White Blood Cell Count Improves Prediction of Delayed Cerebral Ischemia Following Aneurysmal Subarachnoid Hemorrhage

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BACKGROUND: Immune dysregulation has long been implicated in the development of delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH).
OBJECTIVE: To determine the relationship of inflammatory cell biomarkers with DCI.
METHODS: We evaluated 849 aSAH patients who were enrolled into a prospective observational cohort study and had a white blood cell (WBC) differential obtained within 72 h of bleed onset.
RESULTS: WBC count $> 12.1 \times 10^9$/L (odds ratio 4.6; 95% confidence interval [CI]: 1.9–11, $P < 0.001$) was the strongest Complete Blood Count (CBC) predictor of DCI after controlling for clinical grade ($P < .001$), thickness of SAH blood on admission computed tomography ($P = .002$), and clipping aneurysm repair ($P < .001$). A significant interaction between clinical grade and WBC count (odds ratio 0.8, 95% CI: 0.6–1.0, $P = .02$) revealed that good-grade patients with elevated WBC counts (49%: 273/558) had increased odds for DCI indistinguishable from poor-grade patients. Multivariable Cox regression also showed that elevated WBC counts in good-grade patients increased the hazard for DCI to that of poor-grade patients (hazard ratio 2.1, 95% CI 1.3–3.2, $P < .001$). Receiver operating characteristic curve analysis of good-grade patients revealed that WBC count (area under the curve [AUC]: 0.63) is a stronger DCI predictor than the modified Fisher score (AUC: 0.57) and significantly improves multivariable DCI prediction models ($Z = 2.0$, $P = .02$, AUC: 0.73; PPV: 34%; NPV: 92%).
CONCLUSION: Good-grade patients with early elevations in WBC count have a similar risk and hazard for DCI as poor-grade patients. Good-grade patients without elevated WBC may be candidates to be safely downgraded from the intensive care unit, leading to cost savings for both patient families and hospitals.

KEY WORDS: Delayed cerebral ischemia, Inflammatory cells, Subarachnoid hemorrhage, White blood cell count, Neutrophil-lymphocyte ratio

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Aneurysmal subarachnoid hemorrhage (aSAH) continues to be associated with high morbidity and mortality despite advances in neurocritical care.[1] The prevention, detection, and clinical management of complications secondary to SAH generate a large health care burden.[2,3] Delayed cerebral ischemia (DCI) is considered the leading cause of death or major disability in subarachnoid hemorrhage (SAH) after the impact of the initial event and rebleeding.[4,5] Cerebral infarction has been shown to be the strongest predictor of 3-mo Glasgow Outcome Scale.[6]

Failure of treatment strategies targeting cerebral vasospasm to prevent cerebral infarction has led investigators to consider more complicated pathophysiological processes underlying DCI other than cerebral vasospasm.[7] Immune dysregulation has long been implicated in the

ABBREVIATIONS: aSAH, aneurysmal subarachnoid hemorrhage; **AUC,** area under the curve; **CBC,** complete blood count; **CI,** confidence interval; **CT,** computed tomography; **DCI,** delayed cerebral ischemia; **HR,** hazard ratio; **NPV,** negative predictive value; **pAUC,** partial AUC; **PPV,** positive predictive value; **SAH,** subarachnoid hemorrhage; **SIRS,** systemic inflammatory response syndrome; **WBC,** white blood cell; **WFNS,** World Federation of Neurosurgical Societies

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development of DCI following aSAH.[8] Studies investigating the benefits of monitoring inflammation (eg, white blood cells [WBC], platelets, C-reactive protein) to help in the prediction of DCI have provided ambiguous results.[9-15] We sought to investigate whether WBC differential panels in the first 72 h after aSAH may aid in identifying patients at highest risk of DCI.

METHODS

Study Population

We prospectively enrolled 1308 aSAH patients admitted to the Neurological Intensive Care Unit between 2006 and 2015 in the SAH Outcomes Project, a single center, prospective, observational cohort study. Admission computed tomography (CT), or the presence of xanthochromia, was used to diagnosis aSAH. Of these patients, 849 patients had a WBC differential panel in the first 72 h and were included for analysis. This study was approved by the Institutional Review Board. In accordance with New York state laws, written informed consent was obtained from the patient or a surrogate.

Clinical Management

Clinical management conformed to Neurocritical Care Society and American Heart Association guidelines[16,17] Oral nimodipine and intravenous hydration with 0.9% saline and supplemental fluids was used maintain euvolemia. Patients with symptomatic vasospasm received hypertensive hypervolemic therapy. Poor-grade patients having severe angiographic vasospasm may have their systolic blood pressure targeted to 180 to 220 mmHg.[18]

Data Collection

Comprehensive data on each patient are collected including information about prior medical history, history of present illness, admission clinical status, imaging, treatments received, and all other data related to their hospitalization. A follow-up interview is conducted at 3 mo with the patient and/or their families to collect outcome information. Each data point is adjudicated in a weekly meeting with the clinical providers.

Clinical and Radiological Variables

WBC differentials were performed within 24 h of admission as part of the routine clinical workup. The modified Fisher grading scale was used to classify the amount of subarachnoid blood present on admission CT scan.[19]

Clinical Grade

Good-grade patients were defined as those with an admission World Federation of Neurosurgical Societies (WFNS) Grade < 3 versus poor-grade patients having an admission WFNS Grade ≥ 3.

WBC Count

WBC count was dichotomized $> 12.1 \times 10^9$/L to denote moderate inflammation. The normal range for the WBC count in adults was 4400 to 11 000 cells/μL.

Outcome Assessment

The primary outcome measure was the development of DCI. DCI from cerebral vasospasm was defined as: "(1) clinical deterioration (ie, a new focal deficit, decrease in level of consciousness, or both), and/or (2) a new infarct on CT that was not visible on the admission or immediate postoperative scan, when the cause was thought by the research team to be vasospasm."[20]

Statistical Analysis

Data analyses were performed with R statistical software (R, version 2.12.2, R Project, www.r-project.org). $P \leq .05$ were considered significant. A 2-sided power analysis for cohort studies was conducted to determine the probability of detecting an effect given the sample size of the current study. Predictors of DCI were assessed using logistic regression models. The percentage of patients surviving DCI for 30 d was calculated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. Cox regression was used to calculate hazard ratios and 95% confidence intervals (CIs) for risk factors. Area under the curve (AUC) model performance was tested using the Delong–Delong method and partial AUC (pAUC) was compared using bootstrapping.[21]

Multivariable models were generated using standard biostatistical procedures. The initial pool of candidate predictor variables included all available demographic, prior medical history, admission, and surgical aneurysm repair variables that had univariate associations $P < .25$ with the outcome variable. Backward stepwise regression methods were used to produce the final model whereby the least nonsignificant variable was removed from the model 1 at a time until all remaining variables have $P < .05$. Tests for interactions were performed among all significant variables retained in the multivariable models.

RESULTS

Cohort Analysis

A total of 849 patients (65%) had WBC differential performed within the first 72 h after SAH. Patients (n = 459) excluded from analysis were more likely be good-grade Caucasian patients transferred from other hospitals. These patients had less blood present on CT imaging and were less likely to have lost consciousness at ictus. Their course was also less complicated compared to patients included in analysis (Table 1).

Power Analysis

A power analysis was conducted to determine the power to detect effects among WBC count and DCI. Given 477 patients in this cohort exposed to WBC $> 12.1 \times 10^9$/L (70% DCI) versus 372 patients not exposed (52% DCI) the power is >99%.

WBC Differential Panel and DCI

Univariate associations between WBC differential results and DCI were assessed in order to create a multivariable model for DCI. A multivariable model revealed that WBC count $> 12.1 \times 10^9$/L (OR 4.6; 95% CI: 1.9–11, $P < .001$) was significantly associated with DCI after controlling for known predictors including WFNS grade, APACHE-II physiological subscore, thick SAH on admission CT, smoking status, and clipping aneurysm repair. In a competing multivariable model, testing all WBC differential panel results as potential predictors, only WBC

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TABLE 1. Bias Analysis of Patients without Complete Blood Cell Panel in First 72 h

Characteristics	Excluded patients (n = 459)	Study patients (n = 849)	OR (95% CI)	P
Demographics				
Age > 53 yr old	244 (53%)	467 (55%)	0.9 (0.7, 1.2)	.52
Female	322 (70%)	618 (73%)	0.9 (0.7, 1.1)	.31
Non-Caucasian ethnicity	234 (51%)	499 (59%)	0.7 (0.6, 0.9)	.008
Admission predictors				
WFNS grade ≥ 3	139 (33%)	385 (47%)	0.6 (0.4, 0.7)	<.001
Glasgow Coma Score < 8	69 (15%)	209 (25%)	0.5 (0.4, 0.7)	<.001
Sentinel headache	92 (8%)	171 (14%)	1 (0.7, 1.3)	.93
Ictal loss of consciousness	152 (34%)	373 (45%)	0.6 (0.5, 0.8)	<.001
APACHE-II physiological score	6 (3, 8)	6 (4, 9)	0.94 (0.92, 0.97)	<.001
MAP > 112 mmHg	194 (43%)	420 (50%)	0.7 (0.6, 0.9)	.008
Admission CT scan				
Thick SAH	164 (36%)	460 (54%)	0.5 (0.4, 0.6)	<.001
Global cerebral edema	68 (15%)	187 (22%)	0.6 (0.5, 0.8)	.002
Intraventricular hemorrhage	212 (49%)	481 (58%)	0.7 (0.5, 0.9)	.002
Intracerebral hemorrhage	80 (19%)	157 (19%)	1 (0.7, 1.3)	.8
Aneurysm characteristics				
Anterior location	147 (32%)	267 (31%)	1 (0.8, 1.3)	.83
Aneurysm size > 10 mm	177 (41%)	500 (61%)	0.4 (0.4, 0.6)	<.001
Clip repair procedure	282 (61%)	586 (69%)	0.6 (0.5, 0.9)	.004
Neurological complications				
Rebleed	42 (9%)	80 (9%)	1 (0.7, 1.4)	.87
Herniation	39 (8%)	129 (15%)	0.5 (0.4, 0.8)	<.001
Medical complications				
Fever > 101.5°F	217 (47%)	452 (53%)	0.8 (0.6, 1)	.04
Pneumonia	80 (17%)	214 (25%)	0.6 (0.5, 0.8)	.001
Sepsis	40 (9%)	94 (11%)	0.8 (0.5, 1.1)	.18
Cardiac complications				
Arrhythmias	47 (10%)	105 (12%)	0.8 (0.6, 1.2)	.24
Cardiac arrest (in ICU)	30 (7%)	55 (6%)	1 (0.6, 1.6)	.97
Myocardial infarction	33 (7%)	77 (9%)	0.8 (0.5, 1.2)	.24
Pulmonary edema	60 (13%)	176 (21%)	0.6 (0.4, 0.8)	<.001

Values are N (%), mean (SD), median (25%–75%). OR = odds ratio; MAP = mean arterial pressure; ICU = intensive care unit. Thick SAH = Fisher Grade 3 or modified Fisher 3 to 4.

count remained significant. Additionally, in this model, we found a significant interaction between clinical grade and WBC count ($P = .02$). Post-hoc contrasts revealed that good-grade patients having a WBC count $\leq 12.1 \times 10^9$/L were significantly less likely ($P < .01$) to experience DCI than other patient groups, which were not significantly different from one another (Table 2).

Similarly, a Kaplan–Meier analysis revealed that good-grade patients having an elevated WBC count had a similar DCI survival to that of poor-grade patients (Figure 1). A multifactorial Cox regression model of good-grade aSAH patients revealed that the hazard for DCI was significantly associated with Thick SAH on admission CT scan (Hazard Ratio (HR) 1.6, 95% CI 1.2, 2.2, $P = .003$), intracerebral hemorrhage present on admission CT scan (HR 1.5, 95% CI 1.1, 2.1, $P = .04$), WFNS Grade ≤ 3 with WBC > 12.1 (HR 1.8, 95% CI 1.1, 2.9, $P = .015$), WFNS Grade > 3 with WBC ≤ 12.1 (HR 1.9, 95% CI 1.1, 3.4, $P < .02$), and WFNS Grade > 3 with WBC > 12.1 (HR 3.1, 95% CI 2.0, 5.1, $P < .001$).

In this cohort, 49% (273/558) of good-grade patients had elevated WBC count > 12.1×10^9/L. An ROC curve analysis (Figure 2) restricted to good-grade patients revealed that WBC count in the first 72 h (AUC: 0.63; positive predictive value [PPV]: 27%; negative predictive value [NPV]: 87%) was stronger than modified-Fisher score (AUC: 0.63; PPV: 27%; NPV: 87%) and second only to APACHE-II physiological subscore (AUC: 0.63; PPV: 27%; NPV: 87%; Figure 2). In a multivariable model the Delong–Delong test for comparing correlated ROC curves revealed that including WBC significantly improved the prediction of DCI in good-grade patients ($Z = 2.0$, $P = .02$, producing an overall 'fair' AUC and 'excellent' NPV (AUC: 0.73; PPV: 34%; NPV: 92%).

DISCUSSION

In this study of 849 aSAH patients, approximately 56% of all patients and 49% of good-grade patients had abnormal WBC

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TABLE 2. Relationship of Peak Inflammatory Cells in First 72 h to Delayed Cerebral Ischemia

	Unadjusted				Adjusted	
	DCI (n = 196)	No DCI (n = 653)	OR (95% CI)	*P*	OR (95% CI)	*P*
Known predictors						
WFNS Grade ≥ 3	127 (66%)	258 (41%)	2.7 (1.9, 3.8)	<.001	6.4 (2.6, 16)	<.001
Apache-II Phys	7.85 (3.95)	6.62 (4.17)	1.1 (1, 1.1)	<.001		
Thick SAH	130 (66%)	330 (51%)	1.9 (1.4, 2.7)	<.001	1.7 (1.2, 2.5)	.002
ICH present	46 (24%)	111 (18%)	1.5 (1, 2.2)	.05		
Clipping	146 (74%)	440 (67%)	1.4 (1, 2)	.06	2.0 (1.4, 3.1)	<.001
Smoking	84 (43%)	242 (37%)	1.3 (0.9, 1.8)	.14		
Inflammatory cells						
WBC > 12.1	138 (70%)	339 (52%)	2.2 (1.6, 3.1)	<.001	4.6 (1.9, 11)	<.001
RDW > 14.5	33 (19%)	109 (19%)	1 (0.6, 1.5)	.94		
NLR > 5.9	160 (82%)	459 (72%)	1.8 (1.2, 2.7)	.006		
Neutrophil	12 (7.5)	11 (5.9)	1.0 (1.0, 1.1)	<.001		
Neutrophil %	76 (27)	75 (25)	1.0 (1.0, 1.0)	.72		
Lymphocyte	1.4 (1.2)	1.4 (1.1)	1.0 (0.9, 1.2)	.97		
Lymphocyte %	10.3 (11)	11.8 (10)	1.0 (1.0, 1.0)	.07		
Platelet	266 (75)	253 (71)	1.0 (1.0, 1.0)	.02		
Interactions						
WFNS Grade × WBC Count					0.8 (0.6, 1.0)	.02

Values are n (%), mean (SD), median (25%–75%), OR = odds ratio; Thick SAH = Fisher Grade 3 or modified Fisher 3 to 4; ICH = Intracerebral hemorrhage; DCI = Delayed cerebral ischemia; WBC = White blood cell count; NLR = neutrophil-lymphocyte ratio; RDW = red cell distribution width.

count results within the first 72 h of admission. We found that WBC count was the strongest CBC panel predictor of DCI, and that this effect was limited to patients with good admission clinical grade. Good-grade patients with elevated WBC count had a similar odds and hazard for DCI as poor-grade patients and, along with physiological derangement, outperformed classic predictors of DCI including modified Fisher score, aneurysm size, and smoking.

The magnitude of detrimental physiological processes post-aSAH increases with the severity of the bleeding event. Patients having poor clinical grade are more likely to experience a significant catecholamine surge after aSAH resulting in sympathetic activation, evidence of cardiac injury, and poor outcome.[22] Similarly, clinical signs of the early-phase proinflammatory cytokine cascade set off by aSAH are observed at nearly double the rate in poor-grade patients.[23-25] This inflammation has been postulated to play a crucial and unifying role in the pathogenesis of cerebral vasospasm. Indeed, it has been shown that poor-grade patients are much more likely to experience immune dysregulation,[8] systemic inflammatory response syndrome (SIRS),[25] and refractory fever,[26] among other inflammatory complications,[27] all of which have been shown to be associated with the development of DCI.[25]

The WBC differential panel is a routinely collected on aSAH patients and is potentially a simple way for clinicians to determine the DCI risk for patients. Previous studies that have examined the relationship of WBC differential panel labs with DCI have had limitations. McGirt et al[11] showed that peak WBC count was a predictor of DCI; however, peak WBC count may have occurred during the DCI episode making it less helpful for monitoring. Provencio et al[15,28] compared neutrophil percentage in cerebrospinal fluid of patients with aSAH for 3 d to other predictive scales and found that cerebrospinal fluid neutrophil percentage, and DCI were related.[29-37] It is difficult to interpret findings from previous studies in this area,[9-15] because they are limited by small sample sizes and a lack of information regarding potential confounding variables.[28] The current study demonstrates in a large patient cohort that early elevations in WBC predicts DCI even after controlling for confounding variables such as fever and other complications.

Our data suggest that the predictive value of WBC count elevations is limited to good-grade patients. This may be due to the fact that poor-grade SAH patients frequently have immune dysregulation and a complicated clinical course. Poor-grade patients are 2 to 15 times more likely to develop SIRS,[25,38] up to 95% of poor-grade patients,[39] and 1.5 times more likely to develop DCI.[40] Because nearly all poor-grade patients experience significant inflammation and WBC count elevations, it is simply not a good marker to discriminate poor-grade patients that will experience DCI. In contrast, good-grade patients experience much lower rates of severe inflammation (40%–60%)[25,38] and those with elevated admission WBC counts appear to experience a more complicated clinical course comparable to that of poor-grade patients. This is supported by our data that show DCI survival for good-grade patients having elevated WBC count is similar to poor-grade patients without elevated WBC counts.

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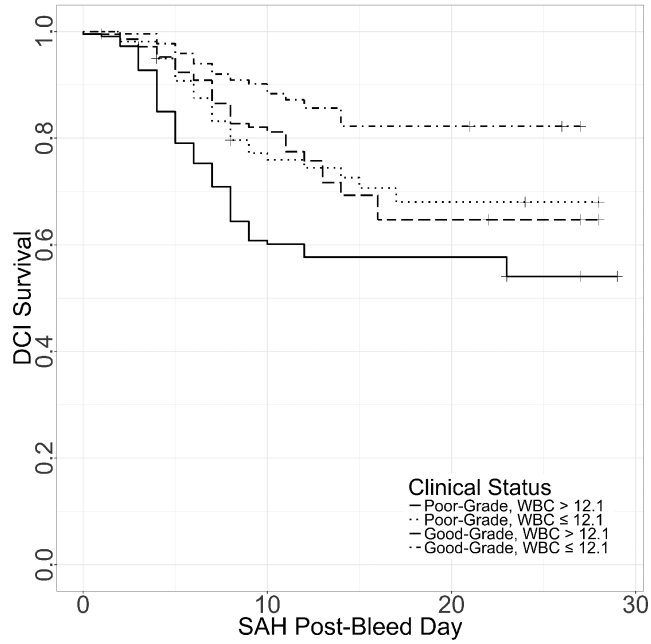

FIGURE 1. *The Kaplan–Meier curve shows a 30-d DCI survival rate of 54% (45%–65%) among poor-grade patients having WBC > 12.1, 68% (58%–80%) among poor-grade patients having WBC ≤ 12.1, 65% (53%–79%) among good-grade patients having WBC > 12.1, and 82% (74%–91%) among good-grade patients having WBC ≤ 12.1. The log rank test gave P < .001. Post-hoc log-rank testing revealed that good-grade patients having WBC ≤ 12.1 had significantly better survival than good-grade patients having WBC > 12.1 (P = .015). Survival for good-grade patients having WBC > 12.1 (P = .015) was not significantly better than poor-grade patients having WBC ≤ 12.1 (P = .85). Lastly, survival for poor-grade patients having WBC ≤ 12.1 was significantly better than for poor-grade patients having WBC > 12.1 (P = .019).*

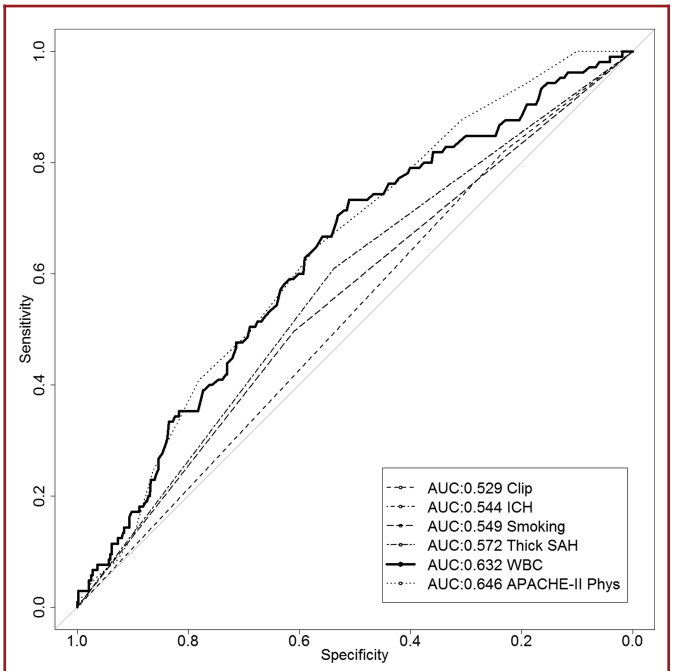

FIGURE 2. *ROC Curve Analysis Comparing DCI Prediction Model With and Without WBC Count (Delong–Delong test: Z = 2.0, P = .02).*

There are several points of clinical value in our study. We found that elevated admission WBC count is more sensitive and specific for DCI than the modified Fisher grade, which is commonly used to assess individual risk of DCI.[19] Although blood on CT and elevated WBC count are both associated with the development of SIRS,[41,42] our data suggest that each contributes to predicting those that will develop DCI. A multivariable model of DCI utilizing modified Fisher grade and elevated admission WBC together had an AUC over 0.7. Our data support clinicians monitoring good-grade patients with both a high Fisher grade and elevated WBC throughout the high-risk period for DCI. Our analysis showed an excellent NPV (92%) for good-grade patients without elevated WBC to develop DCI. These patients may not benefit from surveillance monitoring of DCI and may be good candidates to safely downgrade from intensive care. Future work should evaluate whether this practice would lead to a significant cost saving while maintaining high standards of patient care.

Limitations

Our study has a number of limitations including its observational design. It is possible that the observed effects between WBC elevations and DCI are confounded by other factors (eg, corticosteroids and concomitant infections) despite our methodological and statistical controls. In critically ill patients, multiple potential causes for WBC elevations may coexist making it difficult or impossible to pinpoint a precise cause. A daily DCI risk assessment using WBC was not possible, because it is not standard practice to collect a WBC count on good-grade patients. This may be worth exploring further in a future study. One final limitation to mention is that our study patients tended to be poor-grade non-Caucasian patients, with more blood on initial CT imaging and were more likely to have lost consciousness at ictus. Hence, uncomplicated good-grade patients were relatively less represented.

CONCLUSION

Elevated WBC count in the first 72 h following aSAH is associated with the development of DCI and may have particular clinical value for good-grade patients. The predictive value of WBC count for DCI was stronger than modified Fisher score and could be clinically valuable to assess a patient's individual risk for DCI. Good-grade patients without elevated WBC may be candidates to be safely downgraded from the intensive care unit leading to cost savings for patient families and hospitals. Further research

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is needed to determine whether changes in WBC count over time are related to the onset of DCI.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with high morbidity and mortality rates; even though prognosis has improved in the last decades it still continues to be one of the most dreaded neurological emergencies. Delayed cerebral ischemia (DCI) is considered the leading cause of death or major disability in subarachnoid hemorrhage after the impact of the initial event and re-bleeding. Various biomarkers have been postulated and studied in past to help with early identification and better recognition for patients at high risk of developing DCI without much success. In this article, the authors reported on WBC as a marker for prediction of DCI in aSAH patients. In a large single center prospective observational cohort study, authors found that WBC count $> 12.1 \times 109$/L within 72 hrs of admission was strongest predictor of DCI in good grade (defined as WFNS < 3) aSAH patients.

One of the biggest challenges in treatment of aSAH is predicting patients at risk of DCI and while the mFS (modified Fisher Scale) helps in predicating risk of vasospasm, having a biomarker which is quick, safe, and easy to obtain to predict risk of DCI would be a tremendous help. The impact of such a marker would not just be clinical but also would help in optimizing the use of limited resources. If these results can be replicated in multi-center prospective controlled trials it would help in identifying patients with low risk of DCI and good-grade aSAH who could be safely downgraded or transferred from the intensive care unit earlier than current practice thereby reducing health care cost without endangering safety of the patients.

Does this study end our quest of finding a biomarker to predict DCI in aSAH? No. This study is however a small but important step in the process. Future studies aimed at identifying such biomarkers should be multicenter and include more heterogeneous demographics/ethnicities to increase robustness and generalizability of the results.

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