Predictive value of platelet function assays in traumatic brain injury patients on antiplatelet therapy

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INTRODUCTION: Traumatic brain injury (TBI) patients on antiplatelet therapy face higher mortality because of impaired platelet function, which may be treated by platelet transfusion. The value of testing platelet function in this cohort remains controversial. We aimed to evaluate the relationship between platelet function assays and outcomes in TBI patients on antiplatelet therapy receiving platelet transfusions. We hypothesized that the magnitude of change in platelet assay performance following a transfusion would predict meaningful clinical outcomes.

METHODS: A cohort of patients, aged 18 to 89 years, with a history of preinjury antiplatelet therapy or who required platelet transfusion, and who were deemed at risk for neurosurgical intervention, was selected from a prospective randomized controlled trial of platelet transfusion for TBI. Pre- and posttransfusion blood samples were drawn. Platelet hemostatic function assays (PHFAs) included thromboelastography with platelet mapping (TEG-PM) and VerifyNow. Logistic regression models assessed the association of temporal assay results with 30-day all-cause mortality, need for craniotomy, and initial and follow-up Rotterdam scores.

RESULTS: Data from 94 TBI patients (43% female) with a median age of 76 years were analyzed. The 30-day mortality rate was 14%. VerifyNow aspirin assay was able to capture increases in platelet function following a platelet transfusion in patients on aspirin (significant positive $\Delta = 65$ aspirin response units, $p < 0.001$). Thromboelastography with platelet mapping parameters detected improved platelet function following transfusion, although the absolute value of changes was minimal. Thromboelastography with platelet mapping parameters predicted important clinical outcomes on logistic regression, although no significant associations with clinical outcomes were identified by the change in PHFA after transfusion or after adjusting for multiple comparisons.

CONCLUSION: Higher absolute pre- and posttransfusion values of TEG-PM were associated with decreased mortality, decreased need for neurosurgical intervention, and decreased risk of progression of hemorrhage in TBI patients taking antiplatelet agents, although neither the change in TEG-PM after transfusion nor any other PHFA value predicted outcomes. (*J Trauma Acute Care Surg.* 2025;98: 550–556. Copyright © 2025 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Prognostic and Epidemiological; Level II.

KEY WORDS: Platelet transfusion; traumatic brain injury; platelet function assay.

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality, affecting approximately an annual 69 million individuals globally.[1] Trends reveal a demographic shift in the age of the patient population afflicted by TBI.[2] The most recent CDC data report that individuals 75 years and older have the highest numbers and rates of both TBI-related hospitalizations and deaths.[3] Older individuals often present with pretrauma comorbidities that are treated with medications that inhibit platelet function.[2,4] The management of patients with TBI who are on antiplatelet therapy becomes challenging, as these agents increase the risk of intracranial hemorrhage and subsequent mortality.[2,4–8] Aspirin (ASA), one of the most common antiplatelet medications, prevents platelet aggregation via inhibition of platelet thromboxane A_2 synthesis.[7] Other widely used agents, such as P2Y12 inhibitors (e.g., clopidogrel), block adenosine diphosphate-induced aggregation.[7] The intersection of TBI and antiplatelet therapy necessitates a nuanced approach to clinical management, placing added emphasis on the role of the reversal of antiplatelet effects.

Treatment of bleeding patients on antiplatelet therapy is a contentious topic, with incomplete consensus on an optimal

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strategy. One intervention strategy aims to restore hemostasis via platelet transfusion; however, the efficacy of transfusion remains debatable.[9] The literature is split in suggesting that platelet transfusion may reduce mortality and improve outcomes[10] or, alternatively, that there are no significant benefits and potential harms.[10,11] Because of variability in opinions, as well as clinical responses and outcomes, there exists a need for more effective predictors of transfusion efficacy and patient prognosis in this population.

Platelet hemostatic function assays (PHFAs) are used as potential tools for evaluating the hemostatic status of patients and guiding therapeutic decisions, including in the context of TBI patients taking antiplatelet agents. Platelet hemostatic function assays provide quantitative measures of platelets' hemostatic functions, which can be used to monitor the efficacy of antiplatelet agents and their reversal. Some PHFAs that are deployed clinically include thromboelastography with platelet mapping (TEG-PM) and the VerifyNow point of care aggregometry system.[12,13] Previous research yields contradicting results regarding the utility of PHFAs in predicting patient outcomes. Some studies have established significant correlations between PHFA results and clinical endpoints, such as mortality and functional outcomes, while others have found no such associations.[14–17] This discrepancy underscores the need for further investigations to establish the role of PHFAs in guiding the management of TBI in patients receiving antiplatelet therapy.

From a cohort of samples from TBI patients on antiplatelet therapy receiving platelet transfusions as part of a randomized controlled trial, we aimed to evaluate the association between temporal PHFA results and 30-day all-cause mortality, need for craniotomy, and both initial and follow-up Rotterdam score, a prognostic tool used for TBI patients based on computed tomography (CT) findings, in this cohort. We hypothesized that the absolute change in value from pre- to posttransfusion of clinically used PHFAs, including TEG-PM and VerifyNow, would predict mortality, need for neurosurgical intervention, and progression of intracranial hemorrhage as quantified by Rotterdam scores in this high-risk population.

PATIENTS AND METHODS

Patient Cohort and Sample Collection

This analysis focuses on a cohort, defined a priori as patients with TBI confirmed by CT scan, aged 18 to 89 years on preinjury antiplatelet therapy or who required platelet transfusion as per standard practices, who were enrolled as part of a prospective randomized controlled trial (NCT 04726410). Inclusion criteria for the parent trial were adult patients who sustained TBI, defined by the presence of potential progressive intracranial injury via CT imaging as determined by radiology read, who either had a history of preinjury antiplatelet agent use or need for platelet transfusion determined by the most responsible trauma or neurosurgery clinician. Antiplatelet agents included aspirin, clopidogrel, and ticagrelor. History of antiplatelet therapy here is patient self-reported either by history or medical record. Exclusion criteria included ages younger than 18 years or older than 89 years; penetrating injury (gunshot wound or stabbing); hypotension in emergency department (systolic blood pressure, <90 mm Hg); known prisoner; known pregnancy; going to operating room for nonneurosurgical intervention in the first 60 minutes of arrival; currently on therapeutic anticoagulation in addition to antiplatelet agents including warfarin or direct-acting oral anticoagulants; platelet transfusion contraindication including recent vascular stent, embolic stroke, and intracranial and/or vascular lesions; and objection to the study voiced by subject or family, or wearing a "No CriSP" opt-out bracelet. The present study represents a secondary analysis which received separate institutional review board approval (STUDY24070033) unrelated to the primary aims of the trial and did not stratify by treatment arm of the study. In the parent trial, patients were randomized to receive either room-temperature stored or cold-stored platelet transfusions. Platelet function testing was performed pre- and posttransfusion regardless of treatment arm. Samples were collected by trained research personnel after the patient was enrolled in the trial and immediately prior to platelet transfusion. Platelet transfusion occurred in the emergency department. Posttransfusion samples were collected immediately following the completion of platelet transfusion. Samples were transported immediately for laboratory analysis. Clinical data, including mortality, need for craniotomy, and the Rotterdam score as a marker of progression of intracranial hemorrhage were captured by research staff and abstracted from the study database. The Rotterdam scores were assessed serially on CT imaging over 24 hours by a blinded radiologist. This study was conducted following the STROBE guidelines (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/E233).

Platelet Hemostatic Function Assays

Pre- and posttransfusion blood samples were collected to evaluate platelet hemostatic function and clotting parameters. Thromboelastography with platelet mapping using the TEG6s platform with a platelet mapping cartridge (Haemonetics, Boston, MA) was used to measure clot strength and platelet hemostatic functions. The VerifyNow (Werfen, Bedford, MA) assay was specifically used to analyze platelet reactivity in patients receiving ASA or P2Y12 inhibitors. The ASA platelet reactivity test and the P2Y12 platelet reactivity test were applied universally to all patients, irrespective of which medication the patient was reported to be taking. Where applicable, assay values are reported as pretransfusion, posttransfusion, and the "Δ," which is defined as the posttransfusion value minus the pretransfusion value and is used here to identify changes in the PHFA associated with transfusion.

Statistical Analysis

Logistic regression models were used to assess the association between assay results, including both pre- and posttransfusion, as well as the change from pre- to posttransfusion (hereafter referred to as "Δ"), and 30-day all-cause mortality, need for craniotomy, and both initial and follow-up Rotterdam scores. All outcomes were assessed irrespective of the parent trial's intervention arm. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and a Bonferroni correction was used to adjust for multiple comparisons. Classification and regression

TABLE 1. Demographic, Antiplatelet Therapy, and Outcome Measures by PHFA

Measure	All (N = 94)	PHFA	
		VerifyNow (n = 93)	TEG-PM (n = 94)
Demographics			
Age at randomization	76 [67–81]	76 [67–81]	76 [67–81]
Sex at birth			
Female	43 (45.7)	42 (45.2)	43 (45.7)
Male	51 (54.3)	51 (54.8)	51 (54.3)
Racial identification			
White	77 (89.5)	76 (89.4)	77 (89.5)
Black or African American	8 (9.3)	8 (9.4)	8 (9.3)
Asian	1 (1.2)	1 (1.2)	1 (1.2)
Antiplatelet therapy			
Aspirin	87 (92.6)	86 (92.5)	87 (92.6)
Outcomes			
Died within 30 d of arrival	13 (13.8)	13 (14.0)	13 (13.8)
Need for craniectomy/craniotomy	11 (11.7)	10 (10.8)	11 (11.7)
Rotterdam CT score			
Initial	3 [2–3]	3 [2–3]	3 [2–3]
Follow-up	3 [3–3]	3 [3–3]	3 [3–3]

Data are presented as n (%) or median [Q1–Q3].

tree analysis were used to assess a thresholding cutoff for assay performance and relatedness for outcomes variables.

RESULTS

Of the 101 patients enrolled in the parent trial, data were available on at least one PHFA for 94 total patients, defining our study cohort. The cohort had a median age of 76 years and was 46% female (Table 1). Within our cohort, 12% of patients required craniotomy, and the 30-day mortality rate was 14% (Table 1). For this cohort, all patients were transfused at least 1 U of platelets, and 30 patients were transfused 2 U. Of these 30 patients, 17 had their posttransfusion blood collection drawn after initiation of the second unit of platelets. Thus, most patients in this cohort had their posttransfusion blood collection drawn after completion of 1 U of platelets and before a second unit was transfused, if it was transfused at all. Thromboelastography was used for 94 patients, including 46% female and 88% White (Table 1). VerifyNow assays were conducted on 93 patients (40% female and 89% White) (Table 1). Of the total cohort of 94 patients, 68 (72%) were taking ASA alone, 5 (5%) were taking a P2Y12 inhibitor alone, 19 (20%) were taking both, and 2 (2%) were taking neither (Table 1). Assays analyses were performed on all patients, irrespective of antiplatelet medication, apart from the VerifyNow ASA and P2Y12 assays. The VerifyNow ASA assay analysis was performed on patients taking ASA alone, whereas the VerifyNow P2Y12 assay analysis was performed on patients who were taking both ASA and a P2Y12 inhibitor, since the limited sample size for the latter alone would not have been meaningful.

Following platelet transfusion, VerifyNow ASA results of patients taking ASA alone yielded a significant positive Δ (Δ = 65 ASA response units, $p < 0.001$), indicating that these patients had decreased ASA inhibition following a platelet transfusion (Table 2). All TEG-PM measurements increased from baseline significantly (Table 2), although most were small absolute differences. The largest changes from baseline were seen in arachadonic acid (AA) maximal amplitude (MA) (Δ = 5.2 percentage points, $p < 0.001$), AA %Inhibition (Δ = −6.9 percentage points, $p < 0.001$), and AA %Aggregation (Δ = 6.9 percentage points, $p < 0.001$) (Table 2). Thromboelastography with platelet mapping was the only assay that had universal significant change to all parameters following transfusion.

Clinical outcomes, 30-day mortality, need for craniotomy, and both initial and follow-up Rotterdam scores were regressed on clinical assays at all time points (Table 3). For VerifyNow, only pretransfusion values for patients on ASA, as measured by the

TABLE 2. Descriptive Statistics for All Assays by Time Point

Assay	Pretransfusion		Posttransfusion		Δ (Post- Minus Pretransfusion Values)		p†
	n	Median [Q1–Q3]	n	Median [Q1–Q3]	n	Median [Q1–Q3]	
VerifyNow							
ASA*, ARU	58	427 [403–530]	58	586 [430–616]	50	65 [2–176]	<0.001
P2Y12**, PRU	21	209 [136–265]	19	188 [85–248]	17	11 [−21 to 29]	0.43
Thromboelastography							
Kaolin MA, mm	93	62.4 [58.1–66.7]	92	64.6 [60.5–67.5]	91	1.3 [0–3.1]	<0.001
ActF MA, mm	93	13.9 [9.1–17.9]	93	14.5 [10.6–18.4]	92	0.4 [−0.1 to 1.55]	0.006
ADP MA, mm	91	41.6 [20.3–55.1]	92	46.3 [28.8–56.1]	90	1.85 [−0.6 to 7.6]	<0.001
ADP %Inhibition, %	80	37.8 [17.6–76.3]	86	33.6 [21.9–59]	75	−1.8 [−14 to 5.2]	0.017
ADP %Aggregation, %	80	62.2 [23.7–82.5]	86	66.4 [41–78.1]	75	1.8 [−5.2 to 14.4]	0.017
AA MA, mm	91	19.2 [14.3–35.7]	92	37.9 [18.4–56.5]	90	5.2 [0.7–22.9]	<0.001
AA %Inhibition, %	76	87.8 [51.7–96.5]	84	48.5 [13.7–91.8]	73	−6.9 [−44 to 0.4]	<0.001
AA %Aggregation, %	76	12.3 [3.5–48.3]	84	51.5 [8.2–86.3]	73	6.9 [0.4–43.9]	<0.001

*Restricted to patients with a preinjury history of aspirin use in the absence of P2Y12 use.
**Restricted to patients with a preinjury history of P2Y12 use regardless of aspirin use.
†Parametric one-sided *t* test between Δ and 0.
ADP, adenosine diphosphate; ARU, aspirin response units; n, number of observations; PRU, P2Y12 response units; Q, quartile.

TABLE 3. Logistic Regression Model Results of Outcomes Regressed on Clinically Used Assays

	Died				Craniec-/Craniotomy				Rotterdam Score (Initial)				Rotterdam Score (Follow-up)			
Assay	**n**	**OR (95% CI)**	***p***	***c***	**n**	**OR (95% CI)**	***p***	***c***	**n**	**OR (95% CI)**	***p***	***c***	**n**	**OR (95% CI)**	***p***	***c***
VerifyNow																
Pretransfusion																
ASA*	58	1.00 (0.99–1.01)	0.95	0.457	58	1.00 (1.00–1.01)	0.32	0.640	57	1.01 (1.00–1.01)	0.10	0.608	57	1.01 (1.00–1.01)	0.040	0.632
P2Y12**	21	1.01 (1.00–1.02)	0.20	0.613	21	0.99 (0.98–1.01)	0.37	0.763	19	1.00 (0.99–1.01)	0.65	0.550	19	1.00 (0.99–1.01)	0.84	0.513
Posttransfusion																
ASA*	58	0.99 (0.98–1.00)	0.18	0.647	58	1.04 (1.00–1.08)	0.08	0.838	58	1.00 (1.00–1.01)	0.38	0.558	58	1.00 (1.00–1.01)	0.13	0.620
P2Y12**	19	1.01 (0.99–1.02)	0.45	0.635	19	1.01 (0.99–1.03)	0.44	0.706	18	1.00 (0.99–1.01)	0.53	0.582	18	1.01 (1.00–1.02)	0.27	0.654
Δ																
ASA*	50	0.99 (0.98–1.00)	0.18	0.691	50	1.00 (0.99–1.01)	0.53	0.606	50	1.00 (0.99–1.00)	0.64	0.531	50	1.00 (0.99–1.00)	0.67	0.526
P2Y12**	17	1.02 (0.99–1.05)	0.17	0.679	17	1.04 (0.98–1.10)	0.17	0.900	16	1.02 (1.00–1.03)	0.11	0.669	16	1.02 (1.00–1.04)	0.042	0.711
Thromboelastography																
Pretransfusion																
Kaolin MA	93	0.92 (0.86–0.99)	0.018	0.757	93	0.95 (0.88–1.02)	0.19	0.684	90	0.97 (0.92–1.03)	0.32	0.572	90	0.96 (0.91–1.01)	0.12	0.614
ActF MA	93	0.88 (0.79–0.98)	0.018	0.707	93	0.89 (0.79–0.99)	0.037	0.710	90	0.93 (0.88–0.99)	0.024	0.598	90	0.89 (0.83–0.95)	<.001	0.661
ADP MA	91	0.97 (0.94–1.01)	0.11	0.652	91	0.97 (0.94–1.01)	0.14	0.630	88	0.97 (0.95–1.00)	0.026	0.624	88	0.97 (0.95–0.99)	0.013	0.640
ADP %Inhibition	80	1.01 (0.98–1.03)	0.60	0.544	80	1.01 (0.99–1.03)	0.43	0.561	77	1.01 (0.99–1.02)	0.25	0.566	77	1.01 (0.99–1.02)	0.31	0.551
ADP % Aggregation	80	0.99 (0.97–1.02)	0.60	0.544	80	0.99 (0.97–1.01)	0.43	0.561	77	0.99 (0.98–1.01)	0.25	0.566	77	0.99 (0.98–1.01)	0.31	0.551
AA MA	91	0.99 (0.95–1.03)	0.54	0.602	91	0.97 (0.93–1.02)	0.28	0.691	88	1.00 (0.97–1.02)	0.79	0.540	88	0.99 (0.97–1.01)	0.41	0.593
AA %Inhibition	76	0.99 (0.97–1.01)	0.29	0.536	76	0.99 (0.97–1.01)	0.44	0.574	73	0.99 (0.97–1.00)	0.12	0.629	73	0.99 (0.97–1.00)	0.10	0.662
AA %Aggregation	76	1.01 (0.99–1.03)	0.29	0.536	76	1.01 (0.99–1.03)	0.44	0.574	73	1.01 (1.00–1.03)	0.12	0.629	73	1.01 (1.00–1.03)	0.10	0.663
Posttransfusion																
Kaolin MA	92	0.91 (0.83–0.99)	0.021	0.680	92	0.97 (0.88–1.06)	0.48	0.558	89	0.99 (0.93–1.06)	0.81	0.530	89	0.95 (0.89–1.02)	0.16	0.575
ActF MA	93	0.86 (0.77–0.96)	0.006	0.723	93	0.89 (0.79–0.99)	0.031	0.683	90	0.94 (0.88–1.00)	0.06	0.580	90	0.89 (0.83–0.96)	0.001	0.642
ADP MA	92	0.96 (0.92–0.99)	0.022	0.716	92	0.97 (0.94–1.01)	0.15	0.627	89	0.99 (0.96–1.01)	0.34	0.543	89	0.98 (0.96–1.01)	0.12	0.576
ADP %Inhibition	86	1.01 (0.99–1.04)	0.31	0.625	86	1.00 (0.98–1.03)	0.99	0.504	83	1.00 (0.98–1.01)	0.95	0.509	83	1.00 (0.98–1.01)	0.74	0.493
ADP % Aggregation	86	0.99 (0.96–1.01)	0.31	0.625	86	1.00 (0.97–1.03)	0.99	0.504	83	1.00 (0.99–1.02)	0.95	0.509	83	1.00 (0.99–1.02)	0.74	0.493
AA MA	92	0.97 (0.94–1.01)	0.11	0.646	92	0.98 (0.95–1.02)	0.32	0.613	89	1.00 (0.98–1.02)	0.77	0.525	89	0.99 (0.97–1.01)	0.49	0.539
AA %Inhibition	84	1.00 (0.98–1.02)	0.94	0.504	84	1.00 (0.98–1.02)	0.93	0.499	81	1.00 (0.99–1.01)	0.62	0.535	81	1.00 (0.98–1.01)	0.55	0.538
AA %Aggregation	84	1.00 (0.98–1.02)	0.94	0.504	84	1.00 (0.98–1.02)	0.93	0.499	81	1.00 (0.99–1.01)	0.62	0.535	81	1.00 (0.99–1.02)	0.55	0.538
Δ																
Kaolin MA	91	0.99 (0.88–1.12)	0.91	0.391	91	1.06 (0.96–1.18)	0.24	0.735	88	1.05 (0.97–1.14)	0.20	0.594	88	1.04 (0.96–1.12)	0.36	0.593
ActF MA	92	0.92 (0.74–1.16)	0.50	0.589	92	1.00 (0.81–1.25)	0.96	0.482	89	1.11 (0.97–1.27)	0.14	0.571	89	1.10 (0.96–1.26)	0.17	0.561
ADP MA	90	0.97 (0.90–1.03)	0.32	0.552	90	1.01 (0.95–1.07)	0.84	0.499	87	1.04 (1.00–1.08)	0.06	0.607	87	1.03 (0.99–1.07)	0.13	0.593
ADP %Inhibition	75	1.00 (0.96–1.04)	0.88	0.559	75	0.99 (0.96–1.03)	0.69	0.570	72	0.98 (0.96–1.00)	0.06	0.603	72	0.98 (0.96–1.00)	0.10	0.592
ADP % Aggregation	75	1.00 (0.97–1.04)	0.88	0.559	75	1.01 (0.97–1.04)	0.69	0.570	72	1.02 (1.00–1.05)	0.06	0.603	72	1.02 (1.00–1.04)	0.10	0.592
AA MA	90	0.97 (0.93–1.02)	0.25	0.585	90	1.00 (0.95–1.04)	0.85	0.521	87	1.00 (0.97–1.03)	0.97	0.489	87	1.00 (0.97–1.03)	0.95	0.504
AA %Inhibition	73	1.00 (0.97–1.03)	0.86	0.536	73	1.01 (0.98–1.05)	0.42	0.595	70	1.00 (0.99–1.02)	0.98	0.507	70	1.00 (0.99–1.02)	0.92	0.483
AA %Aggregation	73	1.00 (0.97–1.03)	0.86	0.536	73	0.99 (0.96–1.02)	0.42	0.595	70	1.00 (0.98–1.01)	0.98	0.524	70	1.00 (0.98–1.01)	0.92	0.483

*Restricted to patients with a pre-injury history of aspirin use in the absence of P2Y12 use.
**Restricted to patients with a pre-injury history of P2Y12 use regardless of aspirin use.
No probability values reach statistical significance after a Bonferroni correction of 0.05/120 = 0.0004.
ADP, adenosine diphosphate; n, number of observations; *c*, concordance statistic.

ASA platelet reactivity assay, were associated with any clinical outcome, with an OR of 1.01 (95% CI, 1.00–1.01; $p < 0.040$) (Table 3) for an increase in follow-up Rotterdam score. In the small cohort of patients on P2Y12 inhibitors, there was a modest association with an increased Rotterdam follow-up score and the change in assay value following transfusion (OR, 1.02; 95% CI, 1.00–1.04; $p = 0.042$) (Table 3). No other VerifyNow value, including those recorded at the time of presentation prior to transfusion, was predictive of any clinical outcome.

For TEG-PM, there was a consistent association of higher pretransfusion absolute values with improved clinical outcomes for the ActF agonist MA. This value predicted reduced mortality (OR, 0.88 [95% CI, 0.79–0.98]; $p = 0.018$), reduced need for neurosurgical intervention (OR, 0.89 [95% CI, 0.79–0.99]; $p = 0.037$), and improved Rotterdam scores especially posttransfusion (OR, 0.89 [95% CI, 0.83–0.95]; $p < 0.001$) (Table 3). Both the kaolin and adenosine diphosphate MA values provided additional predictors of outcomes on regression analysis for both

pre- and posttransfusion values (Table 3). Importantly, no Δ TEG-PM values predicted outcome.

A Bonferroni correction was applied because of the presence of multiple comparisons. Following correction, none of the initial significant findings maintained significance (Table 3).

Classification and regression tree analysis was performed on all assays with significant associations resulting from the logistic regression analysis (Table 3) to determine if there are optimal thresholds at which assay values can be dichotomized to more effectively predict outcomes (Table 4). Analysis revealed that segmented PHFA values were unable to significantly predict any outcome with meaningful sensitivity or specificity (Table 4).

DISCUSSION

Here, we evaluated the predictive value of PHFAs for clinical outcomes in TBI patients on antiplatelet therapy after receipt of platelet transfusion. We hypothesized that the change in metrics on PHFA following platelet transfusion (Δ) would predict relevant outcomes in this patient cohort. The data did not support our hypothesis. Our results highlight that certain absolute pre- and posttransfusion values on TEG-PM can predict 30-day mortality, need for craniotomy, or initial and follow-up Rotterdam scores. Although VerifyNow ASA pretransfusion and P2Y12 Δ values were significantly associated with follow-up Rotterdam score, the association would be with worsening intracranial hemorrhage, and the small absolute difference is unlikely to be of clinical significance. Other than TEG-PM, there were no other significant and meaningful associations between PHFAs and clinical outcomes. Importantly and in contrast to our hypothesis, no PHFA, including TEG-PM, demonstrated that an improvement (significant positive Δ) in platelet function after platelet transfusion was associated with any of our predefined clinical outcomes.

VerifyNow ASA was able to detect changes to patient platelet hemostatic function after transfusion. VerifyNow ASA values significantly increased following transfusion, indicative of decreased ASA inhibition. In contrast, VerifyNow P2Y12 assay values did not significantly change following a transfusion, although this may be the result of having a small number of patients on P2Y12 inhibitors alone. Despite the significant change in ASA response units, performance on the ASA assay did not associate meaningfully with clinical outcomes. The same was seen in the P2Y12 assay. Our findings echo other research suggesting that, while VerifyNow can detect platelet inhibition, the predictive utility for outcomes such as mortality and transfusion needs may be limited.[18–21] This is an important observation given that VerifyNow is a common point of care diagnostic in the management of TBI patients on antiplatelet agents.[15]

Similarly, TEG-PM parameters were able to describe changes to platelet hemostatic function following a transfusion, but an improvement in function (positive Δ) after transfusion was not correlated with clinical outcomes. Interestingly, those parameters that sustained the most significant changes following transfusion were measures of ASA-induced platelet inhibition, suggesting, again, that clinical assays of platelet dysfunction can capture ASA-induced inhibition and a small restoration in function. These findings align with what has been described in the literature.[22–24] Thromboelastography with platelet mapping detects the presence of platelet inhibition, and higher values (indicative of preserved platelet hemostatic function despite a history of anti-platelet use) were associated with improved outcomes. However, these results were inconsistent across all agonists and measures of function in TEG-PM, reiterating that the

TABLE 4. Outcomes and Assay Thresholds Estimated by CART and Accuracy Estimates and Model Results of the Thresholds

	Outcome		Accuracy		Model Results			
Outcome/Assay	**Yes**	**No**	**Sensitivity**	**Specificity**	**OR**	**95% CI**	***p***	**AUC**
Death								
Pretransfusion TEG Kaolin MA ≤61.65	12/41 (29.3)	1/52 (1.9)	12/13 (92.3)	51/80 (63.8)	21.10	(2.609–170.7)	0.004	0.780
Pretransfusion TEG ActF MA ≤9.25	8/25 (32)	5/68 (7.4)	8/13 (61.5)	63/80 (78.8)	5.930	(1.717–20.47)	0.005	0.701
Posttransfusion TEG Kaolin MA ≤67.45	12/69 (17.4)	0/23	12/12 (100)	23/80 (28.8)	>999	(<0.001 to >999)	0.96	0.644
Posttransfusion TEG ActF MA ≤11.7	9/32 (28.1)	4/61 (6.6)	9/13 (69.2)	57/80 (71.3)	5.575	(1.561–19.92)	0.008	0.702
Posttransfusion TEG ADP MA ≤55.65	12/67 (17.9)	0/25	12/12 (100)	25/80 (31.2)	>999	(<0.001 to >999)	0.96	0.656
Craniectomy/craniotomy								
Pretransfusion TEG ActF MA ≤6.45	6/15 (40)	5/78 (6.4)	6/11 (54.5)	73/82 (89)	9.733	(2.463–38.46)	0.001	0.718
Posttransfusion TEG ActF MA ≤5.25	5/10 (50)	6/83 (7.2)	5/11 (45.5)	77/82 (93.9)	12.83	(2.885–57.06)	<0.001	0.697
Rotterdam CT score >3, initial								
Pretransfusion TEG ActF MA ≤6.45	5/15 (33.3)	9/75 (12)	5/14 (35.7)	66/76 (86.8)	3.667	(1.020–13.18)	0.047	0.613
Pretransfusion TEG ADP MA ≤29.65	8/31 (25.8)	6/57 (10.5)	8/14 (57.1)	51/74 (68.9)	2.957	(0.920–9.501)	0.07	0.630
Rotterdam CT score >3, follow-up								
Pretransfusion VerifyNow ASA >475.5	8/22 (36.4)	2/35 (5.7)	8/10 (80)	33/47 (70.2)	9.429	(1.773–50.13)	0.008	0.751
Δ VerifyNow P2Y12** >26.5	3/5 (60.0)	0/11	3/3 (100)	11/13 (84.6)	>999	(<0.001 to >999)	0.94	0.923
Pretransfusion TEG ActF MA ≤6.45	7/15 (46.7)	9/75 (12)	7/16 (43.8)	66/74 (89.2)	6.417	(1.875–21.96)	0.003	0.665
Pretransfusion TEG ADP MA ≤29.65	9/31 (29)	7/57 (12.3)	9/16 (56.2)	50/72 (69.4)	2.922	(0.965–8.846)	0.06	0.628
Posttransfusion TEG ActF MA ≤5.25	6/10 (60)	11/80 (13.8)	6/17 (35.3)	69/73 (94.5)	9.409	(2.283–38.78)	0.002	0.649

*VerifyNow ASA models are restricted to participants with a preinjury history of aspirin use in the absence of P2Y12 medications.
**VerifyNow P2Y12 models are restricted to participants with a preinjury history of P2Y12 use regardless of aspirin use.
ADP, adenosine diphosphate; CART, classification and regression tree analysis.

predictive value of TEG for survival and the progression of intracranial hemorrhage remains incompletely understood.[25] Again, a consistent observation remains that, although the absolute value of TEG-PM may predict outcome, an increase in hemostatic function on this assay following transfusion does not predict any improved clinical course.

Together, our results confirm that clinically used measures of platelet hemostatic function are able to detect a change in function following platelet transfusion in TBI patients on antiplatelet therapy. Despite this measurable impact of platelet transfusion, these changes were not found to be predictive of clinical outcomes. This is consistent with literature that suggests platelet transfusion in this population does not reverse the effects of antiplatelet therapy and may contribute to increased risk of mortality.[11] We did identify that TEG-PM had multiple associations with improved clinical outcomes for pre- and posttransfusion absolute values. Further stratification of assay values at all time points via classification and regression tree analysis similarly reveals that there are no specific thresholds for which we can confidently predict clinical outcomes. However, this analysis is limited by the small sample size. Further research is needed to explore both optimal treatment strategies for platelet inhibition rescue in this population and measures of platelet function to assay efficacy of the employed strategies.

Despite the strengths of our study, there are several limitations. Our reporting and analyses are strictly applicable to TBI patients on antiplatelet therapy receiving platelet transfusions and should not be generalized beyond this cohort. Moreover, the variability in predictive value observed among assays could be influenced by the heterogeneous nature of trauma patients and clinical scenarios encountered. Importantly, to achieve statistical rigor, we applied a Bonferroni correction to address multiple comparisons. While our analyses following correction hold no significance, this may be a factor of having a small cohort size relative to the number of tests performed. We acknowledge the lack of significance after correction is important; however, the logistic regression analysis provides hypothesis-generating and biologically plausible results that should be tested in future studies with larger sample sizes and fewer tests. In addition, all assays were not performed on every patient, which may have affected the overall findings. Reasons for varied testing per assay include inability to obtain samples because of clinical condition, inadequate sampling, or technical failure of the assay. This missingness may have biased the results. This study focused on the overall ability of PHFAs to predict outcomes and did not stratify by treatment arm of the parent study; thus, the impact of cold versus room temperature storage on PHFAs remains unexplored in this current cohort analysis.

In conclusion, this secondary analysis of a randomized trial of platelet transfusion in TBI patients on antiplatelet therapy identifies that use of TEG-PM may detect platelet inhibition and predict important clinical outcomes. VerifyNow was able to accurately identify platelet inhibition, but the values did not clinically correlate with outcomes meaningfully. In both, improved platelet function after transfusion could be identified yet held no association with improved clinical outcomes. These observations raise a number of provocative observations and questions. First, the data suggest that there is little utility in serial measurement or obtaining posttransfusion testing, as these results either did not predict outcome or did not change observations made from the initial sample. Second, there appear to be important differences between the two most commonly used PHFAs, an observation that should be confirmed in a well powered study. Finally, the possibility exists that the lack of clinical outcome benefit seen in association with the change in platelet function assays is not a product of the test but rather a lack of clinical benefit of the intervention. While the optimal use of PHFAs in patients with TBI on antiplatelet agents remains unknown, a definitively powered clinical trial to determine whether platelet transfusion improves outcome in TBI patients on antiplatelet agents should be a high priority.

AUTHORSHIP

P.C.S., D.O., F.X.G., J.L.S., S.M.S., and M.D.N. conceived and designed this study. All authors were significantly involved in data acquisition. N.A., R.Y., J.R.K., L.H., A.S., D.M.D., R.K., E.P.M., P.L., S.R.W., J.F.L., J.L.S., S.M.S., and M.D.N. contributed equally to data analysis and interpretation. N.A., R.Y., J.R.K., S.M.S., and M.D.N. prepared the manuscript draft. All authors were significantly involved in revision of this manuscript.

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DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E234).

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