Simultaneous Bayesian Mixed-Effects Regression: Exploratory Analysis of Flocculation in Apheresis Platelet Concentrates

Exploratory observational study — brms v2.21 / RStan — No causal claims

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Background and Aims

White floccular precipitates have been repeatedly observed in apheresis platelet concentrates (PCs) since 2019, causing measurable platelet yield loss — with grade 3 products approaching specification limits. Because the etiology is unknown, this **exploratory, hypothesis-generating** study aimed to: (I) quantify the relative contribution of stable donor disposition versus procedural and physiological covariates to flocculation variance; (II) assess whether double-needle apheresis (DTHA) acts on flocculation primarily via prolonged collection duration rather than directly; (III) characterize high- and low-risk donor phenotypes from posterior random-effect (RE) distributions; and (IV) evaluate post-filtration platelet maturity markers in matched case-control pairs.

Methods

Protocol data from 12,253 research-approved apheresis donations (2,109 donors, 4 centers, from April 2023 to December 2025) were analyzed using a simultaneous Bayesian mixed-effects regression with three linked submodels: DTHA selection (binary outcome, Bernoulli/logit), collection duration (continuous outcome, Gaussian/identity), and flocculation (binary outcome, Bernoulli/logit). All three submodels shared donor-level random intercepts (1 | Donor), capturing stable donor-specific tendency independently of measured covariates. Continuous predictors were z-standardized to make β estimates directly comparable. Weakly regularizing priors were used: β ~ Normal(0, 0.5); intercepts ~ Student-t(3, 0, 2.5); random-effect standard deviations ~ Exponential(1). Markov chain Monte Carlo (MCMC) sampling used 4 chains × 3,000 iterations (1,500 warm-up; adapt_delta = 0.995; brms v2.21 / RStan). Convergence was assessed using Rhat, effective sample size (ESS), divergent transitions, and posterior predictive checks. Variance decomposition used Bayesian R^2 (marginal = fixed effects only; conditional = fixed + donor random effects). Stable high-risk donors were identified from posterior random-effect distributions and matched 1:1 to controls by center and donation count (n = 118 pairs). A within/between-donor decomposition separated session-level deviations from stable donor means. Sysmex XN-3000 measurements on filtered products (IPF%, PCT, MPV) were compared in 64 matched pairs using Bayesian paired models.

Results

Convergence and model fit. Zero divergent transitions occurred and ESS ≥ 400 was achieved for all parameters. Three parameters in the duration submodel showed Rhat marginally above 1.01 (maximum 1.012; minimum ESS = 650). This minor deviation is unlikely to materially affect inference on the primary flocculation outcomes. Maximum treedepth was 7 (limit 15).

Posterior predictive checks showed broadly adequate fit for all three-outcome distributions, with minor residual mismatch in the duration submodel.

Variance decomposition. The flocculation rate was 7.1% (874 events); the DTHA rate was 27.7%. Donor-level random effects explained 42.3% of total flocculation variance (marginal R^2 = 0.3%; conditional R^2 = 42.6%), whereas all measured fixed effects combined explained only 0.3%. The remaining 57.4% was unexplained residual. The random-effect standard deviation for the flocculation submodel was SD = 2.95 (95% credible interval (CrI) 2.67–3.27), confirming substantial inter-individual heterogeneity. Of 2,109 donors, 10.1% (n = 214) had a clearly elevated residual flocculation tendency (lower credible interval bound > 0).

DTHA submodel. Platelet count was the strongest predictor of DTHA procedure assignment (odds ratio OR = 8.02 per +1 SD; 95% CrI 7.25–9.16), confirming that DTHA is selected rather than randomly assigned. The number of prior donations was also strongly positive (OR = 2.55 per +1 SD), indicating that more experienced donors are more frequently selected for double-needle procedures. Body height (OR = 1.55) and weight (OR = 1.45) were independently positive; female sex was protective (OR = 0.40). Centre 300 showed markedly higher DTHA rates than Centre 100 after full adjustment (OR = 5.17).

Duration submodel. DTHA was the single dominant predictor of collection duration (β = +2.53 SD; 95% CrI 2.51–2.55) — an effect far exceeding all other variables in the model. Higher platelet count shortened duration (β = −0.74), while female sex prolonged it (β = +0.36).

Flocculation submodel. Age was the strongest individual predictor of flocculation risk (OR = 1.91 per +1 SD; 95% CrI 1.49–2.43; posterior probability P(β > 0) = 100%). Platelet count was independently associated (OR = 1.56; 95% CrI 1.25–1.93; P = 100%). Longer collection duration also increased risk (OR = 1.38; 95% CrI 1.12–1.70; P = 99.8%). Higher hemoglobin (Hb) was weakly protective (OR = 0.84; 95% CrI 0.71–0.998; P(β < 0) = 97.6%), though this estimate may be partly suppressed by collinearity with hematocrit (Hct; r = 0.72). A higher number of prior donations was protective (OR = 0.68; 95% CrI 0.53–0.87), a novel finding suggesting that more experienced donors may be less susceptible to flocculation. Centre 200 showed higher flocculation risk after adjustment (OR = 1.67; 95% CrI 1.07–2.61). After adjusting for collection duration, the direct effect of DTHA on flocculation was statistically uncertain (OR = 1.37; 95% CrI 0.79–2.40; P(β > 0) = 86.9%), with the credible interval crossing 1.0, consistent with DTHA acting primarily via prolongation rather than directly. Blood group, sex, weight, height, and blood pressure showed no clear independent effects.

Heterogeneity analysis suggested that the residual donor-level susceptibility (captured by the donor random effect after adjustment for measured covariates) was modestly associated with fewer prior donations (Spearman ρ = -0.41), younger donor age (ρ = -0.26), and lower DTHA frequency (ρ = -0.24). These findings characterize the remaining unexplained donor phenotype rather than contradicting the positive donation-level associations of age and DTHA observed in the main model.

Sysmex XN-3000 end-product analysis (64 matched pairs). Plateletcrit (PCT), reflecting total platelet volume in the concentrate, was clearly lower in flocculators (posterior probability P(case < control) = 100%; Cohen's d = −0.60), indicating net platelet loss into aggregates. The immature platelet fraction (IPF%) was directionally lower in flocculators (β = −0.34; 95% CrI −0.72 to +0.04; P(case < control) = 96.3%), representing a suggestive but not definitive

signal that requires prospective confirmation. Mean platelet volume (MPV) showed no clear difference. All Sysmex measurements were taken on the filtered product; it cannot be determined whether the pattern reflects a pre-existing donor trait (more mature circulating platelets with higher adhesive capacity) or selective loss of immature platelets into aggregates during processing.

Conclusions

As an exploratory observational analysis, this study does not establish causality. Stable donor-level heterogeneity explained substantially more flocculation variance than all measured procedural and physiological covariates combined, indicating that risk is dominated by stable donor-level factors not captured by routine variables. DTHA appears to increase risk primarily by prolonging collection duration rather than through a robust direct pathway. Among measured predictors, age and platelet count showed the strongest positive associations. The protective association with a higher number of prior donations is novel and requires independent confirmation. Lower PCT provides a robust post-filtration signal of aggregate-related platelet loss. The directionally lower IPF% represents a biologically plausible exploratory signal, but remains non-definitive and requires prospective pre-donation confirmation.

Priority directions for follow-up: (1) prospective pre-donation whole blood IPF and platelet function measurement in identified high-risk donors; (2) investigation of the protective mechanism associated with donation experience; and (3) intervention studies targeting duration reduction, recognizing that achievable population-level risk reduction is likely limited by the dominant donor-level component.

Limitations

Minor Rhat excess in the duration submodel (three parameters, max 1.012) · Hb/Hct collinearity (r = 0.72) may suppress the Hb signal · DTHA selection confounding (partially addressed by the within/between model) · device type not modelled · Sysmex measurements on filtered end product only · g-computation exploratory (n = 50 draws) · observational design; no causal interpretation intended.

Key Model Parameters

Dataset: 12,253 donations · 2,109 donors · 4 centers · from April 2023 to December 2025

Flocculation: 7.1% (874 events) · DTHA rate 27.7%

Convergence: 0 divergences · ESS ≥400 all · 3 Rhat marginally >1.01 (max 1.012, duration submodel) · max TD = 7

RE variance: RE share 42.3% · Fixed effects 0.3% · Unexplained 57.4% · SD(RE flo) = 2.95 [2.67–3.27]

DTHA submodel: Platelets OR 8.02 · Prior donations OR 2.55 · Centre 300 OR 5.17 · Female OR 0.40

Duration (β): DTHA β = +2.53 SD [dominant] · Platelets β = −0.74 · Female β = +0.36

Flocculation: Age OR 1.91 [1.49–2.43] · Platelets OR 1.56 · Duration OR 1.38 [1.12–1.70]

Hb OR 0.84 [0.71–0.998] (protective, P=97.6%) · Prior donations OR 0.68 [0.53–0.87] (protective)

DTHA direct OR 1.37 [0.79–2.40] P=86.9% — CrI crosses 1.0 · Centre 200 OR 1.67 [1.07–2.61]

Case-control: 118 pairs: cases adj. P = 29.4% · controls 0.1%

Within/between: dur_within β = +0.35 [0.04–0.65] · tc_within β = +0.46 [0.14–0.80] · RE share unchanged 42.3%

Sysmex: 64 pairs · PCT P=100% d=−0.60 (clear) · IPF% P=96.3% CrI crosses 0 (uncertain) · MPV: no effect