



Platelet count is not associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as defined by the 2010 consensus definition

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ABSTRACT

Background: Although delayed cerebral ischemia (DCI) commonly complicates recovery in survivors of aneurysmal subarachnoid hemorrhage (aSAH), its pathophysiology is incompletely understood. Previous studies examining the association of DCI and platelet count have demonstrated contradictory results. This study aimed to investigate this association in a cohort of aSAH patients using the 2010 consensus definition of DCI.

Methods: We conducted a retrospective single-center observational study of consecutive adult aSAH patients admitted to the intensive care unit from January 2010 to December 2014. Platelet count and DCI evaluations were performed daily in the first 14 days after admission. DCI was defined according to the 2010 consensus criteria.

Results: A total of 340 patients were included for analysis. DCI incidence was 37.1%. Platelet count was not significantly associated with occurrence of DCI on any day. Mean platelet count was lowest on day 3 after aSAH and then increased to exceed the count at admission on day 6. Treatment modality and use of dual antiplatelet therapy were not associated with DCI.

Conclusions: Platelet count was not associated with DCI as defined by the 2010 consensus criteria. Future studies adhering to the 2010 consensus definition of DCI are needed to clarify the role of platelets and platelet function in DCI pathophysiology.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating disease. One-year mortality approaches 50%. [1] In those who survive, delayed cerebral ischemia (DCI) can result in poor outcomes. The mechanisms of DCI are incompletely understood. Although vasospasm of large cerebral arteries is one underlying mechanism, other factors are involved. [2,3] Post-mortem studies have shown that microthrombosis is a common finding in aSAH patients and that microclot burden is associated with DCI. [4,5] A recent review of the role of platelets in DCI pathophysiology concluded that platelets are involved at multiple stages. [6] Previous studies have used various

definitions of DCI, which makes interstudy comparisons difficult. The 2010 consensus definition of DCI after aSAH was formulated to provide a clear and consistent definition to be used in future studies to enable valid interstudy comparisons. [7]

Findings regarding platelets and DCI in previous studies have been contradictory. In one study, platelet count in aSAH patients first decreased and then increased to exceed the count at admission. The same study found that platelet consumption was greater in patients with symptomatic vasospasm [8]. However, another study reported a platelet count increase in patients as they developed DCI. [9] Although procedural complications in aSAH patients are common and related to morbidity [10], the association of treatment modality with DCI

Abbreviations: DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage; GOS, Glasgow Outcome Scale; ADP, adenosine diphosphate.

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incidence is not known.

The present study evaluated absolute platelet count and change in platelet count during the first 14 days after aSAH and examined their association with DCI as defined by Vergouwen et al. [7] We also evaluated the effects of treatment modality and antiplatelet therapy on platelet count and their association with DCI.

2. Methods

2.1. Study design

The patients in this retrospective single-center observational cohort were included in our previous study of the predictive value for neurological outcome of the 2010 consensus definition of DCI after aSAH. [11] The local ethics committee of Pirkanmaa approved the study design (approval no. R115508S). The requirement for informed consent was waived because of the retrospective nature of the study.

In brief, adult patients with aSAH admitted to the intensive care unit (ICU) of Tampere University Hospital from January 2010 to December 2014 were eligible for inclusion. Tampere University Hospital is one of five tertiary referral centers in Finland and serves approximately one million inhabitants. All patients who require neurointensive care in its catchment area are treated there. All non-moribund aSAH patients admitted are initially treated in the ICU.

2.2. Selection of patients

Onset of aSAH symptoms was defined as the ictus. Time of ictus onset was obtained from the medical records. Patients with an unknown time of onset and those admitted >48 h after the ictus were excluded. We also excluded moribund patients with unsecured aneurysms and those admitted to the ICU solely because of organ donation. All patients received standardized aSAH care using our hospital protocol, which was created based on international multidisciplinary consensus guidelines. [12,13]

2.3. Blood sampling

Platelet count was performed at admission and daily thereafter while the patient remained in the ICU. After transfer from the ICU, it was performed according to clinical need. If more than one platelet count was obtained on any given day, the average was analyzed. When assessing the effect of circadian rhythm of platelets, only the platelet counts obtained in the morning were assessed.

2.4. Assessment of DCI

Three investigators (AK, AV, and ER) independently evaluated each patient for the development of DCI as defined by Vergouwen et al. [7] using patient data recorded between 48 h and 14 days from ictus onset. Data were obtained from the ICU database (Centricity Critical Care Clinisoft; GE Healthcare, Barrington, IL, USA) and the electronic medical records. In case of any doubt, all investigators thoroughly evaluated the patient's history and made a consensus decision. Detailed DCI criteria are described in our previously published paper [11] and in Supplementary table 1.

2.5. Assessment of other clinical factors

Other information was collected from the neurosurgical aneurysm database, including aneurysm location, treatment modality, Hunt and Hess scale grade, [14] Fisher scale grade, [15] and Glasgow Outcome Scale (GOS) score. [16] We also recorded the use of antiplatelet drugs in patients treated with stent-assisted coiling. All patients treated with stent-assisted coiling in our hospital receive aspirin 100 mg and an adenosine diphosphate (ADP) receptor inhibitor (clopidogrel,

ticagrelor). Abciximab, a glycoprotein IIb/IIIa inhibitor, is used temporarily after stent placement until an ADP receptor inhibitor is initiated.

The Hunt and Hess scale was used to assess severity of early brain injury at hospital admission, which was dichotomized as mild (grades 1–3) and severe (grades 4–5). The Fisher scale was used to assess aSAH severity on the initial computed tomography, which was dichotomized as non-severe (grades 1–2) and severe (grades 3–4). The GOS was used to assess neurological outcome at discharge, which was dichotomized as favorable (scores 4–5) and unfavorable (scores 1–3).

The patients' medical history and medication prior to aSAH was not unambiguously retrievable from the neurosurgical database or electronic medical records.

2.6. Statistical methods

The continuous variables examined in this study (age, platelet count) were normally distributed and are presented as means with standard deviation. They were compared between groups using the *t*-test. The associations of categorical variables and DCI were evaluated using the Pearson chi-square test. Cox proportional hazards regression was used to examine the association of platelet count with DCI; daily platelet counts were used as time-dependent covariates and missing platelet count values were imputed with the last known platelet level. Analysis of variance was used to evaluate the association between platelet count and treatment modality. All statistical analyses were performed using R version 4.0.3 (The R Foundation, Vienna, Austria) and SPSS software version 27 (IBM Corp, Armonk, NY, USA).

3. Results

Four hundred thirty-nine aSAH patients were eligible for inclusion. After excluding 99 based on study criteria, 340 patients were analyzed. [11] Patient characteristics are shown in Table 1. Mean patient age was 56.4 ± 12.4 years. Most patients (60.6%) were women. Location of ruptured aneurysm was the anterior circulation in 80.9% of patients and the posterior circulation in 19.1%. One hundred eighty-one patients underwent endovascular coiling with or without stent assistance (53.5%) and 159 underwent surgical clipping (46.5%). Stent-assisted coiling was performed in 27 patients (7.9%).

One hundred twenty-six patients (37.1%) developed DCI as defined by the 2010 consensus criteria. Mean platelet count reached a minimum on day 3 after the ictus in both the DCI ($196 \pm 51.7 \times 10^9/L$) and no DCI ($196 \pm 50.4 \times 10^9/L$) groups and then increased to exceed the count at admission after day 6. On day 14, mean platelet count was slightly higher in the no DCI group, but the difference was not significant ($391 \pm 91.9 \times 10^9/L$ vs. $362 \pm 115 \times 10^9/L$; $p = 0.2$). Platelet count did not significantly differ between groups on any given day in the first 14 days after ictus (Fig. 1). The time-dependent association of daily platelet count and DCI was assessed and no association was found (hazard ratio, 1.00; 95% confidence interval, 0.998–1.003). The circadian rhythm of platelets had no time-dependent association with DCI (hazard ratio, 1.001; 95% confidence interval, 0.998–1.003).

Treatment modality was not associated with DCI ($p = 0.977$). Mean platelet count on day 9 after the ictus significantly differed between the endovascular coiling without stent assistance ($273 \pm 83.5 \times 10^9/L$), stent-assisted coiling ($304 \pm 52.7 \times 10^9/L$), and surgical clipping ($308 \pm 80.6 \times 10^9/L$) groups ($p = 0.020$; Fig. 2). However, platelet count data were available in only 180 patients (52.9%) on day 9. The incidence of DCI did not significantly differ between patients treated with stent-assisted coiling (37.0%), coiling without stent assistance (37.7%), and surgical clipping (36.5%). Patients with severe aSAH had a significant decline in platelet count on days 1 and 2 after ictus ($p < 0.05$) that was not seen on other days (Fig. 3). Platelet count on days 1–6 after ictus significantly differed between patients who had a favorable neurological outcome and those who had an unfavorable outcome ($p < 0.05$, Fig. 4).

Table 1
Patient characteristics.

	DCI group n = 126		No DCI group n = 214		p-value
	n	%	n	%	
Mean age, years (SD)	55.7	(12.7)	56.8	(12.2)	0.47
Gender					
Male	47	37.0	87	40.7	0.62
Female	79	62.7	127	59.3	
Aneurysm location					
Anterior circulation	105	83.3	170	79.4	0.46
Posterior circulation	21	16.7	44	20.6	
Treatment modality					
Surgical clipping	58	46.0	101	47.2	0.98
Endovascular coiling	58	46.0	96	44.9	
Endovascular stent-assisted coiling	10	7.9	17	7.9	
Anti-platelet medication*					
Aspirin	10	100.0	17	100.0	0.68
ADP receptor inhibitors	10	100.0	17	100.0	
Glycoprotein IIb/IIIa inhibitors	8	80.0	12	70.6	
Hunt and Hess scale					
Grade 1–3	80	63.5	150	70.1	0.26
Grade 4–5	46	36.5	64	29.9	
Fisher scale					
Grade 1–2	6	4.8	20	9.3	0.19
Grade 3–4	120	95.2	194	90.7	
Glasgow Outcome Scale at discharge					
Score 1–3	84	66.7	92	43.0	<0.001
Score 4–5	42	33.3	122	57.0	

DCI, delayed cerebral ischemia; SD, standard deviation; ADP, adenosine diphosphate.

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* only in stent-assisted coiling patients.

4. Discussion

This study evaluated the association of absolute platelet count and change in platelet count with DCI after aSAH as defined by the 2010 consensus criteria. [7] Neither was associated with DCI incidence. Moreover, neither treatment modality nor use of antiplatelet therapy was associated with DCI incidence. Patients with severe aSAH on initial computed tomography (Fisher grade 3–4) had significantly lower platelet count on days 1 and 2 after aSAH.

Contrary to previous speculation, in our patient cohort, platelet count was not associated with DCI after aSAH as defined by the 2010 consensus criteria. [8,9] Kasius et al. found that platelet count increased compared with baseline during the development of DCI in aSAH patients. [9] Hirashima et al. [8] and Schebesch et al. [17] performed similar studies that used a vasospasm-based definition of DCI in a Japanese and Caucasian population, respectively; however, both studies only included patients who underwent surgical aneurysm clipping. In contrast to Hirashima et al., Schebesch et al. found no association between platelet count and vasospasm or clinical outcome and postulated that genetic differences between Asians and Caucasians were responsible for the discrepancy. However, the different definitions of DCI across the above studies may also explain their different findings.

Previous studies have found that the hemostatic system shows significant circadian variation, with platelet counts typically increasing in the afternoon. [18] In our patient cohort there was no time-dependent association of the daily platelet count and DCI when considering the circadian rhythm. It seems that the platelet variability between subjects is greater than the variability within subjects.

In our study, treatment modality was not associated with DCI. Although patients treated with endovascular coiling without stent assistance had a significantly lower platelet count on day 9 after aSAH than those treated with stent-assisted coiling or surgical clipping, this did not have a clinical effect. In a large study that compared DCI incidence between patients treated with endovascular coiling and those treated with surgical clipping, the odds of DCI were 24% higher in the surgical group (95% CI, 1%–51%). However, DCI did not have a greater impact on poor outcome in the surgical group than the endovascular coiling group. [19]

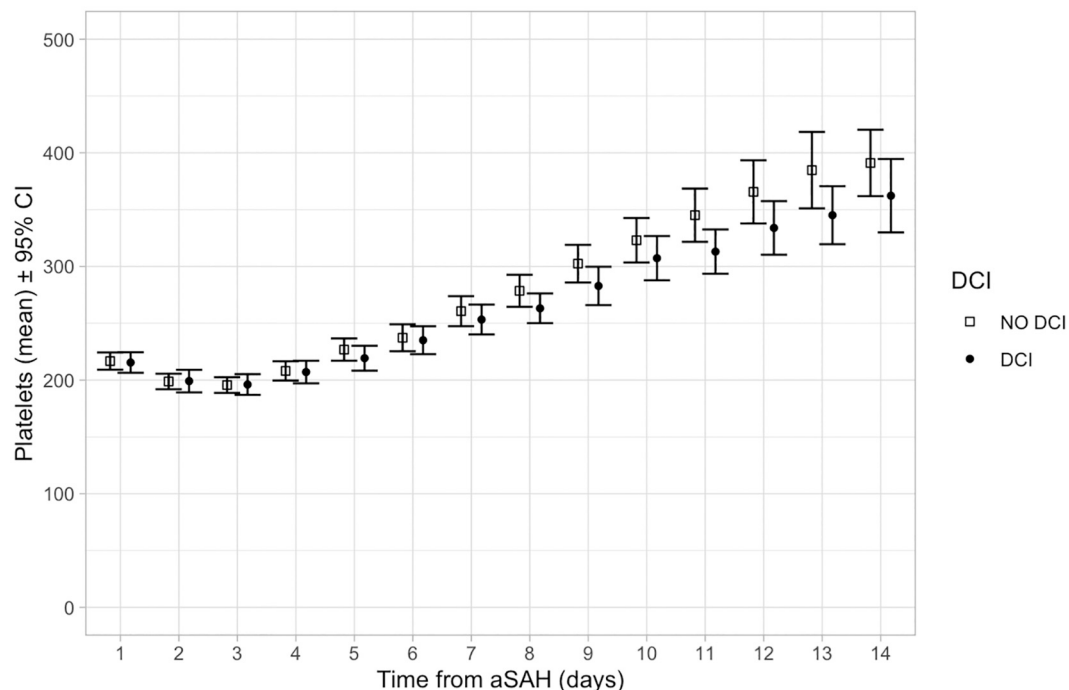


Fig. 1. Mean platelet count over time in patients with and without delayed cerebral ischemia.

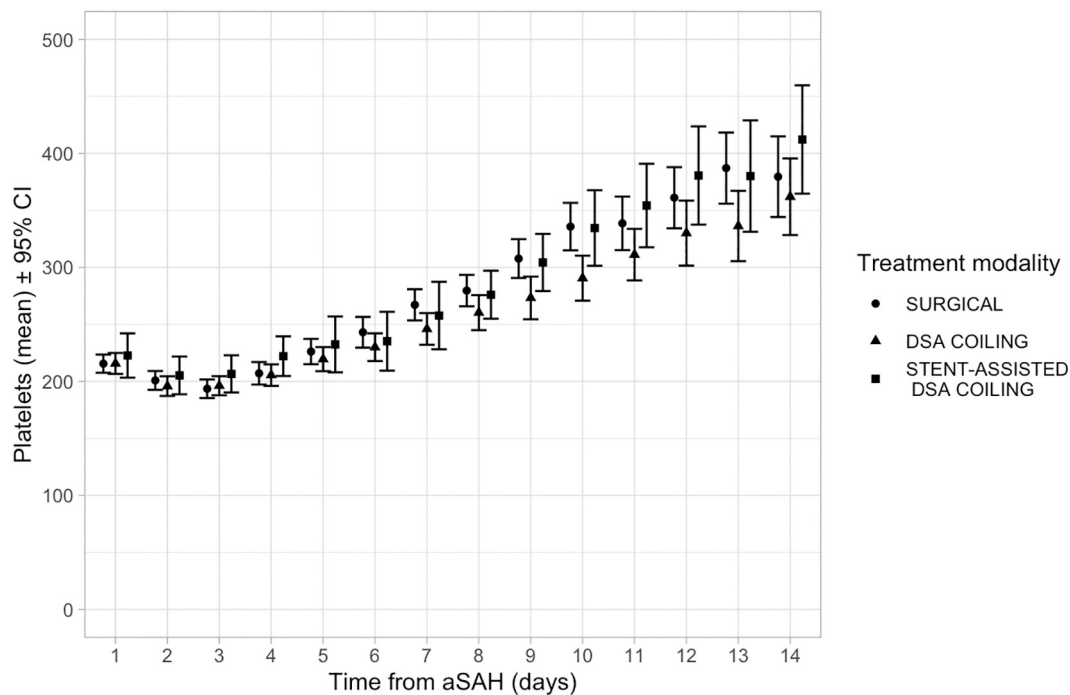


Fig. 2. Mean platelet count over time in patients grouped according to treatment modality.

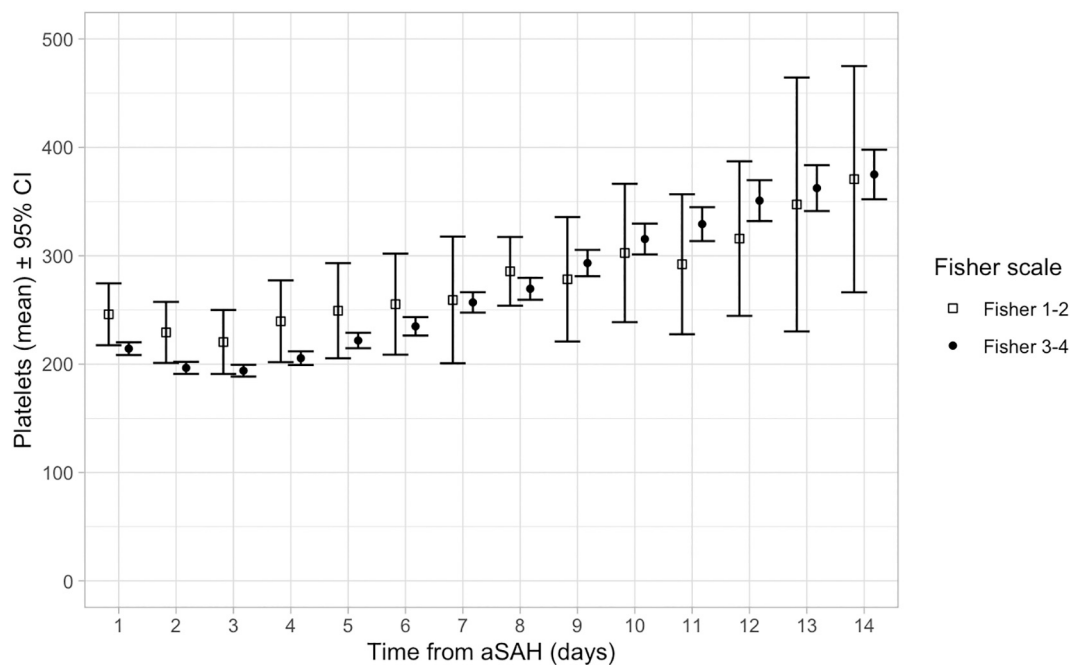


Fig. 3. Mean platelet count over time in patients grouped according to Fisher grade on initial computed tomography.

The use of antiplatelet therapy in stent-assisted coiling patients was not associated with reduced incidence of DCI in our patient cohort. Although preventing microclot formation using antiplatelet medications has been suggested to reduce the risk of DCI [6,20–24], studies have been conflicting, especially those evaluating dual antiplatelet therapy. A recent review of the role of platelets in DCI proposed several platelet-related therapeutic targets to prevent DCI and suggested two main reasons for the lack of clinical benefit from antiplatelet agents: 1) difficulty in predicting which patients develop DCI and 2) lack of understanding the mechanisms of DCI. [6] In a study of antiplatelet

medications after aSAH, Sun et al. found that the incidence of DCI was lower in patients who received dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg daily) than in those who did not. [23] In another study, aspirin use was independently associated with reduced DCI risk. Dual antiplatelet therapy (aspirin and clopidogrel) was not but it was associated with increased risk of clinically relevant bleeding events. [19] Wallace et al. compared dual antiplatelet therapy (aspirin and clopidogrel/ticagrelor) with aspirin monotherapy and found no differences in incidence of DCI or good clinical outcome at 6 months; however, bleeding complications were more frequent in the dual antiplatelet

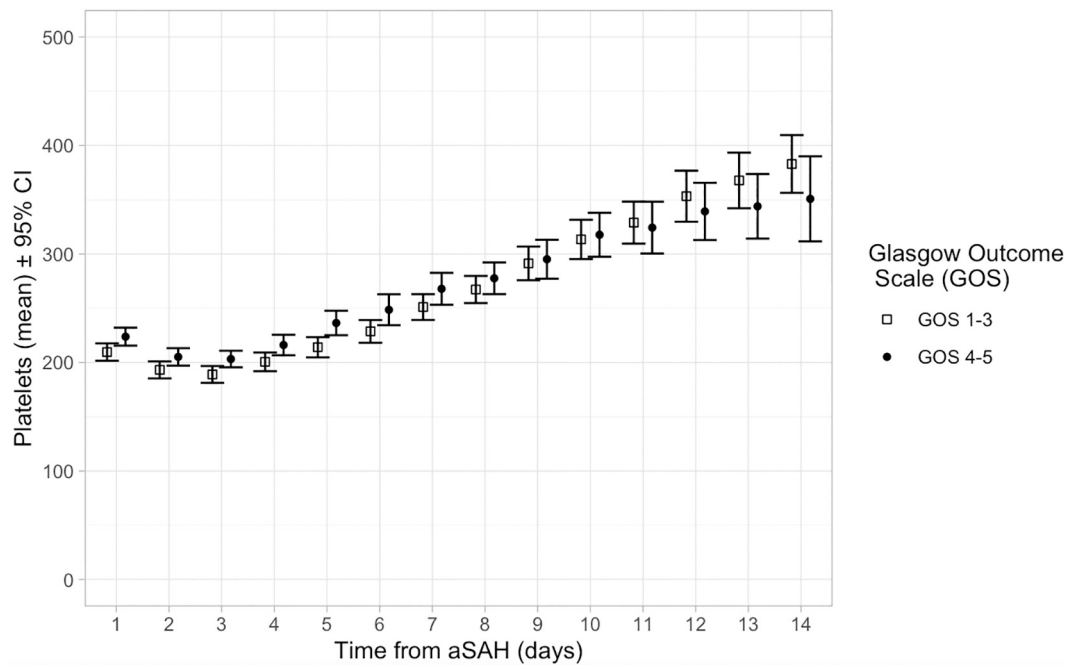


Fig. 4. Mean platelet count over time in patients grouped according to Glasgow Outcome Scale score.

therapy group. [25] Although these studies used different definitions of DCI, most were vasospasm-based.

In our study, the difference in platelet count was significant between patients with non-severe (Fisher grade 1–2) and severe (Fisher grade 3–4) aSAH on days 1 and 2 after, however the non-severe aSAH group consisted of only 26 patients. Nevertheless, previous studies have reported similar findings. Rzepliński et al. found that platelet count was lower in patients with Fisher grade 3–4 aSAH than those with Fisher grade 1–2 aSAH. [26] Similarly, in a thromboelastography and platelet mapping study, patients with severe aSAH (Hunt and Hess grade 4–5) had significantly higher levels of arachidonic acid and ADP inhibition compared with patients with non-severe aSAH. In addition, the degree of platelet dysfunction significantly correlated with Hunt and Hess and Fisher grades on admission. Furthermore, the study found that platelet dysfunction also played a role in rebleeding risk. [27]

4.1. Limitations

Our study has several limitations. As this was a retrospective study, platelet count data were not available for every patient on each day. Patients with better neurological status who did not require a long period of intensive care underwent laboratory testing less frequently. Therefore, information bias was present in the platelet count data. In addition, data regarding past medical history, previous use of antiplatelet drugs, bleeding events, and platelet transfusion were not available. Finally, platelet function testing was not performed, as it is not included in our hospital aSAH treatment protocol.

5. Conclusions

In this cohort of aSAH patients, we found no association between platelet count and DCI as defined by the 2010 consensus criteria. Dual antiplatelet therapy was not associated with DCI incidence. Future studies are warranted to clarify the role of platelets in DCI pathophysiology. These studies should define DCI according to the 2010 consensus criteria and examine platelet function testing in addition to platelet count.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2022.120227>.

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Disclosures

None.

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