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A joint latent class analysis for adjusting survival bias with application to a trauma transfusion study

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Abstract

There is no clear classification rule to rapidly identify trauma patients who are severely hemorrhaging and may need substantial blood transfusions. Massive transfusion (MT), defined as the transfusion of at least 10 units of red blood cells within 24 h of hospital admission, has served as a conventional surrogate that has been used to develop early predictive algorithms and establish criteria for ordering an MT protocol from the blood bank. However, the conventional MT rule is a poor proxy, because it is likely to misclassify many severely hemorrhaging trauma patients as they could die before receiving the 10th red blood cells transfusion. In this article, we propose to use a latent class model to obtain a more accurate and complete metric in the presence of early death. Our new approach incorporates baseline patient information from the time of hospital admission, by combining respective models for survival time and usage of blood products transfused within the framework of latent class analysis. To account for statistical challenges, caused by induced dependent censoring inherent in 24-h sums of transfusions, we propose to estimate an improved standard via a pseudo-likelihood function using an expectation-maximization algorithm with the inverse weighting principle. We evaluated the performance of our new standard in simulation studies and compared with the conventional MT definition using actual patient data from the Prospective Observational Multicenter Major Trauma Transfusion study.

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Supporting information

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Keywords

latent class model; EM algorithm; induced dependent censoring; inverse weighting principle; massive transfusion

1. Introduction

Because the true volume of blood loss and bleeding severity for an individual trauma patient cannot be directly measured or accurately ascertained in a rapid and standardized manner, the timely and appropriate order of a hospital's massive transfusion protocol (MTP) for patients in urgent need of transfusion is compromised. The real-world performance of algorithms developed to rapidly diagnose a trauma patient's need for an MTP order [1, 1–3] has been disappointing [4, 5], and the conventional definition of massive transfusion or MT (i.e., the transfusion of >10 units of red blood cells or RBCs within 24 h of Emergency Department (ED) admission [6]) is inevitably biased. Mortality rates peak in the minutes to hours after injury occurrence [7], and the conventional definition of MT misclassifies seriously hemorrhaging patients who died before receiving the 10th unit [8, 9]. While alternative MT definitions have been proposed (e.g., the critical administration threshold or critical administration threshold for any patient transfused at a rate of three RBC units per hour anytime within 24 h of ED admission [10,11]), they have yet to overcome the problem of misclassification for patients who urgently needed the MTP order despite an inability to attain arbitrary threshold numbers of RBC transfusions before their hemorrhage control or death occurred. Another possible alternative to the MT definition to reduce bias from misclassification and informative censoring is to establish a composite gold standard, for example, all patients who had (1) undergone surgical or endovascular interventions to control serious hemorrhage, (2) received three or more consecutive blood product transfusions within a few hours, or (3) died from hemorrhagic shock or exsanguination. However, because of variations in patient populations and provider resuscitation practices (including MTPs, diagnostic, endovascular, and surgical procedures), even composite gold standards may be biased and irreproducible. We present a latent class (LC) approach to enable the development of more accurate and reliable novel algorithms for the rapid diagnosis of a trauma patient's need for an MTP order. Our latent class approach creates a valid classification scheme to more definitively identify a trauma patient's unobservable need for an MTP order. Our severe hemorrhage or SH classifier takes advantage of a more comprehensive set of key patient and injury characteristics and relevant outcomes in a manner robust to dependent censoring due to successful hemorrhage control or death.

This research is motivated by the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, which was a multicenter prospective observational study of trauma patients at the highest level of activation directly admitted from the scene of an injury to one of 10 level-1 trauma centers in the United States [12, 13]. The primary objectives of PROMMTT were to develop predictive models to help establish MTP and assess the role of blood products, (i.e., RBCs, plasma, and platelets) and time-varying plasma : RBC and platelet : RBC ratios on in-hospital mortality. The study enrolled 1245 trauma patients between July 2010 and October 2011, who survived for at least 30 min after

ED admission and received a transfusion of at least one unit of RBCs within 6 h 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 h, hence classified as MT. The information collected included patient characteristics (e.g., age, gender, race, and 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 examination, injury severity scores (ISS), bleeding site (intracranial or abdominal), and the mechanism of injury (assault, fall, gunshot, motor vehicle accident, stabbing, or 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 severely hemorrhaging patients. In a recent paper [14], our research team utilized latent class models to identify severely hemorrhaging patients [15], but this study did not have detailed information on the survival times, which play an important role in differentiating severely hemorrhaging patients from the trauma population.

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 has been widely used to identify unobservable class membership in practice. Examples include applications in meta-analysis [16], multivariate survival [17], covariate measurement error [18], behavioral sciences [19], biometrical genetics [20], diagnostic accuracy studies [21–24], and joint analysis of a surrogate marker and time-to-event data [25–28]. However, a unique challenge in analyzing trauma transfusion data is the induced dependent censoring for the total amount of RBCs transfused due either to successful interventions to control hemorrhage or the patient's mortality before 24 h. In other words, the total amount of RBC units transfused prior to death or within 24 h of admission is dependent upon the duration of a trauma patient's hemodynamically unstable survival. Our LC models have been enhanced to account for the key underlying patient characteristics and provider interventions. To deal with this type of informative censoring, Lin [29] proposed the inverse probability censoring weighting (IPCW) principle. In this article, we improve existing LC models by applying the inverse probability censoring weighting technique to appropriately adjust for induced dependent censoring.

The remainder of this paper is organized as follows. In Section 2, we describe the proposed joint 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 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

From a clinical perspective, we assume that there are two latent classes that represent trauma patients with severe hemorrhage versus those without severe hemorrhage: $M = 1$ if a patient has severe hemorrhage and $M = 0$ otherwise. We note that the proposed method can be naturally extended to the case with more than two latent classes. 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 h or at the time of death, whatever comes first. In other words, $\tilde{Y}_i = Y_i(\tilde{T}_i)$ if the i th patient before the 24-h mark, and $\tilde{Y}_i = Y_i(24)$ if the i th patient survives up to 24 h. The true value of $\tilde{Y}_i$ is not observable if the i th subject is censored, so we record $Y_i = \min\{\tilde{Y}_i, Y_i(C_i)\}$. Such features are frequently encountered in the censored medical cost data [29, 30]. Notice that in our problem, the presence of induced censoring has an impact on the blood amount $\tilde{Y}_i$ as well as the MT-based classification, and naïve analysis with $\tilde{Y}_i$ would lead to biased results.

The proposed joint LC model includes three modeling 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 h 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 severe hemorrhage with baseline covariates, denoted by Z_1 ,

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

Z_1 may be a subset of Z and include (but not limited to) patient characteristics such as age, systolic blood pressure, abdominal bleeding status, INR, 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,

$$\tilde{Y}_i = Z_{2i}^T \beta_z + h(T_i) \beta_T + M_i \beta_M + \varepsilon_i, \quad (2)$$

where $\beta = (\beta_Z, \beta_T, \beta_M)^T$, $h(\cdot)$ is a pre-specified function and we let $h(T_i) = T_i$; the random error ε_i has a normal distribution with mean zero and variance σ^2 . Here, the covariate vector Z_2 in the model illustrated in equation (2) may be different from the covariate Z_1 used in equation (1). To fully utilize all observed information to improve the classification of

patients with severe hemorrhage versus without severe hemorrhage, we impose the following hazard regression model on survival time:

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

where $\lambda_{0M}(\cdot)$ 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.

2.2. Estimation and inference

In line with massive transfusion in PROMMTT, we consider the outcome as the logarithm of the total number of RBC units transfused at death or 24 h post-ED admission. Because the exact amount of RBCs transfused at 24 h or death is not observable for censored patients, we should account for the impact from the induced dependent censoring when modeling 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 [29]. 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 [29] and modify the likelihood function accordingly to incorporate the adjustment in the proposed joint 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 $\theta = (\alpha, \beta, \gamma, \sigma^2)$. Given this specification, we further incorporate weights to properly account for the incompleteness of observed transfused RBC units for those who die before 24 h. Let $G(t) = \Pr(C \geq t)$ denote the survival function of the censoring time C_i . Then we maximize the following weighted complete data:

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

where $w_i = \delta_i / G(T_i)$ are the weights, $S(\cdot)$ is the survival function of $\tilde{T}_i$ given covariates and latent class membership, corresponding to model (3) in Section 2.1, and $f_{\tilde{Y}}$ is the normal density function defined by the model in equation (2). Under the assumption that the censoring time is independent of the survival time, the unknown survival function of the censoring time in the likelihood function (equation (4)) can be estimated consistently by the Kaplan–Meier method without imposing additional parametric models on the censoring time. Further, the proposed method can be adapted to the conditional independence assumption, in which the censoring time is independent of the survival time conditional on the covariates. In this setting, we need to estimate the covariate-dependent weights using either nonparametric or regression methods. After plugging in the consistent estimator $\hat{G}$,

denoted by $\hat{G}$ and $\hat{w}_i = \delta_i / \hat{G}(T_i)$ for w_i , we use the EM algorithm to obtain parameter estimates given the observed data $O_i = (Y_i, T_i, Z_i, \delta_i)$, $i = 1, \dots, n$.

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 k th 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 $\{O_i, i = 1, \dots, n\}$ and $\theta^{(k)}$ is

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

where

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

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

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

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 [31] 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 $d^T H^{-1} d < \varepsilon$, where d is the gradient vector and H the Hessian matrix (by default $\varepsilon = 10^{-4}$). We define the estimates from the last iteration before convergence as the proposed estimates, denoted by $\hat{\theta}$.

One limitation of the EM algorithm is that the initial values may play an important role in determining the maxima. In fact, extra care must be taken to ensure that a local maxima is not misinterpreted as a true maxima. To address this issue, we repeated the maximization process in the simulation studies 20 times and used random starting values. For the joint 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 [32]. 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 and Peel [33], we estimated the variance by using the empirical observed information matrix, which equals to

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

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 i th observation, the specific formula of which is available in the 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 joint LC model is to identify the latent class membership (e.g., severe hemorrhage versus non-severe hemorrhage) of trauma patients, replace the conventional MT definition with an improved standard, and thereby facilitate the development of better predictive algorithms and the administration of more timely and appropriate treatment. The classification of patients into subgroups is based on the estimated posterior probabilities. Specifically, the posterior probability of the i th patient,

$P_{ik} = P(M_i = k | O_i, \hat{\theta})$, determines how likely it is that the i th patient belongs to group k , while simultaneously taking into account the information regarding observed baseline covariates, amount of RBCs 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 performance of the proposed method in identifying the latent class membership. Finite sample performance was evaluated by using

three sample sizes; 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:

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

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 either the exponential model or the Weibull regression model. We specified the hazard function of survival as

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

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 function/model included $\lambda_0(t; \gamma_1) = \gamma_{11}M + \gamma_{10}(1 - M)$ for the exponential model and

$\lambda_0 = \gamma_{11}\gamma_{12}t^{\gamma_{12}-1}M + \gamma_{13}\gamma_{14}t^{\gamma_{14}-1}(1 - M)$ for the Weibull model. 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 h, (2) 40% mortality rate and 20% random censoring rate at 24 h, and (3) 60% mortality rate and 20% random censoring rate at 24 h.

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

$$\tilde{Y} = \beta_0 + Z_{21}\beta_1 + Z_{22}\beta_2 + \tilde{T}\beta_T + M\beta_M + \varepsilon, \quad (9)$$

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 I summarizes the simulation results over 1000 runs, including the averaged point estimates of the parameters, the empirical standard errors, and the model-based standard errors, based on data from the exponential distributions. 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 with 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 I, 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, the model-based standard errors were close to their empirical values, and the coverage probabilities were all close to the nominal level. As expected, the empirical bias of the estimates decreased with an increased sample size, the mean standardized bias and the mean coefficient of variation decrease with an increased sample size, and the standard error of the estimates decreased with increasing mortality rates (i.e., increase in the rate of informative censoring due to death). We noted that the standard errors were slightly over-estimated by the asymptotic standard error for scenario 1 (i.e., the low mortality rate 20%), perhaps due to the limited observed information, but such a bias decreased with increasing 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. When using an exponential distribution, the levels of agreement were 69.2%, 73.7%, and 88.5% for the three scenarios, respectively, when the sample size was 400, and 70.1%, 75.0%, and 89.0% for the three scenarios, respectively, when the sample size was 800. We observed that the levels of agreement increased with an increasing mortality rate due to the improved performance of the estimates, as shown in Table I. The results from Weibull distribution are summarized in Table S1 of the online Supporting Information. The findings of the results from Weibull distribution were similar to those from the exponential distribution, in that the bias of the estimates were small, the model-based standard errors were close to their empirical values, and the coverage probabilities were all close to the nominal level. It is interesting to note that the findings are little different when the survival data were generated from a Weibull distribution, in that there is no monotonic trend of the performance of the estimates as the mortality rate increased. Specifically, the levels of agreement were 61.4%, 81.0%, and 75.6% for the three scenarios, respectively, when the sample size was 400, and 62.8%, 81.7%, and 77.0% for the three scenarios, respectively, when the sample size was 800.

To compare the results of the proposed approach with those obtained by the method without the IPCW correction, we conducted additional simulations under an exponential model. The results are summarized in Table S2 of the online Supporting Information. As expected, the method without the IPCW correction produced biased results, in which the biases of the estimates were large and the coverage probabilities were much lower than the nominal level. For example, when the sample size is 400, the mean standardized bias under scenario I was 1.44 by the method without the IPCW correction, which was much higher than that 0.07 obtained by the proposed method. We note that such biased results were not improved with increasing sample sizes.

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 10 level-1 trauma centers in the United States. Our analysis included 942 patients with completed data needed for our joint LC model. For each patient, baseline variables were available, as well as various blood assessments measured upon ED

admission. The LC mixture model framework was used to identify severely hemorrhaging 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.

We first calculated the Bayesian information criterion (BIC) values for models with two, three, and four latent classes. The resulting BIC values were -733.0347 , -580.4192 , and -613.1343 , respectively. The two-class model had the smallest BIC values, indicating the model with two latent classes worked reasonably well for the PROMMTT data. We then focused on the two-mixture model because it is the most preferred based on the BIC score and consistent with our objective to classify patients experiencing severe hemorrhage 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 h as an 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 II. The class membership probabilities were then calculated by posterior probabilities through the LC analysis.

We compared the classification results of the joint LC approach with the traditional MT approach. The left panel of Table III is a 2×2 table of patients classified by severe hemorrhage 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 140 (14.9%) patients into severe hemorrhage, and the majority of patients (85.1%) remained non-severe hemorrhage. The overall agreement between the two classifications (i.e., severe hemorrhage versus MT) is 75.7% (i.e., 713 out of 942 patients). The right panel of Table III is a 2×2 table of patients identified by LC analysis versus survival status at 24 h. Out of the 100 patients who died within 24 h, 36 (i.e., 74%) were classified as severe hemorrhage and 45 (i.e., 45%) were classified as MT.

We presented the characteristics of severe hemorrhage patients and non-severe hemorrhage patients in Table S3 of the online Supporting Information. We compared the characteristics of all patients, severe hemorrhage patients, and non-severe hemorrhage patients for variables SBP (<90 mm Hg), HR (<120 bpm), pH (<7.25), Hgb (<11 g/dL), and ISS (>25). Most of the characteristics of the subset of 942 patients with complete data that are included in our analysis were similar to those for the full data set. As shown in Table S3, there were significant differences between the 140 patients who were classified as severe hemorrhage and the 802 patients who were not classified as severe hemorrhage with respect to all variables included ($P < 0.001$).

In Figure 1(a), we displayed estimated Kaplan–Meier survival curves, stratified by severe hemorrhage and MT, respectively. As shown, compared with the MT classification, the severely hemorrhaging patients tend to have substantially higher risk profiles and thus lower survival probabilities. Figure 1(b) shows residuals versus fitted values from the linear regression results for RBC transfusion. Seen from the plot, the means of the residues from the linear regression were around zero, suggesting that the linear regression models of RBC transfusions for both groups were reasonable. Further, the estimated intercept of having SH was much bigger than that of non-SH, which was consistent with the traditional MT definition.

In practice, it is critical to expeditiously identify patients who need activation of MTPs early in trauma care. The results from this study suggest that one could use the new severe hemorrhage classification and LC model to identify early predictors of fatal hemorrhage. It is important to note that for both definitions, MT and severe hemorrhage, one needs to observe patients for 24 h in this current paper. However, future joint LC models could be tailored to look at earlier time points of interest. To demonstrate whether predictions based on MT and severe hemorrhage differ, we performed a multivariable logistic regression with stepwise variable selection procedure, using 870 patients and utilizing information from the following variables: SBP (<90 mm Hg), HR (>120 bpm), pH (<7.25), Hgb (<11 g/dL), INR (>1.3), bleeding type (intracranial or abdomen), and mechanism of injury (fall, gunshot, motor vehicle accident, stabbing, or penetrating). The Wald scores in the left panel of Table IV demonstrate the relative weighted influence of each variable, where HR, pH, abdomen bleeding type, intracranial bleeding type, and gunshot appear to be significant predictors of severe hemorrhage. We also estimate the prediction models based on MT, as shown in the right panel of Table IV, in which INR, pH, abdomen injury, and intracranial bleeding type were identified as significant predictors of MT. It should be emphasized that the purpose of these analyses is to show that if the severe hemorrhage definition was replaced by the MT definition to develop the predictive models, then we obtain different results. However, we acknowledge that additional work is required to obtain and validate a predictive model that also takes into account other measures (e.g., the laboratory data) within the LC framework in order to develop a predictive model with demonstrated clinical utility, which is outside the scope of this current paper.

5. Discussion

Severe hemorrhage is associated with increased morbidity and mortality in critically injured trauma patients. Early and aggressive transfusion of blood products in these patients may correct coagulopathy, promote primary hemostasis, and improve survival. However, it is very challenging and extremely difficult to establish valid criteria to identify patients who may require a massive transfusion protocol due to limited resources within a very short time period. In trauma research, many published works toward this end often report misspecified models based on ad-hoc procedures, and existing MT-based predictive algorithms seem prone to survival bias. In this article, we propose to use a joint model framework to classify severely hemorrhaging trauma patients who may require a massive transfusion protocol. Our method jointly incorporates the baseline vital signs at arrival in ED, number of RBC transfusions (i.e., number of units), and survival time during the first 24 h. With affluent

information from the prospective observational trauma study, the proposed joint model incorporates time-to-event data to improve the classification of patients with severe hemorrhage.

When using the inverse of the censoring survival function as the weight, the stability of the weight function at the tail is of practical concern, because the resulting extremely large weights could mislead the data analysis. Several approaches to reduce the variability of the weights, including stabilization and truncation, have been proposed and discussed in the literature [34–36]. Note that we do not have this particular concern in our data application, because the censoring rate within 24 h after the ED admission is low.

Although we have focused on two latent classes for severe hemorrhage, the proposed methodology can be easily generalized to situations in which there are more than two (i.e., $K > 2$) latent classes. For the extension, we can define the latent variable $M_{ik} = 1$ if the i th subject belongs to subgroup k ($k = 1, \dots, K$), and 0 otherwise. The corresponding logistic models for the latent class membership need to be generalized as

$$P(M_{ik}=1|Z_{1i};\alpha)=\frac{\exp(Z_{1i}^T\alpha_k)}{1+\exp(Z_{1i}^T\alpha_k)}, k=1, \dots, K. \quad (10)$$

Given model (10), the likelihood function and EM algorithm can be straightforwardly modified.

Note that the competing risk model with three status categories (death, SH, and non-SH) is not applicable for the classification in the trauma transfusion study. In the competing risk data, subjects are at risk of failure from multiple different causes [37]. When one event occurs, it precludes the occurrence of any other event. In the trauma transfusion study, although death is one reason to preclude further blood transfusions, it is not a competing risk for the underlying SH latent membership. However, when we are evaluating the time until a subject has received 10 units of RBCs, we need to apply competing risk models by treating death as a competing risk for receiving 10 units of RBCs.

The PROMMTT study is the first large-scale, prospective study of trauma patients admitted directly from the injury scene to 10 level-1 trauma centers in the United States. 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 all types of blood products are received should be the focus of future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 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

$$\begin{aligned} [M_i|Z_{1i}] &= Z_{1i}^T \alpha M_i - \log \left\{ 1 + \exp(Z_{1i}^T \alpha) \right\}, \\ [T_i, \delta_i|Z_{3i}, M_i] &= \log \lambda(T_i|Z_{3i}, M_i; \gamma)^{\delta_i} S(T_i|Z_{3i}, M_i; \gamma), \\ [Y_i|M_i, Z_{2i}, T_i] &= \log f(\tilde{Y}_i|Z_{2i}, M_i, T_i; \beta_Z, \beta, \sigma^2). \end{aligned}$$

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 by $S_c^*(\theta; \theta)$, is

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

Using the asymptotic martingale expression, the independent and identically distributed representation of the Kaplan–Meier estimator can be written as

$$\sqrt{n} \left\{ \hat{G}(t) - G(t) \right\} / \hat{G}(t) = - \frac{1}{\sqrt{n}} \sum_{i=1}^n \int_0^\infty \frac{I(s \leq t) dM_i^C(s)}{G(s)S_T(s)} + o_p(1),$$

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

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

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

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

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

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Figure 1.

(a) Kaplan–Meier estimates for traumatic death stratified by severe hemorrhage (SH, solid) and massive transfusion (MT, dash) classifications and (b) residuals versus fitted values from linear regression results for red blood cell transfusions.

Table I

Parameter estimate (EST), empirical standard error (SSE), standard error (SE), coverage probability (CP), mean standardized bias (MSB), and mean coefficient of variation (MCV) under the exponential baseline function.

<i>N</i>	Scenario	α_0	α_1	α_2	β_M	β_0	β_1	β_2	β_T	$\log 2(\sigma^2)$	γ_{21}	γ_{22}	$\log(\gamma_{11})$	$\log(\gamma_{10})$	
400	I (MSB = 0.07) (MCV = 0.62)	TRUE	0.50	-0.50	0.50	1.00	1.00	-0.50	0.50	0.50	0.00	-5.50	3.50	-2.30	-6.91
		EST	0.49	-0.54	0.54	0.99	1.00	-0.51	0.50	0.50	-0.07	-5.48	3.50	-2.28	-6.95
		SEE	0.31	0.63	0.31	0.49	0.56	0.33	0.17	0.02	0.14	0.41	0.19	0.21	0.46
		SE	0.35	0.98	0.40	0.55	0.63	0.36	0.18	0.02	0.14	0.48	0.20	0.22	0.54
	II	CP	0.97	0.98	0.97	0.94	0.95	0.95	0.95	0.95	0.91	0.96	0.96	0.95	0.97
		TRUE	0.50	-0.50	0.50	1.00	1.00	-0.50	0.50	0.50	0.00	-3.50	3.50	-0.92	-3.22
		EST	0.48	-0.55	0.54	1.09	0.92	-0.50	0.51	0.50	-0.08	-3.48	3.49	-0.89	-3.21
		SEE	0.38	0.63	0.38	0.29	0.31	0.22	0.14	0.02	0.14	0.32	0.19	0.21	0.27
	III	SE	0.37	0.60	0.40	0.25	0.27	0.20	0.14	0.02	0.13	0.30	0.18	0.19	0.27
		CP	0.94	0.94	0.95	0.86	0.91	0.92	0.94	0.91	0.89	0.93	0.93	0.92	0.93
		TRUE	0.50	-0.50	0.50	1.00	1.00	-0.50	0.50	0.50	0.00	-2.50	2.00	0.69	-2.30
		EST	0.51	-0.52	0.52	1.04	0.96	-0.51	0.50	0.50	-0.04	-2.50	2.00	0.71	-2.30
800	I (MSB = 0.07) (MCV = 0.52)	SEE	0.20	0.32	0.19	0.23	0.23	0.15	0.09	0.02	0.10	0.21	0.12	0.13	0.17
		SE	0.20	0.32	0.19	0.21	0.21	0.15	0.09	0.02	0.10	0.20	0.12	0.13	0.18
		CP	0.96	0.96	0.95	0.90	0.91	0.95	0.94	0.92	0.92	0.95	0.93	0.94	0.96
		TRUE	0.50	-0.50	0.50	1.00	1.00	-0.50	0.50	0.50	0.00	-5.50	3.50	-2.30	-6.91
	II	EST	0.49	-0.51	0.53	1.02	0.97	-0.51	0.51	0.50	-0.03	-5.49	3.50	-2.30	-6.92
		SEE	0.19	0.39	0.19	0.33	0.37	0.23	0.12	0.02	0.10	0.26	0.13	0.13	0.32
		SE	0.24	0.62	0.27	0.32	0.37	0.24	0.12	0.01	0.10	0.31	0.14	0.15	0.35
		CP	0.98	0.98	0.99	0.93	0.94	0.95	0.94	0.92	0.93	0.97	0.96	0.96	0.97
	III	TRUE	0.50	-0.50	0.50	1.00	1.00	-0.50	0.50	0.50	0.00	-3.50	3.50	-0.92	-3.22
		EST	0.48	-0.52	0.54	1.07	0.94	-0.51	0.51	0.50	-0.05	-3.49	3.50	-0.91	-3.21
		SEE	0.22	0.37	0.22	0.19	0.20	0.14	0.10	0.01	0.09	0.19	0.11	0.13	0.17
		SE	0.26	0.42	0.28	0.17	0.19	0.14	0.09	0.01	0.09	0.21	0.13	0.14	0.19
	III (MSB = 0.10)	CP	0.97	0.97	0.97	0.88	0.92	0.94	0.94	0.93	0.9	0.96	0.97	0.95	0.95
		TRUE	0.50	-0.50	0.50	1.00	1.00	-0.50	0.50	0.50	0.00	-2.50	2.00	0.69	-2.30
		EST	0.50	-0.51	0.52	1.03	0.97	-0.51	0.50	0.50	-0.03	-2.50	2.00	0.69	-2.30
		SEE	0.50	-0.51	0.52	1.03	0.97	-0.51	0.50	0.50	-0.03	-2.50	2.00	0.69	-2.30

<i>N</i>	Scenario	α_0	α_1	α_2	β_M	β_1	β_2	β_3	$\log 2(\hat{\sigma}^2)$	γ_1	γ_2	$\log 1$	$\log 1$	$\log 1$
	(MCV = 0.35)	0.14	0.22	0.13	0.16	0.15	0.10	0.06	0.01	0.07	0.14	0.07	0.09	0.12
		0.14	0.23	0.14	0.15	0.14	0.10	0.06	0.01	0.07	0.14	0.08	0.09	0.12
		0.95	0.96	0.96	0.92	0.93	0.94	0.94	0.91	0.92	0.95	0.96	0.95	0.95
	SEE													
	SE													
	CP													

MSB is calculated as mean of absolute value of standard biases, and MCV is calculated as mean of standard errors divided by parameter estimates.

Table II

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

	Coefficient	SE	Wald	<i>p</i> -value
Model 1: logistic regression for latent class membership				
Intercept	-2.389	1.773	-1.348	0.178
SBP < 90	-0.057	0.746	-0.077	0.939
HR 120	-2.156	0.920	-2.344	0.019
pH < 7.25	3.417	1.262	2.707	0.007
Hgb < 11	0.755	0.688	1.097	0.273
ISS 25	-1.371	1.006	-1.363	0.173
Model 2: linear regression for log-transformed RBC transfusion				
Intercept (SH)	2.146	0.246	8.715	<0.001
Intercept (non-SH)	0.959	0.259	3.703	<0.001
Time	-0.020	0.014	-1.424	0.154
SBP < 90	0.228	0.199	1.146	0.252
HR 120	0.966	0.214	4.516	<0.001
pH < 7.25	-0.230	0.259	-0.888	0.375
Hgb < 11	-0.029	0.204	-0.143	0.886
ISS 25	0.328	0.189	1.732	0.083
Model 3: proportional hazards model for survival time				
log Shape (SH)	-0.459	0.398	-1.153	0.249
log Scale (SH)	-4.699	1.022	-4.597	<0.001
log Shape (non-SH)	-0.434	0.243	-1.785	0.074
log Scale (non-SH)	-5.362	0.669	-8.014	<0.001
SBP < 90	0.031	0.220	0.140	0.889
HR 120	0.106	0.391	0.271	0.786
pH < 7.25	0.520	0.508	1.024	0.306
Hgb < 11	0.491	0.258	1.903	0.057
ISS 25	0.856	0.291	2.946	0.003

Severe hemorrhage is denoted by SH, and non-severe hemorrhage is denoted by non-SH. SBP, systolic blood pressure; HR, heart rate; Hgb, hemoglobin concentration; ISS, injury severity scores; RBC, red blood cell.

log Shape: shape parameter in Weibull baseline in logarithm scale;

log Scale: scale parameter in Weibull baseline in logarithm scale.

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Table III

Contingency table for trauma patients classified by severe hemorrhage (SH) from the LC model and massive transfusion (MT), and survival status at 24 h of admission.

	Non-MT	MT	Alive	Dead	Total
Non-SH	650	152	738	64	802
SH	77	63	104	36	140
Non-MT			672	55	727
MT			170	45	215
Total	727	215	842	100	942

Table IV

Predictive models for severe hemorrhage (SH) and massive transfusion (MT) using a multivariable logistic regression.

	SH			MT		
	Estimate	SE	Wald	Estimate	SE	Wald
Intercept	-5.452	0.634	-8.604	-2.233	0.181	-12.346
HR 120	-3.785	0.440	-8.609	0.062	0.183	0.338
pH < 7.25	5.529	0.623	8.875	0.922	0.180	5.129
INR > 1.3	0.339	0.295	1.150	0.914	0.180	5.090
Abdomen	0.844	0.308	2.744	0.492	0.181	2.718
Intracranial	-1.546	0.434	-3.563	-0.832	0.274	-3.038
Gunshot	0.778	0.373	2.086	0.176	0.207	0.850

SE, standard errors; HR, heart rate; INR, international normalized ratio.