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

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Abstract

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

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

Results: Baseline systolic blood pressure, heart rate, pH, and hemoglobin were significantly associated with RBC transfusion rates. Increased transfusion rates (per hour) of plasma ($P = 0.05$), platelets ($P < 0.001$), or RBCs were associated with increased 24-hour mortality. Higher ratios of plasma:RBC ($P = 0.107$) and platelet:RBC ($P < 0.001$) were associated with reduced mortality in a time-varying pattern ($P < 0.001$).

Conclusions: The proposed joint analysis of transfusion rates and ratios offers a more valid statistical approach to evaluate survival effects in the presence of informative censoring by early death. © 2016 Elsevier Inc. All rights reserved.

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

1. Introduction

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

Conflict of interest: None.

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What is new?

Key findings

- Our proposed statistical methods to jointly analyze recurrent events for multi-component blood product transfusion (RBC, plasma, and platelets) as well as survival can better estimate time-varying transfusion rates as well as ratios among the blood products (RBC, plasma and platelets) used for massively hemorrhaging trauma patients.
- Our proposed methods can better estimate the overall effect of varying transfusion ratios on mortality.
- Our proposed methods can better account for potential bias from informative censoring due to early death before hemorrhage control.

What is the implication and what should change now?

- Estimation of dynamic blood product ratios (e.g., plasma:RBC) is of great interest to clinicians but is subject to survival bias in the presence of early mortality.
- By considering early mortality as informative censoring, our proposed joint analysis of both blood transfusion and survival is an appropriate approach to reduce potential time-varying biases.

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

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

2. Methods

2.1. PROMMTT study

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

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