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Impaired Platelet Recovery Is Associated with Mortality after Severe Neonatal Intraventricular Hemorrhage Brief Report

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Short Report

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Abstract

Purpose

To determine whether longitudinal platelet recovery differs by survival status after severe neonatal intraventricular hemorrhage (IVH).

Methods

We performed a retrospective secondary analysis of a single-center cohort of 43 infants with grade 3–4 IVH who underwent serial surveillance for post-hemorrhagic ventricular dilatation. The longitudinal subset included infants with at least three numeric platelet measurements and known survival status. Observation-level linear regression was used to display raw platelet trajectories. A linear mixed-effects model with a random intercept for infant, and fixed effects for day of life, survival status, platelet transfusion timing, and their interactions, was used for primary inference.

Results

Sixteen infants died before hospital discharge. The longitudinal subset comprised 17 infants (12 survivors and 5 non-survivors) and 403 platelet measurements. In the unadjusted model, platelet counts increased in survivors (+ 3.47 × 10^9/L/day) and decreased in non-survivors (− 1.34 × 10^9/L/day; interaction $p < 2 \times 10^{-16}$). In the mixed-effects model, survivors showed greater platelet recovery than non-survivors (time-by-death interaction − 1.46 × 10^9/L/day, 95% CI − 2.48 to − 0.44; p = 0.005).

Conclusion

Failure of platelet recovery was associated with mortality after severe neonatal IVH. Platelet trajectory may provide prognostic information beyond a single platelet count, but prospective validation and adjustment for illness severity are required.

What is Known - What is New

What is Known

- Severe neonatal IVH is associated with high mortality and systemic critical illness.
- Single platelet counts have limited prognostic value in critically ill preterm infants.

What is New

- Platelet recovery trajectories differed substantially between survivors and non-survivors.

- The association persisted after accounting for repeated measurements and platelet transfusion timing.

Introduction

Severe neonatal intraventricular hemorrhage (IVH) remains a major complication of extreme prematurity and is associated with mortality, post-hemorrhagic ventricular dilatation (PHVD), neurosurgical intervention, and adverse neurodevelopmental outcomes [1–5]. Risk stratification after severe IVH is driven primarily by cranial ultrasound findings, ventricular measurements, and the infant's clinical course. However, severe IVH occurs within a broader setting of systemic critical illness, inflammation, transfusion exposure, and hematologic instability.

Platelet count is clinically relevant because thrombocytopenia and platelet transfusion are common in critically ill preterm infants, while a single platelet value does not reliably capture bleeding risk or recovery [6–10]. We hypothesized that longitudinal platelet recovery, rather than an isolated count, would differ by survival status after severe IVH. We therefore examined platelet trajectories in a retrospective severe-IVH cohort monitored for PHVD.

Methods

This retrospective secondary analysis used a single-center cohort of neonates with grade 3–4 IVH cared for in the University Hospital neonatal intensive care unit between January 2010 and January 2025. The parent cohort included 43 infants, 347 cranial ultrasounds, a mean birth weight of 895 g (standard deviation 471), a mean gestational age of 25.9 weeks (standard deviation 3.7), and 16 deaths (37.2%). Severe IVH was defined by cranial ultrasound documentation of grade 3 or grade 4 hemorrhage. The outcome for this analysis was survival status at hospital discharge.

All available platelet counts were linked to infant identifier, survival status, postmenstrual age, day of life, and platelet transfusion timing when available. Infants were included in longitudinal modeling when they had at least three numeric platelet measurements and known survival status. This yielded 17 infants (12 survivors and 5 non-survivors) and 403 platelet observations for mixed-effects modeling. The descriptive observation-level regression included 359 measurements with postmenstrual age available (255 survivor observations and 104 non-survivor observations).

Two complementary approaches were used. First, platelet measurements were plotted against postmenstrual age and stratified by survival status; observation-level linear regression was used to display the raw pattern. Because repeated measurements from the same infant are correlated, this model was considered descriptive. Second, a linear mixed-effects model was fitted by restricted maximum likelihood with a random intercept for infant. Fixed effects included day of life, survival status, same-day platelet transfusion, a delayed platelet transfusion indicator, and interaction terms with survival status. P values used the Satterthwaite approximation. Because of the small analytic subset, the model was not adjusted for all markers of illness severity.

Results

The raw observation-level trajectories diverged sharply by survival status (Fig. 1a). Platelet counts increased with postmenstrual age among survivors (slope + 3.47 x 10^9/L/day, p < 0.001) but decreased among non-survivors (slope − 1.34 x 10^9/L/day, p < 0.001). The time-by-survival interaction was highly significant (p < 2 x 10^-16). Exploratory plots of white blood cell count, hemoglobin, and red blood cell count did not show a comparably pronounced separation by survival status.

In the mixed-effects model, the direction of association persisted but the effect size was attenuated (Fig. 1b). Survivors demonstrated platelet recovery over time (slope + 2.22 × 10^9/L/day; approximate 95% CI + 1.82 to + 2.63). The time-by-death interaction was − 1.46 × 10^9/L/day (95% CI − 2.48 to − 0.44; p = 0.005), corresponding to an estimated non-survivor slope of approximately + 0.76 × 10^9/L/day (approximate 95% CI − 0.17 to + 1.70). Thus, the patient-level model supported impaired platelet recovery in non-survivors rather than the steep decline suggested by the unadjusted observation-level model.

Same-day platelet transfusion was associated with lower measured platelet counts (coefficient − 79.33 x 10^9/L, p = 0.002), consistent with transfusions being administered at lower counts. The delayed transfusion term was not significant (coefficient − 12.05 x 10^9/L, p = 0.629). These terms should not be interpreted as causal treatment effects because transfusion was strongly confounded by clinical indication.

Discussion

In this exploratory analysis, platelet recovery differed by survival status after severe neonatal IVH. The raw observation-level plot provides a striking visualization, but it treats repeated measurements as independent and allows infants with more frequent testing to exert greater influence. The mixed-effects model was therefore used for primary inference. Although it produced more conservative slopes, it confirmed significantly impaired platelet recovery among non-survivors.

The central finding is not that a single platelet count predicts mortality, but that failure of recovery may reflect an adverse physiologic trajectory. Possible explanations include ongoing platelet consumption, systemic inflammation, sepsis, necrotizing enterocolitis, coagulopathy, marrow suppression, or the overall severity of illness accompanying fatal neonatal brain injury. The underlying cohort was medically heterogeneous and included substantial respiratory, infectious, gastrointestinal, cardiovascular, and transfusion-related morbidity. Platelet trajectory may therefore be a marker of global illness severity rather than a mechanism specific to IVH or PHVD.

This study has important limitations. It was retrospective, single-center, and exploratory. The mixed-effects analysis included only 17 infants (12 survivors and 5 non-survivors) with at least three analyzable platelet measurements, and death truncated follow-up, creating potential survivorship and informative-missingness bias. The model did not include all relevant confounders, including standardized illness-severity scores, detailed sepsis and necrotizing enterocolitis timing, vasopressor exposure,

disseminated intravascular coagulation, or respiratory severity. The observation-level p value is also likely overly precise because it does not account for within-infant correlation.

Despite these limitations, the concordance between the raw visualization and the patient-level mixed-effects model supports platelet recovery as a candidate prognostic signal. Multicenter validation should determine whether platelet trajectory improves prediction beyond gestational age, birth weight, IVH burden, PHVD velocity, infection, and transfusion exposure.

Conclusion

Impaired platelet recovery was associated with mortality after severe neonatal IVH. Serial platelet trajectory may complement ultrasound-based and clinical risk stratification, but it should not be used for prognostication until validated prospectively in a larger cohort.

Abbreviations

IVH
intraventricular hemorrhage
NICU
neonatal intensive care unit
PHVD
post-hemorrhagic ventricular dilatation

Declarations

Competing interests:

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval:

This retrospective study was approved by the Rutgers Institutional Review Board (Study ID: Pro2024002316) and was conducted in accordance with the Declaration of Helsinki and applicable institutional requirements.

Consent to participate:

The requirement for informed consent was waived by the Rutgers Institutional Review Board because of the retrospective design and use of existing clinical data.

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No funding was received for this study.

Author Contribution

G.G. conceived the study question, contributed to cohort development and interpretation, and drafted the manuscript. M.L.C. contributed to data review, manuscript preparation, and critical revision. O.F. supervised the study, contributed to interpretation, and critically revised the manuscript. All authors read and approved the final manuscript.

Data Availability

The de-identified data supporting the findings of this study are not publicly available because they contain sensitive clinical information and are subject to patient privacy, institutional, and ethics restrictions. Data may be made available from the corresponding author upon reasonable request, subject to approval by the Rutgers Institutional Review Board and completion of any required institutional data-use agreements.

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Figures

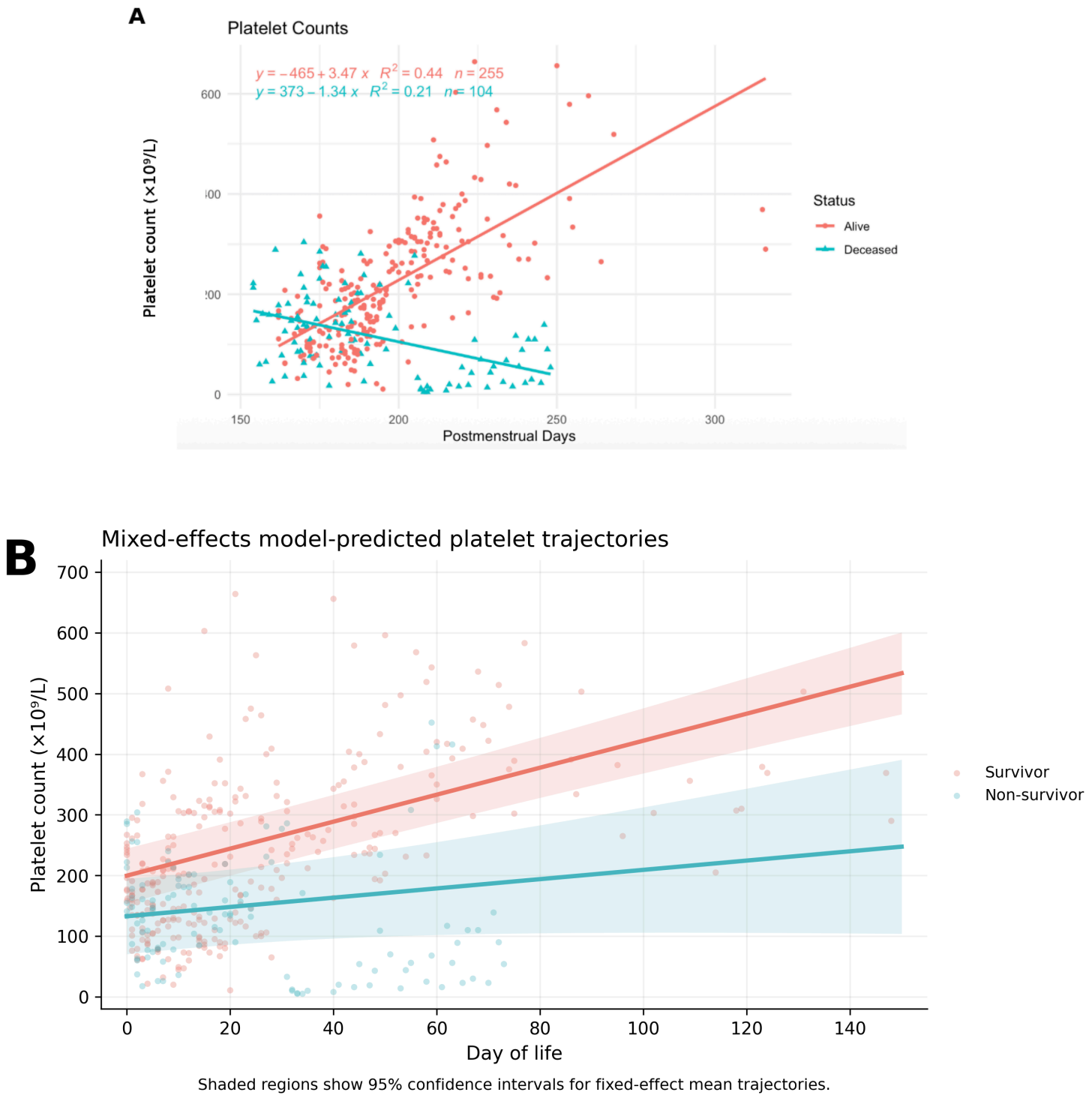


Figure 1

Platelet trajectories by survival status after severe neonatal intraventricular hemorrhage. a Raw platelet measurements plotted against postmenstrual age with observation-level linear regression lines. This panel displays the unadjusted pattern and treats repeated measurements as independent observations. b Mixed-effects model-predicted trajectories over day of life, with raw measurements in the background and 95% confidence intervals for the fixed-effect mean trajectories. Survivors demonstrated greater

platelet recovery than non-survivors; the time-by-death interaction was −1.46 × 10^9/L/day (95% CI −2.48 to −0.44; p = 0.005).