A latent class model for defining severe hemorrhage

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Abstract: There is no diagnostic test to identify trauma patients who have had severe hemorrhage (SH) and may need a massive transfusion protocol (MTP). However, several predictive models have been developed based on the traditional definition of massive transfusion, which is transfusion of 10 units of red blood cells (RBCs) within 24 hours of Emergency Department (ED) admission. This definition excludes patients with severe bleeding who died before a 10^{th} unit of RBCs could be transfused, resulting in survival bias. The lack of a valid definition for severe hemorrhage calls these prediction models into question. We proposed a latent class model for identifying a subgroup of patients with SH. We developed an EM algorithm for estimating the posterior probability of being an SH patient based on information at ED admission, blood product utilization, and survival status during the first 24 hours. We assessed the performance of our latent class model in classifying SH patients and compare to the traditional massive transfusion definition using data from a retrospective trauma transfusion study.

1 Introduction

Hemorrhagic shock accounts for the largest proportion of mortality occurring within the first hour of trauma center care, over 80% of operating room deaths after major trauma, and almost 50% of deaths in the first 24 hours of trauma care [1, 2, 3, 4]. A massive transfusion protocol (MTP) is defined as an order to the blood bank for the rapid delivery of multiple blood products typically including at least six units of red blood cells (RBCs) along with plasma and platelets and is often required for the treatment of uncontrolled hemorrhage. The traditional massive transfusion protocol, as codified in the Advanced Trauma Life Support manual [5], supports the sequential use of crystalloid, followed by red blood cells and then plasma and platelets. The central problem of research in this area is that there is no diagnostic test to identify patients who have had serious blood loss and/or are bleeding severely and are in need of receiving MTP.

Recently, Brohi et. al [6] and MacLeod et. al [7] reported that 25% of trauma patients are coagulopathic upon ED admission and have increased mortality. With this new finding, a transfusion strategy has been proposed which advocates the use of 1:1 ratios of plasma to RBC and platelets to RBC, which are the ratios inherent in whole blood. Several recent observational studies have associated decreased mortality with higher ratios in both combat and civilian trauma [8, 9, 10, 11, 12, 13, 14, 15, 16], but relevant randomized clinical trials have not been reported although several are ongoing.

There are potential adverse effects associated with the transfusion of plasma and platelets, such as acute lung injury and acute respiratory distress syndrome [17, 18, 19]. Most importantly, higher ratios are only intended for patients with coagulopathy and maybe harmful to other patients. Therefore, while estimating the treatment effects of higher ratios, it is critical to identify the subgroup of patients with severe bleeding/severe blood loss.

The term massive transfusion (MT), commonly defined as the transfusion of ≥ 10 units of RBCs within 24 hours of ED admission, has been used to describe this subgroup. However, this definition of MT 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, a massively bleeding patient who died within 24 hours of ED admission and before the 10^{th} unit of RBCs was transfused will not be considered as a MT patient. This is an important source of survival bias and hence causes bias in findings reported in many observational studies. Second, although the amount of RBCs transfused has a direct relationship with the patient's need for massive transfusion, it is also highly affected by the treatments he or she receives after ED admission. Cotton et. al [9] reported that the 24-hour total blood product (RBCs, plasma and platelet) consumption as well as the 24-hour platelet transfusion were reduced with a MTP, but this observational study is also susceptible to survival bias. With this information in mind, it may be questionable to apply a uniform MT definition for different patients under various treatments. Other definitions of MT can be found in the literature using different cut points for total number of RBCs [20] or time periods [21], however, they suffer from the same limitations.

The correct classification of patients at highest risk of exsanguination or other hemorrhage-related mortality is critical in order for MTP to be restricted to these patients because there are risks associated with unnecessary transfusion. Several predictive models using early physiologic and laboratory values available soon after ED arrival, e.g., heart rate, systolic blood pressure, mechanism of injury, focused assessment for the sonography of trauma (FAST), pH, hematocrit have been proposed, including the work by McLaughlin [22], TASH-score by Yucel [23] and ABC-score by Nunez [24]. These models used the traditional MT definition, which is subject to survival bias.

We propose a latent class model to identify a subgroup of patients with severe hemorrhage. This model incorporates plasma:RBC and platelet:RBC ratios, total transfusions, and 24-hour survival. The path diagram in Figure 1 illustrates the relationships among all the variables including the latent class membership. This model captures the nature of the problem and provides an alternative method to existing analysis based on the traditional definition of massive transfusion. The remainder of this paper is organized as follows. Section 2 formally introduces the latent class model. Section 3 describes the estimation procedure for the latent class model. Section 4 provides a real data analysis using civilian trauma patients. Section 5 is devoted to discussion of the strengths and limitations of this approach.

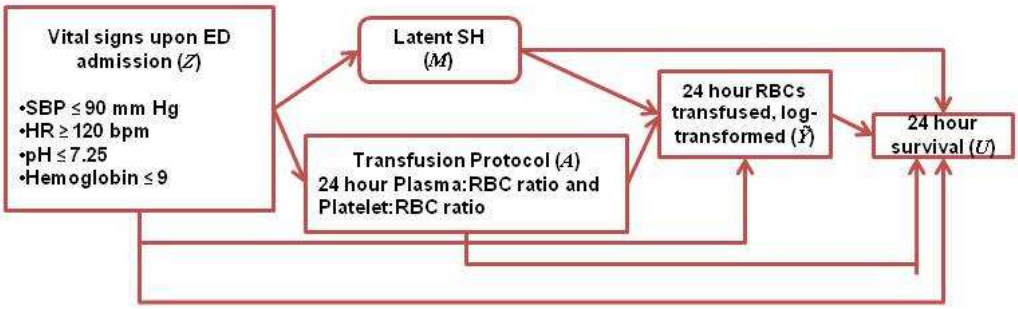

Figure 1: The relationships between the latent variable and the observed variables including initial vital signs, blood transfusion and survival status.

2 The latent class model

Assume that the patients consist of 2 subgroups: $M = 1$ if a patient has SH and $M = 0$ otherwise. Let Z denote the baseline covariates available at ED arrival, A denote the treatment (plasma:RBC and platelet:RBC ratios), $\tilde{Y}$ denote the logarithm of the total amount of RBCs transfused within 24 hours, and U denote whether the patient survives 24 hours. We can observe $\tilde{Y}$ only if the patient survives 24 hours ($U = 1$). Let Y denote the logarithm of the observed total amount of RBC transfused within 24 hours or up to death, whichever comes first. That is, $\tilde{Y} = Y$ if $U = 1$ and $\tilde{Y} \geq Y$ if $U = 0$.

The complete data likelihood is

$$L(Z, M, A, \tilde{Y}, U) = f(Z)P(M|Z)f(A|Z, M)f(\tilde{Y}|A, M, Z)P(U|\tilde{Y}, A, M, Z)$$

Since the treatment A is completely decided by the physicians based on observed variables Z, not the unobserved latent variable M, it is reasonable to assume that $A \perp M|Z$, that is, $f(A|Z, M) = f(A|Z)$ which does not involve M and will be omitted together with $f(Z)$ from the above equation.

We impose the following models for each component in the complete likelihood.

(M1). A logistic model for the latent class membership:

$$P(M|Z; \alpha) = \frac{\exp\{\mu_1(Z; \alpha)M\}}{1 + \exp(\mu_1(Z; \alpha))}.$$

(M2). A multiple linear regression model with dependent variable having normal distribution for the log-transformed 24 hours RBCs utilization with density function:

$$f(\tilde{Y}|A, M, Z; \beta, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{\{\tilde{Y} - \mu_2(A, M, Z; \beta)\}^2}{2\sigma^2}\right],$$

(M3). A logistic model for 24 hour mortality:

$$P(U|\tilde{Y}, A, M, Z; \gamma) = \frac{\exp\{\mu_3(\tilde{Y}, A, M, Z; \gamma)U\}}{1 + \exp\{\mu_3(\tilde{Y}, A, M, Z; \gamma)\}}.$$

Here μ_1 is a function of the regression parameter vector α and the baseline vector of variables, Z. Similarly, μ_2 is a function of the regression parameter vector β and the treatment vector of variables, A; baseline variable vector Z; and latent variable M (an indicator of SH status). Finally, μ_3 is a function of the regression parameter vector γ, and the log-transformed 24-hour total RBC units ($\tilde{Y}$), the treatment vector A, baseline vector Z, and latent variable M.

Consider n independent, identically distributed (i.i.d.) complete samples $(Z_i, M_i, A_i, \tilde{Y}_i, U_i)$ for $i = 1, ..., n$. The values of M_i are not observed and the values of $\tilde{Y}_i$ can not be observed for subjects who die within 24 hours of ED admission. The observed samples are (Z_i, A_i, Y_i, U_i), $i = 1, \cdots, n$. Since the likelihood of the observed data is very complicated involving integrations, for computational convenience, we maximize the likelihood function of the complete data instead of observed data, which

is equal to

$$
\begin{aligned}
l = & \sum_{i=1}^{n} \mu_1(Z_i;\alpha) M_i - \sum_{i=1}^{n} \log[1+\exp\{\mu_1(Z_i;\alpha)\}] - \frac{1}{2} n \log \sigma^2 \\
& + \sum_{i=1}^{n} \Big[-\frac{1}{2\sigma^2} \{\tilde{Y}_i - \mu_2(A_i, M_i, Z_i;\beta)\}^2 + \mu_3(\tilde{Y}_i, A_i, M_i, Z_i;\gamma) U_i \\
& - \log(1+\exp\{\mu_3(\tilde{Y}_i, A_i, M_i, Z_i;\gamma)\}) \Big].
\end{aligned}
$$

Since the likelihood of the complete data includes the latent variable M and partially observed variable $\tilde{Y}$, we use the expectation-maximization (EM) algorithm to obtain parameter estimates. The standard errors of the estimates are calculated via the bootstrap method.

3 Model Fitting

The EM algorithm starts with an initial value of the model coefficients. Let $\theta = (\alpha^T, \beta^T, \sigma, \gamma^T)^T$ and $\theta_{(t)}$ denote the estimate of coefficients θ in the t^{th} iteration. The iteration $t+1$ of EM is as follows:

E step: Find the expected probability of $M_i = 1$ given the observed data and $\theta_{(t)}$. For $i = 1, ..., n$, if $U_i = 1$,

$$
\begin{aligned}
\hat{p}_{i(t)} &= P(M_i = 1 | Z_i, A_i, Y_i, U_i; \theta_{(t)}) \\
&= \frac{L(Z_i, M_i = 1, A_i, Y_i, U_i; \theta_{(t)})}{L(Z_i, M_i = 1, A_i, Y_i, U_i; \theta_{(t)}) + L(Z_i, M_i = 0, A_i, Y_i, U_i; \theta_{(t)})}. \qquad (1)
\end{aligned}
$$

If $U_i = 0$, the value of $\tilde{Y}_i$ is censored. However, based on the model assumptions, the conditional expectation of M_i given the observed data is

$$
\hat{p}_{i(t)} = \int_{Y_i}^{\infty} \frac{1}{C_i} \rho_{i1}(y;\theta_{(t)}) dy, \qquad (2)
$$

where

$$
C_i = \int_{Y_i}^{\infty} [\rho_{i1}\{y;\theta_{(t)}\} + \rho_{i0}\{y;\theta_{(t)}\}] dy,
$$

and

$$\rho_{i1}(y;\theta_{(t)}) = \frac{\exp\{\mu_1(Z_i;\alpha_{(t)})\}}{1+\exp\{\mu_1(Z_i;\alpha_{(t)})\}} \exp\left[-\frac{\{y-\mu_2(A_i,M_i=1,Z_i;\beta_{(t)})\}^2}{2\sigma^2_{(t)}}\right] \frac{1}{1+\exp\{\mu_3(y,A_i,M_i=1,Z_i;\gamma_{(t)})\}},$$

$$\rho_{i0}(y;\theta_{(t)}) = \frac{1}{1+\exp\{\mu_1(Z_i;\alpha_{(t)})\}} \exp\left[-\frac{\{y-\mu_2(A_i,M_i=0,Z_i;\beta_{(t)})\}^2}{2\sigma^2_{(t)}}\right] \frac{1}{1+\exp\{\mu_3(y,A_i,M_i=0,Z_i;\gamma_{(t)})\}}.$$

Then calculate the expected complete data log-likelihood given the observed data and $\theta_{(t)}$:

$$\begin{aligned}
l(\theta|\theta_{(t)}) = &\sum_{i=1}^{n}\mu_1(Z_i;\alpha)\hat{p}_{i(t)} - \sum_{i=1}^{n}\log(1+\exp(\mu_1(Z_i;\alpha)) - \frac{1}{2}n\log\sigma^2 \\
&+\sum_{i=1}^{n}U_i\hat{p}_{i(t)}[-\frac{1}{2\sigma^2}\{Y_i-\mu_2(A_i,M_i=1,Z_i;\beta)\}^2 + \mu_3(Y_i,A_i,M_i=1,Z_i;\gamma) \\
&\qquad -\log(1+\exp(\mu_3(Y_i,A_i,M_i=1,Z_i;\gamma)))] \\
&+\sum_{i=1}^{n}U_i(1-\hat{p}_{i(t)})[-\frac{1}{2\sigma^2}(Y_i-\mu_2(A_i,M_i=0,Z_i;\beta))^2 \\
&\qquad +\mu_3(Y_i,A_i,M_i=0,Z_i;\gamma) \\
&\qquad -\log(1+\exp(\mu_3(Y_i,A_i,M_i=0,Z_i;\gamma)))] \\
&+\sum_{i=1}^{n}(1-U_i)\int_{Y_i}^{\infty}[-\frac{\{y-\mu_2(A_i,M_i=1,Z_i;\beta)\}^2}{2\sigma^2} \\
&\qquad -\log(1+\exp\{\mu_3(y,A_i,M_i=1,Z_i;\gamma)\})]\frac{\rho_{i1}(y,\theta_{(t)})}{C_i}dy \\
&+\sum_{i=1}^{n}(1-U_i)\int_{Y_i}^{\infty}[-\frac{\{y-\mu_2(A_i,M_i=0,Z_i;\beta)\}^2}{2\sigma^2} \\
&\qquad -\log(1+\exp\{\mu_3(y,A_i,M_i=0,Z_i;\gamma)\})]\frac{\rho_{i0}(y,\theta_{(t)})}{C_i}dy.
\end{aligned}$$

M step: Estimate $\theta_{(t+1)}$ by maximizing $l(\theta|\theta_{(t)})$. Specifically, the estimates of θ can be updated by solving the corresponding score equation, defined as the first derivative of the expected complete data likelihood, for which the Newton-Raphson algorithm is used.

Table 1: Summary characteristics of trauma patients in the retrospective study.

Mortality	
Mortality at 24 hour (%)	15
Mortality at 30 day(%)	25
Clinical outcomes	
Ventilation days	5 ± 10
ICU days	7 ± 11
Hospital days	15 ± 20
Patient characteristics	
Age (year)	42 ± 20
Men (%)	73
Penetrating injury (%)	36
Systolic blood pressure (mmHg)	115 ± 35
Diastolic blood pressure (mmHg)	71 ± 23
Heart rate (bpm)	104 ± 27
Respiratory rate	21 ± 7
Temperature (°C)	36 ± 1
pH	7.24 ± 0.15
International Normalized Ratio	1.4 ± 1.0
Base deficit	-8.7 ± 6.5
Glasgow Coma Scale	10.9 ± 6.0
Injury severity score	26 ± 16
Blood products usage	
RBC 0-6 hrs (units)	7.8 ± 10.9
RBC 0-24 hrs (units)	10.1 ± 12.6
Plasma 0-6 hrs (units)	4.0 ± 6.7
Plasma 0-24 hrs (units)	5.8 ± 8.9
Platelets 0-6 hrs (units)	2.5 ± 6.1
Platelets 0-24 hrs (units)	4.1 ± 8.8
Plasma:RBC ratio 0-24 hrs	0.49 ± 0.76
Platelet:RBC ratio 0-24 hrs	0.32 ± 1.05

4 Application to retrospective data

Data in this section came from a multicenter retrospective study of transfused trauma patients conducted by Holcomb et al. (2009) [15]. The original dataset included 1574 adult trauma patients ($\geq$ 16 years old) admitted to 16 level 1 trauma centers between July 2005 and June 2006 and received $\geq$ 1 unit of RBC within 24 hours of ED admission. Included in these data analysis was a subset of 950 patients admitted to 10 out of the 16 trauma centers, among which 337 were massively transfused, that is, transfused with $\geq$ 10 units of RBCs within 24 hours of ED admission. Table 1 describes the study population.

The baseline covariates Z used in our latent class model include the following patient admission characteristics

- ED systolic blood pressure (SBP) of 90 mm Hg or less (0=no, 1=yes)
- ED heart rate (HR) of 120 bpm or greater (0=no, 1=yes)
- ED pH of 7.25 or less (0=no, 1=yes)
- ED Hemoglobin of 9 or less (0=no, 1=yes)

Table 2: Estimates and Standard Errors of the regression coefficients in the three components of the latent class model

Variables	Coefficient	Standard Error
Model M1		
(Intercept)	-1.84	0.13
SBP	0.30	0.13
HR	0.37	0.10
pH	1.15	0.12
Hemoglobin	0.41	0.17
Model M2		
(Intercept)	1.01	0.04
latent SH	3.07	0.18
Plasma:RBC ratio	0.42	0.16
Platelet:RBC ratio	1.32	0.18
SBP	0.17	0.04
HR	0.24	0.03
pH	0.21	0.05
Hemoglobin	0.41	0.04
latent SH*Plasma:RBC ratio	-1.61	0.26
latent SH*Platelet:RBC ratio	-2.23	0.29
Model M3		
(Intercept)	5.95	3.26
latent SH	-11.72	2.80
logRBC24	0.59	0.21
Plasma:RBC ratio	-1.16	1.36
Platelet:RBC ratio	-3.45	2.33
pH	-0.92	0.34
latent SH*Plasma:RBC ratio	6.11	1.50
latent SH*Platelet:RBC ratio	8.36	2.38

The analysis includes 471 patients without any missing data. To choose the initial values for model parameter θ, we first fix the latent class membership M to be the traditional definition of ≥ 10 units of RBC transfused within 24 hours of ED admission. The maximum likelihood estimates for parameters in models M1, M2

and M3 are then taken as $\theta_{(0)}$. The EM algorithm was then applied until the estimation converged. Table 2 lists the EM estimate $\hat{\theta}$ together with the corresponding standard errors which were computed based on the bootstrap method, resampling 471 patients with replacement 500 times. For each resample, we calculated the estimated coefficients, and from these 500 estimates we calculated the standard errors displayed in Table 2.

Table 3: Comparison between the results from the new definition and the traditional definition.

	traditional non-MT	traditional MT
latent non-SH	221	38
latent SH	39	173

Given the observed variables and estimated coefficients, we define SH as the posterior probability of $M = 1$ being greater than 0.5 (equations 1 and 2). Table 3 compares our new definition of SH with the traditional definition of whether a patient was transfused $\geq$ 10 units of RBCs within the first 24 hours and shows that these two agree for 84% of patients. Among the 17 patients who died before receiving 10 units of RBCs, 13 are classified as SH. Therefore our new definition is advantageous in identifying the majority of these bleeding patients who didn't survive long enough to receive 10 units of RBC transfusion within 24 hours of ED admission

Further comparison between the traditional MT definition and the new one based on the latent class model is illustrated in Figure 2. In Figure 2b, the distribution of the posterior probabilities is displayed and is bimodal, indicating a more distinct separation between patients with severe hemorrhage and those who do not have severe hemorrhage. In contrast, the distribution of the total 24-hour number of RBCs is unimodal and does not indicate a clear cut point as shown in Figure 2a.

5 Discussion

In this paper, we propose a new likelihood based method to classify patients with severe hemorrhage. The new definition is based on the posterior probability of being an SH patient based on information at ED admission, blood product utilization, and survival status during the first 24 hours. Our new definition is different from the traditional MT definition which requires at least 10 units of RBC transfused within 24 hours. The major advantage of our new definition over the traditional one is that it classifies based on available information during the first 24 hours rather than only the amount of RBCs transfused within this period. One limitation is that we used a simple latent class model which is fully parametric and therefore may not be robust to model misspecification. We also acknowledge that the blood product ratios may have been impacted by survival status of patients during the first 24 hours. In future work, we will incorporate survival analysis techniques to more accurately utilize the blood product ratio information in our latent class model. More specifically, we will

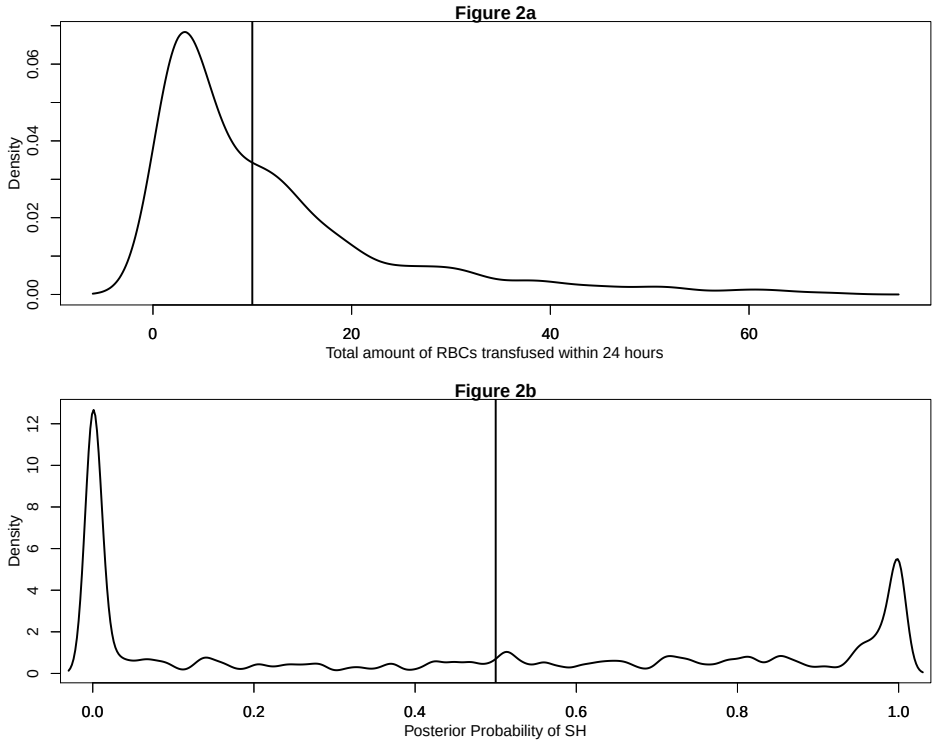

Figure 2: 2a: distribution of total amount of RBCs transfused within 24 hours of ED admission (RBC24). 2b: posterior distribution of SH based on our latent class model. The vertical lines represent the cutoff.

replace the linear model with a recurrent event model for the timing of each RBC transfusion. Similarly, we will replace the logistic model with a Cox proportional hazards model for time to death counted from ED admission.

Our next step is to apply this analysis method to data from the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, which is the first large scale, prospective study of trauma patients admitted directly from the injury scene to Level 1 Trauma Centers [25]. We expect to have improved classification of patients with severe hemorrhage since PROMMTT has additional data fields and collected detailed timing of treatments and blood product utilization.

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