12}	1.00	0.985	0.069	0.062		α_{12}	1.00	0.932	0.080	0.072
	μ_{ξ_2}	1.50	1.596	0.165	0.166		μ_{ξ_2}	5.00	4.898	0.529	0.524
	α_{21}	1.50	1.501	0.117	0.114		α_{21}	2.00	1.986	0.120	0.116
	α_{22}	0.50	0.500	0.055	0.055		α_{22}	0.50	0.491	0.067	0.063
	β_1	-0.50	-0.506	0.150	0.147		β_1	-1.00	-1.050	0.118	0.115
	β_2	0.50	0.484	0.074	0.071		β_2	0.50	0.442	0.064	0.060
	ρ	1.20	1.181	0.129	0.127		ρ	1.80	1.755	0.159	0.152

Note: EST: empirical mean; SD: empirical standard error; SE: average of bootstrapping standard error estimates

Table 2

Estimated regression coefficients of joint models of three transfusion rates

	Coefficient	SE	Wald	p-value
RBC transfusion				
SBP < 90	0.244	0.087	2.801	0.005
HR 120	0.145	0.078	1.862	0.063
Hgb < 11	0.360	0.091	3.939	<0.001
pH < 7.25	0.652	0.079	8.212	<0.001
Bleeding sites				
Head	-0.111	0.108	-1.027	0.304
Face	-0.130	0.077	-1.688	0.091
Neck	-0.246	0.146	-1.684	0.092
Chest	0.209	0.087	2.409	0.016
Abdomen	0.369	0.085	4.339	<0.001
Pelvis	0.518	0.094	5.492	<0.001
Limb	0.047	0.080	0.583	0.560
Unknown	0.102	0.153	0.667	0.505
Plasma transfusion				
SBP < 90	0.295	0.097	3.052	0.002
HR 120	0.115	0.089	1.301	0.193
Hgb < 11	0.306	0.109	2.805	0.005
pH < 7.25	0.810	0.096	8.432	<0.001
Bleeding sites				
Head	0.084	0.118	0.716	0.474
Face	-0.033	0.093	-0.357	0.721
Neck	-0.126	0.240	-0.524	0.600
Chest	0.173	0.096	1.815	0.070
Abdomen	0.437	0.098	4.453	<0.001
Pelvis	0.675	0.107	6.332	<0.001
Limb	0.069	0.100	0.685	0.493
Unknown	0.086	0.163	0.529	0.597
Platelet transfusion				
SBP < 90	0.217	0.136	1.591	0.112
HR 120	0.142	0.140	1.012	0.312
Hgb < 11	0.741	0.151	4.904	<0.001
pH < 7.25	0.626	0.148	4.235	<0.001
Bleeding sites				
Head	0.168	0.193	0.869	0.385
Face	-0.082	0.159	-0.517	0.605
Neck	0.119	0.379	0.315	0.753
Chest	0.080	0.146	0.547	0.584
Abdomen	0.644	0.151	4.274	<0.001

	Coefficient	SE	Wald	p-value
Pelvis	0.749	0.153	4.901	<0.001
Limb	0.100	0.145	0.691	0.490
Unknown	0.095	0.239	0.397	0.691

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Table 3

Estimated regression coefficients of the ratio models of transfusion rates.

	Coefficient	SE	Wald	p-value
Plasma/RBC ratio transfusion				
SBP < 90	0.052	0.052	0.996	0.319
HR 120	−0.030	0.050	−0.596	0.552
Hgb < 11	−0.054	0.050	−1.088	0.277
pH < 7.25	0.158	0.048	3.290	0.001
Bleeding sites				
Head	0.195	0.071	2.750	0.006
Face	0.097	0.060	1.604	0.109
Neck	0.121	0.148	0.815	0.415
Chest	−0.036	0.059	−0.607	0.544
Abdomen	0.068	0.053	1.274	0.203
Pelvis	0.157	0.043	3.654	<0.001
Limb	0.022	0.050	0.431	0.666
Unknown	−0.016	0.091	−0.176	0.860
Platelet/RBC ratio transfusion				
SBP < 90	−0.026	0.101	−0.261	0.794
HR 120	−0.004	0.113	−0.031	0.975
Hgb < 11	0.382	0.105	3.651	<0.001
pH < 7.25	−0.026	0.105	−0.244	0.808
Bleeding sites				
Head	0.278	0.155	1.797	0.072
Face	0.048	0.126	0.380	0.704
Neck	0.365	0.294	1.242	0.214
Chest	−0.129	0.121	−1.066	0.286
Abdomen	0.275	0.112	2.444	0.015
Pelvis	0.231	0.102	2.272	0.023
Limb	0.053	0.102	0.522	0.602
Unknown	−0.008	0.192	−0.039	0.969