Day 2 neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for prediction of delayed cerebral ischemia in subarachnoid hemorrhage

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OBJECTIVE Recent evidence has suggested that an admission neutrophil-to-lymphocyte ratio (NLR) of ≥ 5.9 predicts delayed cerebral ischemia (DCI) in aneurysmal subarachnoid hemorrhage (aSAH). The primary aims of this study were to assess reproducibility and to ascertain the predictive ability of NLR on subsequent days postictus. Secondary aims included identification of additional inflammatory markers.

METHODS A single-center, retrospective study of all patients aged ≥ 18 years with aSAH between May 2014 and July 2018 was performed. Patient characteristics, DCI incidence, operative features, and outcomes (on discharge and at 3 months postictus) were recorded. C-reactive protein (CRP) and full blood count differentials were recorded on admission and through day 8 postictus or at discharge. In total, 403 patients were included in the final analysis.

RESULTS Ninety-six patients (23.8%) developed DCI with a median time from ictus of 6 days (IQR 3.25–8 days). A platelet-to-lymphocyte ratio (PLR) cutoff ≥ 157 and CRP cutoff ≥ 27 was used in our cohort. In a multiple binary logistic regression model, after controlling for known DCI predictors, day 2 NLR ≥ 5.9 (OR 2.194, 95% CI 1.099–4.372; $p = 0.026$), day 1 PLR ≥ 157 (OR 2.398, 95% CI 1.1072–5.361; $p = 0.033$), day 2 PLR ≥ 157 (OR 2.676, 95% CI 1.344–5.329; $p = 0.005$), and CRP ≥ 27 on days 3, 4, and 5 were predictive of DCI.

CONCLUSIONS The results of this study have confirmed the association between NLR and DCI and have demonstrated the predictive potential of PLR and CRP, suggesting that NLR and PLR at day 2, and CRP from day 3 onward, may be better predictors of DCI than those measurements at the time of ictus.

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KEYWORDS subarachnoid hemorrhage; biomarkers; blood cell count

THERE are approximately 4800 cases of subarachnoid hemorrhage (SAH) in the United Kingdom each year, of which 70% are caused by a ruptured cerebral aneurysm.¹ SAH is a type of hemorrhagic stroke caused by bleeding in the subarachnoid space, and treatment often involves neurosurgical or endovascular intervention and medical stabilization.² Approximately 15% of patients with SAH die before they reach the hospital, and for those who receive treatment, SAH carries a high morbidity risk and a 30-day mortality rate of 12.9%.^{1,2} A subset of patients with SAH experience a further neurological impairment in the form of delayed cerebral ischemia (DCI), which confers a poorer clinical prognosis.³

DCI is defined as a new neurological impairment within 6 weeks of SAH onset and is estimated to affect 30% to 40% of patients with SAH.³ The pathophysiology of DCI is poorly understood, and being able to predict those patients at greatest risk of developing DCI is an ongoing research priority.³

While identifying patients at greatest risk may allow prompt intervention before the onset of DCI and, thus, improve outcomes, predictive variables have been challenging to identify.⁴ Recently, Al-Mufti et al. demonstrated an association between the admission neutrophil-to-lymphocyte ratio (NLR) and DCI in patients with aneurysmal SAH (aSAH).⁵ The authors concluded that an admission

ABBREVIATIONS aSAH = aneurysmal SAH; CRP = C-reactive protein; DCI = delayed cerebral ischemia; GOS = Glasgow Outcome Scale; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; ROC = receiver operating characteristic; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

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NLR of ≥ 5.9 was predictive of DCI.⁵ Exploring multiple inflammation markers over time throughout the hospital stay and validating NLR as a predictor in multiple cohorts is essential to providing robust evidence for its prognostic utility.⁵ The primary aims of this study were to assess the reproducibility of NLR to predict DCI and to evaluate how this varies from day to day following the ictus of hemorrhage. Secondary aims included the identification of other inflammatory markers, clinical parameters, and operative parameters as predictors of DCI in aSAH.

Methods

Study Population

A single-center, retrospective study of all patients aged ≥ 18 years admitted with aSAH between May 2014 and July 2018 was performed at the Leeds General Infirmary. Patients with nonaneurysmal hemorrhage (SAH secondary to perimesencephalic hemorrhage, SAH related to trauma, rupture of an arteriovenous malformation, or other causes) and those aged < 18 years were excluded.

Clinical Management

On confirmation of SAH, patients were transferred from their local emergency department to a large, tertiary, neurosurgical center that covers a catchment population of approximately 2 million people, under the care of a specialist neurovascular neurosurgeon and managed in a critical care environment until stabilized (typically ≥ 48 hours following definitive aneurysm treatment).

Patients were considered to have sustained nonaneurysmal SAH if another clear causal pathology was demonstrated or following both negative CTA and DSA studies. Where a high index of clinical suspicion remained, further images were acquired through repeat CTA or DSA investigations or through MRI of the head and spine.

Unless medically contraindicated, all patients were administered nimodipine prophylaxis at a dose of 60 mg every 4 hours from neurosurgical admission until 21 days postictus. The modality of aneurysm treatment was determined on a case-by-case basis through multidisciplinary discussion between the consultant neurovascular neurosurgeon and consultant interventional neuroradiologist. The majority ($n = 353$, 87.6%) of patients were treated by endovascular means, in line with other centers in the United Kingdom.⁶

Data Collection

Patient demographics, comorbidities, clinical findings, imaging characteristics, incidence of DCI, and interventions were recorded. Outcomes were measured during hospitalization, on discharge, and at 3 months postdischarge. Full blood count differentials were used to identify the absolute neutrophil, lymphocyte, and platelet counts, and these were recorded daily from the date of ictus (day 0/admission) through day 8 postictus or discharge (if discharge occurred < 8 days after ictus). If > 1 sample was taken on a specific day, the mean value was used for analysis. Admission values were collected on the day of ictus, such that day 1 values were 1 day postictus and so on. These values were used to calculate the NLR

and platelet-to-lymphocyte ratio (PLR). C-reactive protein (CRP) measurements were also recorded as an additional marker of inflammation.

Clinical and Radiological Variables

The diagnosis of SAH was established by admission CT or by the presence of xanthochromia with lumbar puncture, if the initial CT scan was nondiagnostic. NLR was analyzed using a ≥ 5.9 cutoff point, as this value was found to be predictive in previously reported similar studies.^{5,7}

DCI was defined as the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect) or a decrease of at least two points on the Glasgow Coma Scale that was not apparent immediately after aneurysm occlusion.⁸

Outcome Assessment

The primary outcome of the study was the incidence of DCI. The Glasgow Outcome Scale (GOS) was used to measure functional outcome at discharge and 3 months postictus. The GOS allows for objective assessment of functional recovery and is scored from 1 to 5 (1 = death to 5 = low disability). A GOS score ≤ 3 was considered a poor functional outcome at both assessment time points. A modified Fisher scale grade ≥ 3 was considered to indicate a dense SAH. Analyses explored which variables might predict DCI.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 24.0.0.0 (IBM Corp.). Descriptive statistics were performed and tabulated on Microsoft Excel version 16.15 to generate summaries of patient baseline characteristics and clinical features, incidence of DCI, and operative features and outcomes. Unless otherwise stated, $p < 0.05$ determined statistical significance.

Logistic regression models were selected via the process outlined below to estimate associations between predictor variables of interest and the primary outcome measure of DCI (yes vs no). The results were expressed as adjusted odds ratios with 95% confidence intervals. Model selection was performed as follows. 1) The set of predictor variables of interest (see below) were each fitted in a univariate logistic regression model to estimate their (unadjusted) association with incidence of DCI. 2) Those variables that were significantly associated with the outcome of interest at the univariate logistic regression stage were then taken forward as candidate variables for testing in the multiple binary logistic regression stage. 3) A multiple binary logistic regression model was then fitted after controlling for known predictors of DCI, including age, a modified Fisher scale grade of 3 or 4, history of smoking, and history of hypertension, to estimate their (adjusted) association with the incidence of DCI.^{3,4}

The initial set of predictor variables of interest were NLR ≥ 5.9 on admission and for each inpatient day to day 8, PLR ≥ 157 on admission and for each inpatient day to day 8, CRP ≥ 27 on admission and for each inpatient day to day 8, age, sex, hypertension, ischemic heart disease, smoking, World Federation of Neurosurgical Societies

TABLE 1. Patient baseline characteristics and clinical features

Variable	DCI (n = 96)	Non-DCI (n = 307)	Overall (n = 403)	p Value
Mean age $\pm$ SD, yrs	54.7 $\pm$ 10.9	56.0 $\pm$ 12.1	55.7 $\pm$ 11.8	0.348
Sex, M/F ratio	21:75	94:213	115:288	0.098
Hypertensive	26 (40.0)	78 (28.9)	104 (31.1)	0.086
Status unknown or missing data	31	38	69	
History of IHD	1 (1.5)	10 (3.9)	11 (3.4)	0.342
Status unknown or missing data	30	51	21	
History of smoking	32 (47.1)	124 (46.2)	156 (46.6)	0.827
Status unknown or missing data	29	39	68	
WFNS grade				
I	37 (38.5)	185 (60.2)	222 (55.1)	<0.001*
II	24 (25.0)	49 (16.0)	73 (18.2)	0.045*
III	2 (2.1)	10 (3.3)	13 (3.2)	0.555
IV	15 (15.6)	24 (7.8)	39 (9.7)	0.024*
V	18 (18.8)	38 (12.4)	56 (13.9)	0.115
Modified Fisher grade				
1	0 (0)	13 (4.2)	13 (3.2)	
2	0 (0)	19 (6.2)	19 (4.7)	
3	33 (34.4)	146 (47.6)	179 (44.5)	0.022*
4	63 (65.6)	128 (41.7)	191 (47.5)	<0.001*

IHD = ischemic heart disease.

Values represent the number of patients (%) unless indicated otherwise.

* $p < 0.05$.

(WFNS) grade, modified Fisher scale grade, and endovascular treatment.

Receiver operating characteristic (ROC) analysis was performed to evaluate the sensitivity and specificity of $\text{NLR} \geq 5.9$ to predict DCI in our cohort, and this was used to identify the corresponding cutoff point, described above, for PLR and CRP.

Results

Patient Baseline Characteristics and Clinical Features

A total of 403 patients were included in the final analysis. Patient baseline characteristics and clinical variables are summarized in Table 1. The mean age $\pm$ SD of the population was 55.7 ± 11.8 years, and there were almost twice as many females as males (M/F ratio 1:1.91). The majority presented with a WFNS grade of I ($n = 222$, 55.1%), and almost all patients had a modified Fisher scale grade of 3 or 4 ($n = 370$, 91.8%).

Incidence of DCI

Ninety-six patients (23.8%) developed DCI at a median time from ictus of 6 days (IQR 3.25–8). Those patients in whom DCI developed were more likely to have a WFNS grade of IV ($p = 0.024$), and all had a modified Fisher scale grade of 3 or 4; significantly more patients in the DCI group had a modified Fisher scale grade of 4 than did patients in the non-DCI group ($p < 0.001$) (Table 1).

Operative and Outcome Data

SAH treatment and outcomes are summarized in Table

2. The majority of patients received endovascular treatment for the primary hemorrhage ($n = 353$, 87.6%). After treatment, a smaller proportion of patients with DCI were discharged directly to home (39.6% vs 68.9%, $p < 0.001$), more patients with DCI required time in a rehabilitation unit (41.6% vs 14.4%, $p < 0.001$), and patients with DCI had a longer mean length of stay (38.8 ± 37.4 days vs 22.3 ± 27.7 days, $p < 0.001$).

The overall mortality rate was 11.4% ($n = 46$), which was higher in patients with DCI at 14.6% ($n = 14$), although this difference did not reach statistical significance ($p = 0.273$). The proportion of patients with DCI with a GOS score at discharge ≤ 3 was 41.6% ($n = 48$) compared with 19.5% ($n = 60$) of patients without DCI, indicating that the former had poorer function ($p < 0.001$). This effect remained constant when the GOS score was measured at 3 months postictus. Neither group made a clinically significant functional improvement between assessments (DCI, $n = 30$, 36.1% vs non-DCI, $n = 48$, 16.8%; $p = 0.010$).

ROC Analysis

Based on ROC analysis, a value of $\text{NLR} \geq 5.9$ yielded a sensitivity of 78.2% and a specificity of 34.4% in our cohort. A PLR cutoff ≥ 157 and a CRP cutoff ≥ 27 yielded the same sensitivity and specificity as $\text{NLR} \geq 5.9$ in our cohort.

Univariate Analysis of Covariates and the Primary Endpoint

The unadjusted OR estimates, 95% CIs, and p values for the univariate logistic regression models of DCI (yes/

TABLE 2. Operative and treatment outcome data

Variable	DCI (n = 96)	Non-DCI (n = 307)	Overall (n = 403)	p Value
Treatment for hemorrhage				
MDT involved	21 (56.1)	96 (58.5)	117 (57.0)	0.777
Status unknown or missing data	55	143	198	
Combined	3 (3.1)	3 (1)	6 (1.4)	0.129
Endovascular	86 (89.5)	267 (87)	353 (87.6)	0.498
Microsurgical	7 (7.2)	22 (7.2)	29 (7.2)	0.967
None	0 (0)	15 (4.9)	15 (3.7)	
Median day of vasospasm postictus (IQR)	6 (3.25–8)			
Vasospasm treatment				
Medical	96 (100)			
Balloon	28 (29.2)			
Intraarterial nimodipine	42 (43.8)			
Any endovascular treatment	49 (51.0)			
Death	14 (14.6)	32 (10.4)	46 (11.4)	0.273
Repatriated to local district hospital	4 (4.2)	19 (6.2)	23 (5.7)	0.448
Discharge home	38 (39.6)	210 (68.9)	248 (61.5)	<0.001*
Discharge to rehabilitation unit	40 (41.6)	44 (14.4)	84 (20.8)	<0.001*
Mean length of stay $\pm$ SD, days	38.8 $\pm$ 37.4	22.3 $\pm$ 27.7	26.2 $\pm$ 30.7	<0.001*
GOS score $\leq$ 3 at discharge	40 (41.6)	60 (19.5)	108 (26.8)	<0.001*
GOS score $\leq$ 3 at 3 mos postictus	30 (36.1)	48 (16.8)	78 (21.1)	0.010*
Status unknown or missing data	13	22	35	

MDT = multidisciplinary team.

Values represent the number of patients (%) unless indicated otherwise.

* $p < 0.05$.

no) versus each of the predictor variables of interest are presented in Table 3. In our study population, an NLR ≥ 5.9 on days 2, 3, and 5 was associated with DCI; a PLR ≥ 157 on days 1, 2, and 3 was associated with DCI; and CRP ≥ 27 on days 2, 3, 4, and 5 was associated with DCI.

Multivariate Analysis of Covariates and the Primary Endpoint

The multivariate predictive model for the endpoint DCI (yes/no) took the form of a multiple binary logistic regression analysis of the endpoint versus each predictor variable of interest after controlling for known predictors of DCI including age, a modified Fisher scale grade of 3 or 4, history of smoking, and history of hypertension.

The final model suggests that after controlling for confounders, the following inflammatory markers remained predictors of DCI (Table 4): day 2 NLR ≥ 5.9 (OR 2.194, 95% CI 1.099–4.372; $p = 0.026$), day 1 PLR ≥ 157 (OR 2.398, 95% CI 1.072–5.361; $p = 0.033$), day 2 PLR ≥ 157 (OR 2.676, 95% CI 1.344–5.329; $p = 0.005$), day 3 CRP ≥ 27 (OR 2.742, 95% CI 1.372–5.479; $p = 0.004$), day 4 CRP ≥ 27 (OR 3.268, 95% CI 1.504–7.101; $p = 0.003$), and day 5 CRP ≥ 27 (OR 3.07, 95% CI 1.221–7.721; $p = 0.017$).

Discussion

The results of the current study demonstrate that DCI remains a common complication after aSAH, especially in patients with high WFNS and modified Fisher scale

grades. Patients with DCI had longer hospital stays, required more rehabilitation, and had poorer immediate and medium-term clinical functional outcomes. Our data collection did not extend beyond 3 months, but the literature has suggested that a proportion of these patients will experience poor functional outcomes in the long term as well.⁹ A predictive DCI model based on routinely collected inflammatory biomarkers may allow for early identification of patients at increased risk of DCI and could guide pre-emptive management to improve their outcomes.

While previous studies have investigated the predictive potential of inflammatory biomarkers at admission only, we have demonstrated the temporal changes in the predictive potential of these markers in patients with aSAH over multiple days after hemorrhage. Our results not only demonstrate the reproducibility of NLR, PLR, and CRP as variables associated with subsequent DCI but also suggest that the predictive potential of these markers is low or absent at admission; rather, they are potentially more predictive when measured on and after day 2 postictus. A recent study exploring the effect of invasive neuromonitoring has demonstrated that the first DCI event was detected earlier, at a mean of 2.2 days postictus.⁹ This earlier detection was associated with a favorable outcome at 12 months.⁹ Our study demonstrates the predictive potential of easily obtained routine biomarkers that are most strongly associated with developing DCI from day 2 onward, representing a new finding, and increases the potential clinical utility of these markers.

TABLE 3. Univariate binary logistic regression analysis of the endpoint (DCI yes/no) versus each predictor variable of interest

Variable	OR	95% CI	p Value
Admission NLR ≥ 5.9	1.573	0.762–3.248	0.220
Day 1 NLR ≥ 5.9	1.717	0.965–3.046	0.066
Day 2 NLR ≥ 5.9	2.463	1.401–4.329	0.002*
Day 3 NLR ≥ 5.9	1.970	1.152–3.392	0.013*
Day 4 NLR ≥ 5.9	1.749	0.991–3.087	0.054
Day 5 NLR ≥ 5.9	2.202	1.187–4.086	0.012*
Day 6 NLR ≥ 5.9	1.824	0.963–3.453	0.065
Day 7 NLR ≥ 5.9	1.110	0.538–2.29	0.778
Day 8 NLR ≥ 5.9	1.253	0.525–2.992	0.612
Admission PLR ≥ 157	1.717	0.834–3.526	0.142
Day 1 PLR ≥ 157	2.143	1.128–4.069	0.020*
Day 2 PLR ≥ 157	2.613	1.503–4.543	0.001*
Day 3 PLR ≥ 157	1.995	1.163–3.422	0.012*
Day 4 PLR ≥ 157	1.772	1.001–3.139	0.050
Day 5 PLR ≥ 157	1.607	0.847–3.047	0.147
Day 6 PLR ≥ 157	1.303	0.675–2.514	0.431
Day 7 PLR ≥ 157	1.550	0.66–3.605	0.309
Day 8 PLR ≥ 157	1.131	0.443–2.887	0.798
Admission CRP ≥ 27	1.347	0.333–5.442	0.676
Day 1 CRP ≥ 27	1.236	0.653–2.338	0.516
Day 2 CRP ≥ 27	1.772	1.025–3.061	0.040*
Day 3 CRP ≥ 27	2.649	1.502–4.673	0.001*
Day 4 CRP ≥ 27	2.839	1.517–5.315	0.001*
Day 5 CRP ≥ 27	1.920	1.003–3.764	0.049*
Day 6 CRP ≥ 27	1.844	0.942–3.607	0.074
Day 7 CRP ≥ 27	1.333	0.625–2.843	0.457
Day 8 CRP ≥ 27	1.876	0.777–4.526	0.162
Age	0.991	0.972–1.010	0.354
Female sex	1.576	0.917–2.708	0.100
Hypertension	1.632	0.931–2.863	0.087
IHD	0.494	0.062–3.924	0.505
Smoking	1.062	0.621–1.815	0.827
Endovascular treatment	1.742	0.75–4.046	0.197

* $p < 0.05$.

The predictive potential of different variables has been explored in the past. In a prospective clinical study of biomarker predictors, the best admission cutoff values were NLR 14.3 (sensitivity 87.3% and specificity 48.4%) and PLR 193.0 (sensitivity 55.3% and specificity 78.5%) as independent predictors of DCI.¹⁰ A 2017 review demonstrated a wide variety of biomarkers that had been explored in the literature, including various cytokines, white blood cell differentials, and CRP, as well as physiological systemic inflammatory response syndrome markers, including pyrexia and tachycardia.¹¹ While it is clear from our study and the supporting literature that monitoring inflammatory processes can predict DCI, no consensus has been reached as to which parameters, and at what cutoffs, are clinically most useful.

TABLE 4. Multiple binary logistic regression analysis of the endpoint (DCI yes/no) versus each predictor variable of interest

Variable	OR	95% CI	p Value
Day 2 NLR ≥ 5.9	2.194	1.099–4.372	0.026
Day 1 PLR ≥ 157	2.398	1.072–5.361	0.033
Day 2 PLR ≥ 157	2.676	1.344–5.329	0.005
Day 3 CRP ≥ 27	2.742	1.372–5.479	0.004
Day 4 CRP ≥ 27	3.268	1.504–7.101	0.003
Day 5 CRP ≥ 27	3.07	1.221–7.721	0.017

Model is controlling for known predictors of DCI including age, a modified Fisher scale grade of 3 or 4, history of smoking, and history of hypertension.

Limitations

A weakness of the current study is the retrospective design. A prospective study would benefit from more uniform patient populations and data sets that are less susceptible to bias; however, this would take many years to complete. While our models revealed some interesting associations, they may be underpowered, and any inference should be treated with caution. The estimates of associations between the outcome of interest (DCI) and the predictive variables tested may also be influenced by confounding variables not included in our models, despite our best efforts to include those known to influence the incidence of DCI. For instance, a potential confounder is infection, which was not included in our model. Finally, the majority of patients in this study had modified Fisher scale grades of 3 or 4, which may limit the generalizability of the results for populations with low blood-load aSAH.

Conclusions

The evidence that inflammatory processes are involved in the pathophysiology of DCI continues to grow. The identification of optimal biomarkers and understanding of how they contribute to a multiparametric predictive model remain an unmet need. The current study advocates for the inclusion of NLR, PLR, and CRP as biomarker candidates for involvement in future studies, both clinical and mechanistic. We recommend the collection of these markers at admission and to at least day 5 postictus, and for surgeons to consider the early trajectory of these parameters, particularly in patients with aSAH with high WFNS and modified Fisher scale grades.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Anderson, Akhunbay-Fudge, Chumas, Mathew. Acquisition of data: all authors. Analysis and interpretation of data: Anderson, Bolton, Ghariel, Akhunbay-Fudge, Mathew. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Anderson. Statistical analysis: Bolton. Administrative/technical/material support: Bolton, Ghariel, Mathew. Study supervision: Anderson, Akhunbay-Fudge, Chumas, Mathew.

Supplemental Information

Previous Presentations

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