A Joint Latent Class Analysis for Adjusting Survival Bias with Application to Trauma Transfusion Study

Jing Ning[1], Mohammad H. Rahbar*[2,3], Sangbum Choi[3], Chuan Hong[4], Jin Piao[4], Deborah J. del Junco[5], Erin E. Fox[5], Elaheh Rahbar[5], and John B. Holcomb[5]

[1]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Division of Clinical and Translational Sciences, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston, TX, USA
[3]Division of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Sciences Center at Houston, Houston, TX, USA
[4]Division of Biostatistics, School of Public Health, The University of Texas Health Sciences Center at Houston, Houston, TX, USA
[5]Center for Translational Injury Research, Division of Acute Care Surgery, Department of Surgery, The University of Texas Health Science Center at Houston, Houston, TX, USA

Abstract

There is no clear classification rule to identify trauma patients who have severely hemorrhaged and may need substantial blood transfusions. A surrogate measure of severe hemorrhage, massive transfusion, has traditionally been defined as the transfusion of at least 10 units of red blood cells (RBCs) within 24 hours of emergency department admission. This definition suffers from misclassification due to a survival bias that arises because such patients may die before 24 hours. Accordingly, we propose a latent class model that adjusts for the survival bias by incorporating baseline information at emergency department admission, observed number of RBC units transfused, and survival time. The statistical challenges include induced dependent censoring for the amount of RBCs transfused. We propose a pseudo-likelihood function by using the inverse weighting principle and develop an expectation-maximization algorithm for the estimation. We evaluate the performance of the proposed method in classifying patients with severe hemorrhage and compare it to the existing definition of massive transfusion through simulations and an application to the Prospective Observational Multi-center Major Trauma Transfusion study.

Key Words: Latent class model, EM algorithm, induced censoring, inverse weighting principle, massive transfusion, survival analysis.

1. Introduction

There is no universal diagnostic test to identify trauma patients who are severely hemorrhaging (SH), although hemorrhagic shock accounts for the largest proportion of early mortality within the

*Corresponding author: Mohammad H. Rahbar, e-mail: mohammad.h.rahbar@uth.tmc.edu, Phone: +1 713 500 7901, Fax: +1 713 500 0766

first hour of a patient receiving care in a trauma center (Kauvar *et al.*, 2006). Such patients may require a substantial transfusion of blood to survive. A massive transfusion protocol (MTP) is an order given to the blood bank for the rapid delivery of multiple blood products, typically including at least six units of packed red blood cells (RBCs) along with plasma and platelets, which are often required for the treatment of uncontrolled hemorrhage (Yücel *et al.*, 2006). As there is no universally accepted criteria to measure the severity of ongoing hemorrhage, massive transfusion (MT) has been conventionally used as a binary surrogate in the trauma literature. MT, historically defined as the transfusion of $\geq$ 10 units of packed RBCs within 24 hours of emergency department (ED) admission (Como *et al.*, 2004), has been used to develop prediction rule to trigger MTP (Holcomb *et al.*, 2008). Although the term MT has been widely used to identify the subgroup of patients in need of MTP, this definition has several recognized limitations. First, a patient must survive until 10 units of RBCs have been transfused to be counted as MT. As a result, an individual who experienced exsanguination and died within 24 hours of ED admission and/or before the 10th unit of RBCs was transfused will not be considered as a patient who needed MTP. This important source of bias, termed survival bias, excludes some patients who die quickly, and leads to misclassification of some patients who have had SH and needed MTP. Second, the parameters defining MT, at least 10 units of RBCs and within 24 hours, have not been validated. These recognized limitations have results in a number of definitions of MT, such as at least 5-6 RBC units in 4-6 hours (Levi *et al.*, 2011). Alternatively, Savage et al. considers rates of RBC transfusion and defined "critical administration thresholds" (CAT) of $\geq$ 3 units of RBC/hr to identify hemorrhaging patients (Savage *et al.*, 2013). However, this definition is still limited to RBC transfusions and does not account for plasma, platelet transfusions or crystalloids and colloids. Rahbar et al. reported that 4 units of any resuscitative fluid including blood products, crystalloids and colloids, referred to as the "early resuscitation intensity", within the first 30 minutes was predictive of 6 hours portability in the PROMMTT study (Rahbar *et al.*, 2013a). Despite these improvements, no universally accepted and proven definition for MT exists. In addition to the inherent biases of the MT definition itself, several existing predictive algorithm in the trauma literature (McLaughlin *et al.*, 2008) are based on the conventional MT definition as a reference standard, and thus may perform poorly when predicting which patients need MTP. Last, the conventional MT definition, solely determined by the amount of RBC units transfused, may fail to capture other patient characteristics that the clinician may have immediately available and which may be useful during the initial resuscitation.

This research is motivated by the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, which is a 10-center prospective observational study of trauma patients admitted directly from the scene of an injury to a level-1 trauma center (Holcomb *et al.*, 2013; Rahbar *et al.*, 2012). The primary objectives of PROMMTT were to develop predictive models for initiating MTP as well as assessing the role of blood products, (i.e., RBCs, plasma, and platelets) and time-varying plasma: RBC and platlet:RBC ratios on in-hospital mortality. The study enrolled 1245 adults who were trauma patients between July 2010 and October 2011, who survived for at least 30 minutes after ED admission and received a transfusion of at least 1 unit of RBCs within 6 hours of admission. The study documented the timing of transfusions during active resuscitation and the patient outcomes. Among the participating trauma patients, 297 (23.9%) received at least

10 units of RBCs within 24 hours, hence classified as MT. The information collected included patient characteristics (e.g., age, gender, race, weight), international normalized ratio (INR), systolic blood pressure (SBP), hemoglobin concentration (Hgb), heart rate (HR), pH, body temperature, base deficit, positive results for Focused Assessment for the Sonography of Trauma (FAST) examination, injury severity scores (ISS), bleeding site (intracranial, abdominal), and the mechanism of injury (assault, fall, gunshot, motor vehicle accident, stabbing, other penetrating wound). The correct classification of patients at higher risk of exsanguination is critical in order for MTP to be restricted to these patients because of the risks associated with unnecessary blood transfusions. The collection of large-scale, time-dependent, complex data through PROMMTT has produced a unique opportunity to establish a valid classification system for patients in need of MTP, herein referred to patients experiencing SH. In a recent paper (Rahbar *et al.*, 2013b), our research team realized the need to redefine patients in need of MT and utilized latent class models to identify SH patients based on data from a retrospective study (Holcomb *et al.*, 2008), but the retrospective study did not have detailed information regarding the survival time, which could play an important role to differentiate the patients experiencing SH or not.

In this paper, we take advantage of data from PROMMTT, which had detailed information regarding the survival time, and extend our previous work by proposing a joint latent class (LC) model to identify a subgroup of patients with SH, in which the indicator of SH is treated as a latent variable. The proposed joint LC modeling fully utilizes the observed data, including patient characteristics, total amount of RBCs transfused, and survival time. This model captures the nature of the problem without a reference standard and provides a method to adjust for survival bias. LC analysis to identify unobservable class membership has been widely used in practice. Examples include applications in multivariate survival (e.g., Hougaard & Hougaard (2000)), covariate measurement error (e.g.,Carroll *et al.* (2006)), diagnostic accuracy studies (e.g., Luo *et al.* (2014)) and joint analysis of a surrogate marker and time-to-event data (Proust-Lima *et al.*, 2007). However, a unique challenge in analyzing trauma transfusion data is the induced dependent censoring for the total amount of RBCs transfused due to mortality before 24 hours. In other words, the total amount of RBC units transfused prior to death or within 24 hours of admission can be censored by the censoring time. On the other hand, even though the censoring is purely random and is not informative for the occurrence of death, the observed total amount of RBC units transfused at the time of censoring is positively correlated with the true but unobserved total amounts of RBC units transfused at death or within 24 hours of ED admission (Lin, 2000). Therefore, the existing LC models cannot be directly applied without making improvements to address the aforementioned subtle features. In this article, we fill the gap in the available methods by applying an inverse probability censoring weighting technique in the presence of induced dependent censoring.

The remainder of this paper is organized as follows. In Section 2, we describe the proposed LC model and inference procedure, including an Expectation-Maximization (EM) algorithm for parameter estimation. In Section 3, we conduct simulation studies to evaluate finite sample sample performance of the proposed method. In Section 4, we will demonstrate application of our method to data from the PROMMTT study. We provide a brief discussion in Section 5.

2. Statistical Model and Likelihood Inference

2.1 Notation and model

In clinical point of view, we assume that there are two latent classes that represent trauma patients with SH versus those without SH: $M = 1$ if a patient has SH and $M = 0$ otherwise. Consider a study of n patients. For patient i, let $\tilde{T}_i$ and C_i denote the survival time and censoring time from the time of ED admission, respectively, and Z_i denote the p-vector of the baseline covariates. With the potential right censoring, the observed survival time is $T_i = \min(C_i, \tilde{T}_i)$ and the corresponding censoring indicator is $\delta_i = I(\tilde{T}_i \leq C_i)$. We make the standard assumption that the censoring time is independent of the survival time. Let $Y_i(t)$ be the logarithm of the observed total number of RBC units transfused until time t. Then $Y_i(\tilde{T}_i)$ is the logarithm of the total of RBC units transfused. The major sampling constraint is that $Y_i(\tilde{T}_i)$ is censored by $Y_i(\tilde{C}_i)$, which subsequently induces dependent censoring because $Y_i(\tilde{T}_i)$ is positively correlated with $Y_i(\tilde{C}_i)$. In our case, we define the response variable $\tilde{Y}_i$ as the logarithm of the total number of RBC units transfused at 24 hours or death, whatever comes first. In other words, $\tilde{Y}_i = Y(\tilde{T}_i)$ if the ith patient dies within 24 hours, and $\tilde{Y}_i = Y_i(24)$ if the ith patient survives up to 24 hours. Note that the true value of $\tilde{Y}_i$ is not observable if the ith subject is censored, so we record $Y_i = \min\{\tilde{Y}_i, Y_i(C_i)\}$.

The proposed joint LC model includes three components: a logistic regression model for the latent class membership, a linear regression model for the logarithm of the total number of RBC units transfused at 24 hours or death, and a parametric hazard regression model for the survival time. Specifically, first, we introduce a logistic regression model that links the probability of having SH with baseline covariates, denoted by Z_1,

$$P(M_i|Z_{1i};\alpha) = \frac{\exp\{(Z_1^T\alpha)M\}}{1+\exp(Z_1^T\alpha)}. \tag{1}$$

Here, the covariate vector Z_1 may be a subset of Z and include patient characteristics such as age, systolic blood pressure, abdominal bleeding status, initial international normalized ratio, and mechanism of injury measured at ED admission. We next consider a multiple linear regression model of $\tilde{Y}_i$ on covariate vector Z_2, the survival time, and latent class membership,

$$\tilde{Y}_i = Z_{2i}^T\beta_Z + T_i\beta_T + M_i\beta_M + \epsilon_i, \tag{2}$$

where $\beta = (\beta_Z, \beta_T, \beta_M)^T$ and the random error ϵ_i has a normal distribution with mean zero and variance σ^2. Here, the covariate vector Z_2 in model (2) may be different from the covariate Z_1 used in model (3). To fully utilize all observed information to improve the classification of patients as SH vs non- SH, we impose the following hazard regression model on survival time,

$$\lambda(t|Z_{3i}, M_i;\gamma) = \lambda_{0M}(t;\gamma_1)\exp(Z_{3i}^T\gamma_2), \tag{3}$$

where λ_{0M} is the pre-specified parametric class-specific baseline hazard, $M = 0, 1$, and Z_3 denotes the subset of the baseline covariates Z related to survival. Here, we adopt a parametric specification

for the class-specific baseline hazard function, which is commonly used in the LC model literature to avoid computational complexity and non-identifiability due to the nonparametric assumption of the baseline hazard. This helps to avoid having a strong modeling assumption on the baseline hazard by using sufficiently flexible class of functions of time, such as polynomial functions or regression splines.

2.2 Estimation and inference

In line with blood transfusion as our motivating example, we consider the outcome as the logarithm of the total number of RBC units transfused at death or 24 hours post-ED admission. As stated previously, the exact amount of RBCs transfused at 24 hours or death is not observable for censored patients, and consequently we have an induced dependent censoring issue for the blood transfusion outcome $\tilde{Y}_i$. This phenomenon is also encountered in medical cost data, in which some patients are not followed for the full duration of the study, and thus their total costs are informatively censored (Lin, 2000). To deal with this informative censoring and adjust for potential bias due to the positive correlation between $\tilde{Y}_i$ and $Y_i(C_i)$, we apply the inverse probability censoring weighting principle (Lin, 2000) and modify the likelihood function accordingly to incorporate the adjustment in the proposed LC model.

It should be noted that the values of latent class membership M_i are predicted through a logistic regression model. To avoid computational difficulties, we treat the latent class membership as missing data, and maximize the likelihood function of the complete data instead of the observed data to estimate the parameter vector $\theta = (\alpha, \beta, \gamma, \sigma^2)$. On the other hand, we do not treat the censored (unobserved) blood transfusion outcome as missing data due to informative censoring, and instead we use weights to properly account for the incompleteness of observed transfused RBC units for patients who die before 24 hours. Specifically, the weighted complete likelihood to be maximized is

$$L(\theta) = \prod_{i=1}^{n} \left\{ \frac{\exp(Z_{1i}^T \alpha M_i)}{1+\exp(Z_{1i}^T \alpha)} \right\} \lambda(T_i|Z_{3i}, M_i; \gamma)^{\delta_i} S(T_i|Z_{3i}, M_i; \gamma) f_{\tilde{y}}(Y_i|Z_{2i}, M_i, T_i; \beta, \sigma^2)^{w_i}, \tag{4}$$

where $w_i = \delta_i / G(T_i)$ are the weights, $G(\cdot)$ is the survival function of the censoring time, and $f_{\tilde{y}}$ is the normal density function defined by model in equation (2). Given the observed survival information, the unknown survival function of the censoring time in the likelihood function (4) can be estimated consistently based on Kaplan-Meier method. After plugging in the consistent Kaplan-Meier estimator, denoted by $\hat{G}_i$, we use the EM algorithm to obtain parameter estimates given the observed data $O_i = (Y_i, T_i, Z_i, \delta_i), i = 1, \cdots, n$.

We first select initial values $\theta^{(0)} = (\hat{\alpha}^{(0)}, \hat{\beta}^{(0)}, \hat{\gamma}^{(0)}, \hat{\sigma}^{(0)})$, and let $\theta^{(k)} = (\hat{\alpha}^{(k)}, \hat{\beta}^{(k)}, \hat{\gamma}^{(k)}, \hat{\sigma}^{(k)})$ denote the estimates of the parameters in the kth iteration. Following the principle of the EM algorithm, in the E step of the $(k+1)th$ iteration, we first evaluate the conditional probability of the latent class membership based on the observed data and the estimated parameters from the last iteration $\theta^{(k)}$. Then we calculate the conditional expectation of the complete log-likelihood

given the observed data and $\theta^{(k)}$. Specifically, the posterior probability of $M_i = 1$ given $\{O_i, i = 1, \cdots, n\}$ and $\theta^{(k)}$ is

$$\hat{P}_i^{(k)} \quad = \quad P(M_i = 1|O_i; \theta^{(k)}) = \frac{P(M_i = 1, O_i; \theta_{(k)})}{P(M_i = 1, O_i; \theta^{(k)}) + P(M_i = 0, O_i; \theta^{(k)})},$$

where

$$P(M_i = j, O_i; \theta^{(k)}) = \left\{ \frac{\exp(Z_{1i}^T \alpha^{(k)} j)}{1 + \exp(Z_{1i}^T \alpha^{(k)})} \right\} \lambda(T_i|Z_{3i}, j; \gamma^{(k)})^{\delta_i} S(T_i|Z_{3i}, j; \gamma) f_{\tilde{y}}(Y_i|Z_{2i}, j, T_i; \beta^{(k)}, \sigma^{2(k)})^{w_i}.$$

It follows that the conditional expectation of the complete log-likelihood given the observed data and $\theta^{(k)}$,

$$\begin{aligned} l(\theta|\theta^{(k)}) \quad = \quad & \sum_{i=1}^{n} \hat{P}_i^{(k)} \Bigg[Z_{1i}^T \alpha + \frac{\delta_i}{\hat{G}_i} \left\{ -\frac{(Y_i - Z_{2i}^T \beta_Z - T_i \beta_T - \beta_M)^2}{2\sigma^2} - \log \sigma \right\} \\ & - \log\{1 + \exp(Z_{1i}^T \alpha)\} + \delta_i \left\{ \lambda_{01}(T_i; \gamma_1) \exp(Z_{3i}^T \gamma_2) \right\} - \Lambda_{01}(T_i; \gamma_1) \exp(Z_{3i}^T \gamma_2) \Bigg] \\ + \quad & \sum_{i=1}^{n} (1 - \hat{P}_i^{(k)}) \Bigg[\frac{\delta_i}{\hat{G}_i} \left\{ -\frac{(Y_i - Z_{2i}^T \beta_Z - T_i \beta_T)^2}{2\sigma^2} - \log \sigma \right\} \\ & - \log\{1 + \exp(Z_{1i}^T \alpha)\} + \delta_i \left\{ \lambda_{00}(T_i; \gamma_1) \exp(Z_{3i}^T \gamma_2) \right\} - \Lambda_{00}(T_i; \gamma_1) \exp(Z_{3i}^T \gamma_2) \Bigg], \end{aligned} \tag{5}$$

where Λ_{0M} denotes the cumulative baseline hazard function.

In the maximization step, we maximize the expected complete log-likelihood function (5) to update the parameter estimates. The estimates can be updated by solving the corresponding score equation, defined as the first derivative of the expected complete log-likelihood, for which the Newton-Raphson algorithm can be used. These updated parameters are then used to determine conditional expectations in the expectation step. This procedure is repeated until a specified criterion for convergence is achieved. Specifically, the Marquardt algorithm with stringent convergence criteria (Marquardt, 1963) is used to determine the convergence of the log-likelihood. In addition to the parameter stability and log-likelihood stability, we ensure that the convergence is reached only when $d^T H^{-1} d < \epsilon$, where d is the gradient vector and H the Hessian matrix (by default $\epsilon = 10^{-4}$). We define the estimates from the last iteration before convergence as the proposed estimates, denoted by $\hat{\theta}$.

One possible limitation of the EM algorithm is that the initial values may play an important role and the maxima may be a local maxima. To address this issue, we repeated the maximization process in the simulation studies 20 times and used random starting values. For the LC model specified in this paper, the algorithm converged fairly quickly and the use of multiple starting points was not computationally intensive. We compared the estimates from one initial value with the estimates that represent the maximizer over the 20 maximizations that used different initial values. Louis provided a variance estimation procedure for estimates obtained from the EM algorithm by computing

the observed information matrix, in which the conditional expectations of the complete-data score and Hessian are evaluated (Louis, 1982). However, the proposed likelihood involves estimating the weights by using the Kaplan-Meier estimator, and hence cannot be treated as the standard likelihood. To study these and account for the additional variation due to the estimated weights using the Kaplan-Meier estimator, we revised the score function using the martingale expression of the Kaplan-Meier estimator. The details regarding the revised score function are provided in Appendix A. For a finite sample, the empirical Hessian may be unstable and cannot even be guaranteed to be a negative definite matrix, which is also observed in our simulation study. Accordingly, following McLachlan & Peel (2000), we estimated the variance by using the empirical observed information matrix, which equals to

$$I_c(\hat{\theta};\mathcal{O}) = \sum_{i=1}^{n} S_c(O_i;\hat{\theta}) S_c(O_i;\hat{\theta})^T - \frac{1}{n} S_c^*(\mathcal{O};\hat{\theta}) S_c^*(\mathcal{O};\hat{\theta})^T, \tag{6}$$

where $\mathcal{O}$ denotes the observed data, $S_c(\mathcal{O}_i;\hat{\theta})$ is the score function with respect to the vector of parameters θ from the ith observation, the specific formula of which is available in appendix, and $S_c^*(\mathcal{O};\hat{\theta}) = \sum_{i=1}^{n} S_c(O_i;\hat{\theta})$, both evaluated at $\hat{\theta}$. The covariance matrix of the parameter estimates is then approximated by the inverse of the empirical observed information matrix (6).

One purpose of the proposed LC model is to identify the latent class membership (e.g., SH vs non- SH) of patients, to aid in the decision making regarding treatments. The classification of patients into subgroups is based on the estimated posterior probabilities. Specifically, the posterior probability of the ith patient, $P_{ik} = P(M_i = k|O_i,\hat{\theta})$, determines how likely it is that the ith patient belongs to group k, while simultaneously taking into account the information regarding observed baseline covariates, amount of blood transfused, and the survival information. In our example with two latent classes, we classify patient i into class 1 if and only if $P_{i1} > P_{i0}$, and into class 0 otherwise.

3. Simulations

We conducted simulation studies to evaluate the finite sample performance in the performance of the proposed method in identifying the latent class membership. We used sample sizes of 400 and 800, with 1000 repetitions comprising each scenario. Mimicking the PROMMTT study, we set the latent variable indicating class membership as a binary value, and generated results from the following logistic regression model,

$$\text{logit}P(M = 1|Z_1,\alpha) = \alpha_0 + Z_{11}\alpha_1 + Z_{12}\alpha_2, \tag{7}$$

where Z_{11} is a binary covariate following a Bernoulli distribution with probability of success equal to 0.5, and Z_{12} is a continuous covariate following a standard normal distribution. We chose the regression coefficients to be $\alpha = (0, -0.5, 0.5)^T$. Given the latent variable M, we generated the survival time from the Weibull regression model. We specified the hazard function of survival as

$$\lambda(t|Z_3, M;\gamma) = \lambda_0(t;\gamma_1)\exp(Z_{31}\gamma_{21} + Z_{32}\gamma_{22}), \tag{8}$$

where Z_{31} is a binary covariate following a Bernoulli distribution with probability of success equal to 0.5, and Z_{32} is a continuous covariate following a standard normal distribution. We varied the regression coefficients of γ_2. The baseline hazard considered was $\lambda_0 = \gamma_{11}\gamma_{12}t^{\gamma_{12}}M + \gamma_{13}\gamma_{14}t^{\gamma_{14}}(1-M)$. We generated the censoring time from a uniform distribution on the interval $[0, \tau_c]$. We chose different combinations of parameters in order to cover a wide range of scenarios. Specifically, we considered three scenarios: 1) 20% mortality rate and 20% random censoring rate at 24 hours; 2) 40% mortality rate and 20% random censoring rate at 24 hours; and 3) 60% mortality rate and 20% random censoring rate at 24 hours.

The logarithm of the number of transfused RBC units at death was generated from a linear regression model,

$$\tilde{Y} = \beta_0 + Z_{21}\beta_1 + Z_{22}\beta_2 + \tilde{T}\beta_T + M\beta_M + \epsilon, \tag{9}$$

where Z_{21} is a binary covariate following a Bernoulli distribution with probability of success equal to 0.5, Z_{22} is a continuous covariate following a standard normal distribution, and ϵ distributed as normal $N(0,1)$. By letting $\beta_Z = (0, -0.5, 0.5)$, $\beta_T = 0.1$, and $\beta_M = 1$, we assumed that patients in class 0 are more likely to receive a smaller number of cumulative RBC transfusion units such that patients in class 1 may represent the subgroup with a higher likelihood of a larger number of cumulative RBCs, hence needing MTP. Table 1 summarize the simulation results over 1000 runs, including the averaged point estimates of the parameters, the empirical standard errors, and the model- based standard error, respectively. Given a generated data set, in order to avoid local maxima, we repeated the maximization process 20 times using different and randomly chosen starting values for parameters, and then used the average values over the 20 maximizations as the estimates. We compared these results to simulation results using only one starting value and one maximization. The results were very similar, suggesting that the proposed method is quite robust with respect to the initial values. As shown in Table 1, the parameters in all three sub- models were estimated reliably by the proposed method in such a way that the bias of the estimates were small and the model-based standard errors were close to their empirical values. As expected, the empirical bias of the estimates decreased with an increased sample size, and the standard error of the estimates decreased with an increased mortality rate. We noted that the standard errors were slightly overestimated by the asymptotic standard error for the low mortality rate (20%) scenario, perhaps due to the limited observed information, but such a bias decreased with an increased mortality rate.

Based on the results of the fitted model, we estimated the latent class memberships by comparing two posterior probabilities, and further evaluated the level of agreement between the true latent class memberships and the estimated ones from simulation study. Under the scenario with an Weibull distribution, the levels of agreement were 67.1%, 83.8%, and 76.3% for the three scenarios, respectively, when the sample size was 400, and 67.9%, 84.0%, and 77.7% for the three scenarios, respectively, when the sample size was 800. It is interesting to note that the levels of agreement increased with an increasing mortality rate due to the improved performance of the estimates, as shown in Table 1.

Table 1: Simulation results for three different scenarios when using the Weibull baseline function.

N	Scen.		α_0	α_1	α_2	β_M	β_0	β_1	β_2	β_T	$\log(\sigma^2)$	γ_{21}	γ_{22}	$\log(\gamma_{11})$	$\log(\gamma_{12})$	$\log(\gamma_{13})$	$\log(\gamma_{14})$
400	I	TRUE	0.00	-0.50	0.50	1.00	0.00	-0.50	0.50	0.10	0.00	-2.50	2.50	-0.92	-2.30	-2.30	-3.00
		EST	-0.13	-0.59	0.55	1.15	-0.07	-0.49	0.50	0.10	-0.19	-2.57	2.58	-0.86	-2.33	-2.25	-3.01
		SEE	0.50	0.72	0.34	0.45	0.42	0.33	0.21	0.03	0.25	0.36	0.24	0.14	0.31	0.27	0.43
		SE	0.85	0.99	0.58	0.41	0.43	0.34	0.21	0.03	0.23	0.43	0.28	0.16	0.38	0.32	0.43
	II	TRUE	0.00	-0.50	0.50	1.00	0.00	-0.50	0.50	0.10	0.00	-1.00	1.00	-0.22	-1.61	-2.30	-1.61
		EST	-0.04	-0.56	0.53	1.06	-0.03	-0.47	0.48	0.10	-0.09	-0.99	1.01	-0.19	-1.64	-2.26	-1.61
		SEE	0.23	0.34	0.20	0.28	0.23	0.19	0.10	0.02	0.14	0.22	0.11	0.10	0.20	0.20	0.20
		SE	0.29	0.38	0.23	0.27	0.23	0.17	0.10	0.02	0.13	0.22	0.13	0.11	0.21	0.22	0.22
	III	TRUE	0.00	-0.50	0.50	1.00	0.00	-0.50	0.50	0.10	0.00	-2.50	2.50	0.41	-1.39	-0.22	-1.39
		EST	-0.05	-0.54	0.53	1.34	-0.19	-0.51	0.50	0.10	-0.27	-2.49	2.50	0.40	-1.39	-0.20	-1.40
		SEE	0.36	0.51	0.29	0.28	0.23	0.23	0.13	0.02	0.21	0.23	0.18	0.10	0.18	0.09	0.18
		SE	0.34	0.45	0.26	0.19	0.19	0.18	0.11	0.02	0.14	0.22	0.16	0.08	0.17	0.09	0.18
800	I	TRUE	0.00	-0.50	0.50	1.00	0.00	-0.50	0.50	0.10	0.00	-2.50	2.50	-0.92	-2.30	-2.30	-3.00
		EST	-0.08	-0.51	0.53	1.06	-0.03	-0.50	0.50	0.10	-0.08	-2.54	2.54	-0.89	-2.32	-2.27	-3.01
		SEE	0.34	0.53	0.25	0.33	0.30	0.23	0.14	0.02	0.16	0.27	0.17	0.10	0.22	0.19	0.28
		SE	0.59	0.67	0.39	0.30	0.31	0.23	0.14	0.02	0.15	0.29	0.18	0.11	0.25	0.21	0.29
	II	TRUE	0.00	-0.50	0.50	1.00	0.00	-0.50	0.50	0.10	0.00	-1.00	1.00	-0.22	-1.61	-2.30	-1.61
		EST	-0.03	-0.50	0.50	1.05	-0.03	-0.49	0.49	0.10	-0.06	-1.01	1.00	-0.21	-1.61	-2.28	-1.60
		SEE	0.16	0.24	0.12	0.20	0.16	0.13	0.07	0.01	0.09	0.15	0.08	0.06	0.13	0.12	0.14
		SE	0.20	0.26	0.16	0.18	0.16	0.12	0.07	0.01	0.09	0.15	0.08	0.08	0.15	0.15	0.15
	III	TRUE	0.00	-0.50	0.50	1.00	0.00	-0.50	0.50	0.10	0.00	-2.50	2.50	0.41	-1.39	-0.22	-1.39
		EST	-0.05	-0.52	0.55	1.30	-0.17	-0.49	0.49	0.10	-0.21	-2.46	2.46	0.38	-1.35	-0.20	-1.39
		SEE	0.28	0.35	0.20	0.21	0.17	0.15	0.09	0.01	0.15	0.16	0.13	0.07	0.13	0.06	0.13
		SE	0.26	0.33	0.18	0.14	0.14	0.13	0.08	0.01	0.10	0.15	0.11	0.06	0.12	0.06	0.13

Note: SSE, empirical standard errors; SE, mean of estimated standard errors;
Scenario I, 20% mortality within 24 hours, and 20% random censoring;
Scenario II, 40% mortality within 24 hours, and 20% random censoring;
Scenario III, 60% mortality within 24 hours; 20% random censoring.

4. Applications

We illustrated an application of the proposed method with the data from the PROMMTT study, which is the first large scale, prospective study of trauma patients admitted directly from the injury scene to ten level-1 trauma centers in the US. Our analysis included 942 patients with completed data needed for our LC model. For each patient, baseline variables were available, as well as various blood assessments measured after ED arrival. The LC mixture model framework was used to identify SH patients, assuming that the study population could be split into two latent subgroups. The baseline covariates in the analysis, selected by exploratory analysis and the clinical investigators' consideration, included the following patients' characteristics at admission: SBP, HR, pH, Hgb and ISS. For the purpose of our analysis we categorized these into two categories using the following cut-points: SBP less than 90 mm Hg, HR greater than or equal to 120 bpm , pH less than 7.25, Hgb less than 11 and ISS greater than or equal to 25. In addition, the cumulative ratio of blood products at 24 hours, such as plasma:RBC and platelet:RBC ratios were included in the models for blood transfusion and survival time.

Our analysis focused on the two-mixture model because it is the most preferred based on the Bayesian information criterion (BIC) score and consistent with our objective to classify patients experiencing SH or not. To choose the initial values for the proposed LC analysis, we first fixed the LC membership at the traditional binary MT status and conducted naïve analysis based on MT. We then obtained 20 initial values by randomly perturbing the estimates based on MT. In our LC analysis, the class membership probability, given the observed variables in ED, including SBP, HR, pH, Hgb and ISS, were estimated through estimated coefficients of the logistic model. We treated the time to death within 24 hours as outcome in a proportional hazards model that specifies the class-specific baseline risk functions with Weibull baseline, and modeled the log-transformed RBCs transfusion using a class-specific linear model. The results, including estimated regression coefficients, are summarized in Table 2. The class membership probabilities were then calculated by posterior probabilities through the LC analysis. We also evaluated the discrimination of the latent classes by using the measure of entropy (Proust-Lima *et al.*, 2014). The result of $1-\frac{En}{N\log K}$ is 0.730 indicating a good classification for the proposed model, where $En = -\sum_{i=1}^{N}\sum_{k=1}^{K}\hat{\pi}_{ik}\log(\hat{\pi}_{ik})$, $\hat{\pi}_{ik}$ is the estimated latent-class probability defined in equation 1, and K is the number of latent classes.

We compared the classification results of the LC approach with the traditional MT approach. The left panel of Table 3 is a 2×2 table of patients classified by SH and MT. Among 942 patients considered in the analysis, there were 215 (22.8%) MT patients. On the other hand, our joint LC model classified 85 (9.0%) patients into SH and the majority of patients (91.0%) remained non-SH. The overall agreement between the two classifications (i.e., SH vs. MT) is 74.3% (i.e., 700 out of 942 patients). The right panel of Table 3 is a 2×2 table of patients identified by LC analysis versus survival status at 24 hours. Out of the 100 patients who died within 24 hours, 74 (i.e., 74%)were classified as SH.

In Figure 1(a), we displayed estimated Kaplan-Meier survival curves, stratified by SH and MT, respectively. As shown, compared to the MT classification, the SH patients tend to have substan-

Table 2: Estimated regression coefficients along with standard errors (SE), Wald test and p-values.

	Coefficient	SE	Wald	p-value
Model 1: Logistic regression for latent class-membership:				
Intercept	-3.499	0.311	-11.235	<0.0001
SBP < 90	-0.290	0.282	-1.028	0.3041
HR ≥ 120	-0.094	0.280	-0.334	0.7388
pH < 7.25	0.430	0.273	1.579	0.1143
Hgb < 11	0.876	0.254	3.451	0.0006
ISS ≥ 25	1.037	0.297	3.490	0.0005
Model 2: Linear regression for log-transformed RBC transfusion				
Intercept(SH)	1.431	0.141	10.154	<0.0001
Intercept(non-SH)	3.256	0.261	12.489	<0.0001
Time	-0.095	0.011	-8.900	<0.0001
SBP < 90	0.292	0.059	4.957	<0.0001
HR ≥ 120	0.195	0.059	3.307	0.0009
pH < 7.25	0.321	0.059	5.458	<0.0001
Hgb < 11	0.323	0.057	5.682	<0.0001
ISS ≥ 25	0.220	0.056	3.957	0.0001
Plasma:RBC ratio	0.037	0.038	0.972	0.3313
Platelet:RBC ratio	0.175	1.000	0.175	0.8608
Model 3: Proportional hazards model for survival time				
Shape(SH)	0.011	0.003	3.037	0.0024
Shape(non-SH)	1.219	0.056	21.597	<0.0001
Scale(SH)	5.895	0.381	15.465	<0.0001
SBP < 90	0.272	0.259	1.053	0.2925
HR ≥ 120	0.338	0.287	1.178	0.2387
pH < 7.25	1.751	0.344	5.087	<0.0001
Hgb < 11	-0.119	0.276	-0.432	0.6660
ISS ≥ 25	0.053	0.282	0.187	0.8517
Plasma:RBC ratio	-0.142	0.180	-0.790	0.4295
Platelet:RBC ratio	-0.295	0.120	-2.464	0.0137

Note: Shape, shape parameter in Weibull baseline; Scale, scale parameter in Weibull baseline.

tially higher risk profiles and thus lower survival probabilities. Figure 1(b) shows the estimated class-specific survival functions from the parametric (two-parameter Weibull) specification, which appears to be reasonably close to the nonparametric estimates.

Table 3: Contingency table for trauma patients classified by SH (from the LC model) and MT, and survival status at 24 hours of admission.

	non-MT	MT	Alive	Dead	Total
non-SH	671	186	831	26	857
SH	56	29	11	74	85
Total	727	215	842	100	942

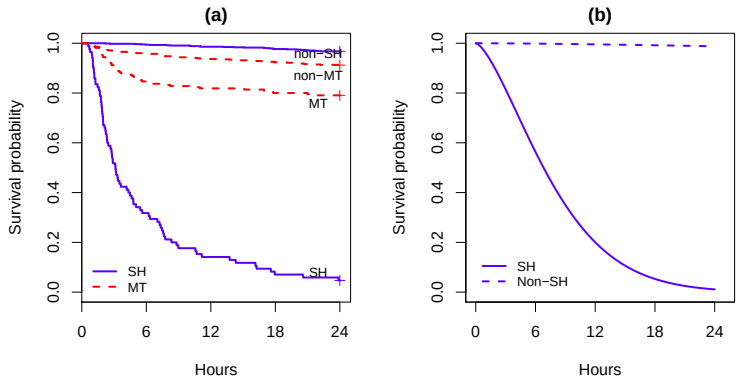

Figure 1: (a) Kaplan-Meier estimates for traumatic death stratified by SH (solid) and MT (dash) classifications, and (b) class-specific survival estimates from the proposed model.

5. Discussion

Severe hemorrhage is often associated with increased morbidity and mortality in critically injured trauma patients. Early and aggressive transfusion of blood products in these patients may correct coagulopathy, control bleeding, and improve survival. However, determining the criteria to use to identify which patients have a severe hemorrhage is challenging due to the survival bias. Our methodology uses a joint model framework to classify severely hemorrhaging trauma patients who may require a massive transfusion protocol. Our method jointly incorporates the baseline information at arrival in the emergency department, RBC utilization (number of units), and survival time during the first 24 hours. Different from previous work (Rahbar *et al.*, 2013b), the proposed joint model is the first to incorporate time-to-event data to improve the classification of patients with severe hemorrhage. Although we have focused on two latent classes for SH, the proposed methodology can be easily generalized to situations in which there are more than 2 (i.e., $K > 2$) latent classes.

The PROMMTT study is the first large- scale, prospective study of trauma patients admitted directly from the injury scene to ten level-1 trauma centers in the US. The study collected detailed information on the timing of the use of blood products, including RBC units, plasma, and platelets. To avoid computational complexity, we included only the total number of RBC units transfused

in the joint LC model. Extending the proposed approach to accommodate the timing and order in which blood products are received should be the focus of future research.

In this paper, our focus is the classification of trauma patients with and without severe hemorrhage based on observed information such as the baseline characteristics at emergency department arrival, RBC utilization, and survival time. A more clinically meaningful question is how to build an enhanced predictive algorithm using the new approach to identifying severe hemorrhage, in which only the baseline information at emergency department arrival will be utilized. Developing rigorous statistical tools for prediction algorithms and the patient evaluation procedures is beyond the scope of this paper, and is a worthy objective for future research.

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Appendix

In the following we provide the revised score function of the complete log-likelihood that accounts for the additional variation due to the estimated survival function and its independent and identically distributed (i.i.d.) representation. Let $l_{\hat{G}}(\theta)$ denote the weighted complete log- likelihood after plugging in the Kaplan-Meier estimator. Denoting $[A|B]$ as the log of the conditional distribution of A given B, we have $l_{\hat{G}}(\theta) = \sum_{i=1}^{n} \left\{ [M_i|Z_{1i}] + [T_i, \delta_i|Z_{3i}, M_i] + \frac{\delta_i}{\hat{G}(t_i)}[Y_i|Z_{2i}, M_i, T_i] \right\}$, where $[M_i|Z_{1i}] = Z_{1i}^T \alpha M_i - \log\{1+\exp(Z_{1i}^T\alpha)\}$, $[T_i, \delta_i|Z_{3i}, M_i] = \log \lambda(T_i|Z_{3i}, M_i; \gamma)^{\delta_i} S(T_i|Z_{3i}, M_i; \gamma)$, $[Y_i|M_i, Z_{2i}, T_i] = \log f(\tilde{Y}_i|Z_{2i}, M_i, T_i; \beta_Z, \beta, \sigma^2)$.

Let $\mathcal{D}(\cdot)$ denote the first-order derivative. The score function of the weighted complete log-likelihood after plugging in the Kaplan- Meier estimator, denoted as $S_c^*(\mathcal{O}; \theta)$, is

$$\sum_{i=1}^{n} \left\{ \mathcal{D}([M_i|Z_{1i}]) + \frac{\delta_i}{\hat{G}(t_i)} \mathcal{D}([Y_i|M_i, Z_{2i}, T_i]) + \frac{\delta_i(G(t_i) - \hat{G}(t_i))}{G(t_i)\hat{G}(t_i)} \mathcal{D}(T_i|M_i, Z_{3i}]_\lambda) \right\} + \sum_{i=1}^{n} \mathcal{D}([T_i, \delta_i|M_i, Z_{3i}]).$$

By using the asymptotic martingale expression, we have $\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \frac{\delta_i(G(t_i) - \hat{G}(t_i))}{G(t_i)\hat{G}(t_i)} \mathcal{D}([Y_i|M_i, Z_{2i}, T_i])$

equals

$$\frac{1}{n}\sum_{i=1}^{n}\left\{\frac{1}{\sqrt{n}}\sum_{j=1}^{n}\int_0^\infty \frac{I(s\le t)dM_j^c(s)}{G(s)S_T(s)}\right\}\frac{\delta_i\mathcal{D}([Y_i|M_i,Z_{2i},T_i])}{G(t_i)}+o_p(1),$$

where $S_T(s)=P(T\ge s)$, $M_i^c(s)=I(T_i\le t,\delta_i=0)-\int_0^s I(T_i\ge u)d\Lambda_c(u)$ is the martingale for the censoring times, and $\Lambda_c(u)$ is the cumulative hazard function of the censoring times C.

Using the fact that $\frac{1}{n}\sum_{i=1}^n I(T_i\ge s)\delta_i\mathcal{D}([Y_i|M_i,Z_{2i},T_i])/G(t_i)$ converges to $D(s)$, we have

$$\begin{aligned}\frac{1}{\sqrt{n}}S_c^*(\mathcal{O};\theta) &= \frac{1}{\sqrt{n}}\sum_{i=1}^{n}\left\{\mathcal{D}([M_i|Z_{1i}])+\frac{\delta_i}{G(t_i)}\mathcal{D}([Y_i|M_i,Z_{2i},T_i])+\int_0^\infty\frac{D(s)}{G(s)S_T(s)}dM_i^c(s)\right\}\\ &+ \sum_{i=1}^{n}\mathcal{D}([T_i,\delta_i|M_i,Z_{3i}])+o_p(1).\end{aligned}$$

The revised score function is then used in equation (6) of Section 2.2 for the variance estimation.

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