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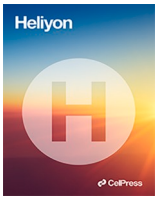

Research article

The dynamic changes of peripheral blood cell counts predict the clinical outcomes of aneurysmal subarachnoid hemorrhage

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ABSTRACT

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is a serious type of hemorrhagic stroke. It is very important to predict the prognosis at early phase. In this work, we intend to characterize early changes in peripheral blood cells after aSAH and explore the association between peripheral blood cells and clinical outcomes after aSAH.
Methods: aSAH patients admitted between December 2019 and September 2022 were enrolled. A retrospective observational study was performed. Total leukocytes, monocytes, neutrophils, erythrocytes, lymphocytes and platelets counts were recorded on the day of admission (day 1), day 3, day 5 and day 7. Statistical tests included Chi-square test, analysis of variance and multivariate logistic regression (MLR) models. 197 patients were analyzed.
Results: Leukocytes and neutrophils were higher in poor outcome groups from day 1 to day 7 and in delayed cerebral ischemia (DCI) groups from day 3 to day 7. Lymphocytes were higher at day 5 and day 7 in good outcome groups and no DCI groups. Neutrophil-to-lymphocyte ratio (NLR) was lower from day 3 to day 7 in good outcome groups and no DCI groups. Erythrocytes were higher from day 3 to day 7 in good outcome groups and no DCI groups. Lymphocytes were negatively related to poor outcomes on day 1 (OR = 0.457), indicating higher lymphocytes predicted good outcomes, Neutrophils were positively related to poor outcomes on day 3 (OR = 3.003) indicating higher neutrophils predicted poor outcomes. Lymphocytes were negatively related to DCI on day 5 (OR = 0.388) indicating higher lymphocytes predicted no DCI, Erythrocytes were negatively related to DCI on day 5 (OR = 0.335) and day 7 (OR = 0.204) indicating higher erythrocytes predicted no DCI. The improved ability of neutrophils, lymphocytes and erythrocytes to predict DCI or poor functional outcomes were revealed by ROC curve analysis.
Conclusions: The dynamic changes of peripheral blood cell counts were related to poor functional outcomes and DCI after aSAH. Elevated neutrophils, leukocytes, NLR, and decreased lymphocytes, erythrocytes were accompanied by DCI and poor outcome. Neutrophils, lymphocytes and erythrocytes counts could be beneficial to predict DCI and outcomes after aSAH.

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1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a serious type of hemorrhagic stroke. The rupture of intracranial aneurysms results into aSAH and aSAH results in significant mortality and disability. The fatality rate of aSAH has been significantly reduced by effective intensive care units, intravascular embolization and craniotomy clipping recently, but poor clinical outcome was still resulted from hydrocephalus, rebleeding, and other complications in a lot of aSAH subjects [1–3]. Delayed cerebral ischemia (DCI) is a prominent and modifiable prognostic factor and a late complication after aSAH. Arterial constriction, thrombosis, cortical spreading depolarization and angiographic vasospasm cause DCI. It usually appears at 1–2 weeks after first symptom in 1/3 of aSAH. DIC is one of primary contributors to poor clinical outcomes [4,5]. Timely preventing and treating afore-mentioned complications are very important, but it is extremely considerable to predict the prognosis because it could help medical staff to judge whether more post-operative monitoring and extra treatments are needed.

Peripheral blood cell count is an easy-to-measure indicator. A large number of researches have been focused on peripheral blood cell count as a predictive or diagnostic indicator of disease. Infections, inflammatory diseases, types of cancers, cardiovascular diseases, and psychosis have used peripheral blood cell count as an indicator for predicting outcomes [6–11]. A strong correlation between peripheral blood cell counts and cerebrovascular diseases has been widely studied. Delayed neurological impairment was caused by subsequently a large amount of systemic inflammatory response following aSAH [12]. It has been demonstrated that peripheral leukocytes migrate to the cerebrospinal fluid and brain and activated neutrophils damages cerebral microvascular after SAH occurs [13]. Early increase in total white blood cells in peripheral blood has been associated with the occurrence of functional impairment [14,15] while, leukocyte subtypes may play different roles. Neutrophil to lymphocyte ratios (NLR) is related to bad outcomes [16]. The development of DCI has also been related to monocytosis [13,17]. Anemia is common in patients presenting with aSAH. According to reports, erythrocyte parameters can predict adverse outcomes after aSAH [18]. While the increase in average platelet volume measured during the acute phase of aSAH has been identified as a risk factor for unfavorable neurological outcomes [19]. Although there have been many reports about the peripheral cell counts and ratios in aSAH, the dynamic changes in peripheral blood cell counts (white blood cells, lymphocytes, neutrophils, erythrocytes, platelets, monocytes) and clinical outcomes after aSAH has not been elucidated.

Our institutional bias for aSAH is to perform routine blood test on the day of admission, 3rd day, 5th day, and 7th day similar to other centers [13]. As DCI typically appears 1–2 weeks after onset. We conduct a retrospective analysis of total leukocytes, neutrophils, lymphocyte, monocytes, erythrocytes and platelets at admission day, third, fifth and seventh days, as in most patients, this time period was considered to precede the development of DCI, intending to find the relationship of dynamic changes of peripheral blood cell counts at early stage between DCI and poor clinical outcomes. This study will provide early guidance for the treatment and prevention of DCI and poor clinical outcomes after aSAH.

2. Methods

2.1. Patient selection

The preliminary screening included 231 patients who received aSAH treatment at the First People's Hospital of Jing zhou from December 2019 to September 2022. The inclusion criteria and exclusion criteria are according to previous studies with modifications [13,20]. Inclusion criteria: (1) Patients with aSAH confirmed by presence of xanthochromia in cerebrospinal fluid or CT. This is the diagnostic criteria; (2) age above 18 years and admitted within 24 h after onset of bleeding. The age of patients admitted at our center was above 18 years. Admission within 24 h after onset can reduce bias of blood routine on day 1; (3) The treatment for ruptured aneurysms was performed within 24 h after admission. This inclusion criteria can reduce bias of blood routine on day 3,5 and 7; Exclusion criteria: (1) Patients with SAH associated with trauma (not aneurysmal subarachnoid hemorrhage), arteriovenous malformation (not aneurysmal subarachnoid hemorrhage), auto-immune diseases or a history of malignancy (These factors affect the blood routine results). There are lower likelihood, lower risk of aneurysm etiology and lower development of DCI, subjects with perimesencephalic SAH were excluded [21]; (2) Patients died within 7 days of admission, unable to collect data of 7 days. The final analysis included 197 patients (34 patients excluded: Patients died within 7 days n = 7; A history of malignancy n = 5; Arteriovenous malformation n = 6; History of auto-immune diseases n = 6; Perimesencephalic SAH n = 9; Trauma n = 1). Blood was routinely collected immediately upon admission and at 6am for day 3, day 5, day 7 to reduce potential confounding factors.

2.2. Clinical data

Baseline clinical data of all patients were collected, including demographic information (age, gender), risk factors (hypertension, alcohol drinking, diabetes mellitus and smoking), neuroradiological data (mFisher grade, intraventricular hemorrhage), admission status (GCS score, Hunt Hess Scale), treatment methods (interventional embolization or craniotomy clipping), laboratory indicators (leukocytes, neutrophils, monocytes, lymphocytes, NLR, erythrocytes and platelets) and complications (intracranial infection, DCI, rebleeding, pneumonia and hydrocephalus) were also collected. NLR is calculated by dividing the absolute count of neutrophils by the absolute count of lymphocytes.

2.3. Functional outcome

Through clinical follow-up, the modified Rankin Scale (mRS) was evaluated for the prognosis 3 months after aSAH. mRS $\geq$3 is defined as a poor clinical outcome.

2.4. Statistical analysis

The SPSS Statistics 18.0 software (Chicago, Illinois, SPSS Inc.) was used for our statistical analyses. The numerical values were expressed as median (interquartile range [IQR]) or mean $\pm$ standard error of continuous variables, and categorical variables were expressed as the number of subjects (percentage). The normality of distribution was analyzed by Kolmogorov Smirnov test. We used t-tests or analysis of variance to evaluate the differences between mean values. Non normally distributed variables were compared by Kruskal Wallis and Mann Whitney U-tests. Frequency and percentage were expressed as categorical data, and data were evaluated using chi square test. Binary correlation used Spearman rank correlation. The independent correlation of significant variables found in univariate models was determined using multivariable logistic regression (MLR) models. Area under the curve (AUC) and receiver operating characteristic (ROC) curves were calculated. When the P-value is $\leq$ 0.05, the result was considered significant.

3. Results

3.1. Baseline characteristics

Among the 197 eligible patients in this study (Supplementary Fig. 1), 73 (37.1 %) were male. Clinical outcomes and demographic characteristics of patients were collected as described in Table 1. The mean value of age was 60 (IQR 53, 67), 124 (62.9%) were female, 96 (48.7%) had hypertension, 11 (5.6%) had diabetes, 51 (25.9%) had smoking and 46 (23.3%) had alcohol consumption history. 77 (39.1%) presented with intraventricular hemorrhage (IVH), and 21 (10.7%) had Hunt Hess Scale (HH) $\geq$4 on admission. In treatment methods for aneurysms, surgical clipping was 24 (12.2%) and coiling was 160 (81.2%) while no treatment was 13 (6.6%). Patients in poor outcomes (mRS $\geq$3) were older [63 (IQR 56, 68) vs.59 (53, 64), P = 0.005], while subjects with lower GCS [12 (IQR 8, 15) vs.14 (15, 15), P < 0.001], higher HH grade [16 (24.6%) vs. 5 (3.8%), P < 0.001], higher mFS scores [35 (53.8%) vs. 25 (18.9%), P < 0.001] had more poor outcomes. Subjects with poor outcomes had higher proportion of IVH [42 (64.6%) vs. 35 (26.5%), P < 0.001], higher hospitalization time [28 days (IQR 19, 30) vs. 19 days (IQR 16, 22), P < 0.001], higher probability of DCI [60 (92.3%) vs. 21 (15.9%), P < 0.001], higher probability of hydrocephalus [46 (70.8%) vs. 8 (6%); P < 0.001], and larger proportion of rebleeding [15 (23.1%) vs. 4 (3%), P < 0.001] and higher probability of pneumonia [62 (95.4%) vs. 103 (78%), P = 0.002]. Subjects received intravascular embolization had a lower rate of poor outcomes [No treatment 8 (61.5%), clipped 11 (45.8%), coiled 46 (28.8%), P = 0.008]. Subjects developed DCI were older [62 (IQR 53, 68) vs.59 (53, 64), P = 0.033], while subjects with lower GCS [12 (IQR 8, 15) vs.14 (15, 15), P

Table 1
Demographics and clinical outcomes.

	Total	mRS (0–2)	mRS (3–6)	P	DCI (−)	DCI (+)	P
N	197	132	65		116	81	
Demographics							
Age	60 (53,67)	59 (53,64)	63 (56,68)	**0.005**	59 (53,64)	62 (53,68)	**0.033**
Gender (F)	197 (124)	132 (86)	65 (38)	0.361	116 (76)	81 (48)	0.371
Hypertension	197 (96)	132 (61)	65 (35)	0.313	116 (59)	81 (37)	0.474
Diabetes	197 (11)	132 (8)	65 (3)	0.678	116 (7)	81 (4)	0.742
Smoking	197 (51)	132 (32)	65 (19)	0.452	116 (26)	81 (25)	0.183
Alcohol	197 (46)	132 (30)	65 (16)	0.856	116 (25)	81 (21)	0.475
GCS	13 (14,15)	14 (15,15)	12 (8,15)	**<0.001**	15 (15,15)	12 (8,15)	**<0.001**
HHS (4,5)	197 (21)	132 (5)	65 (16)	**<0.001**	116 (3)	81 (18)	**<0.001**
mFS (3,4)	197 (60)	132 (25)	65 (35)	**<0.001**	116 (20)	81 (40)	**<0.001**
IVH	197 (77)	132 (35)	65 (42)	**<0.001**	116 (31)	81 (46)	**<0.001**
Aneurysm treatment:							
No treatment	13	5	8	**0.024**	5	8	0.122
Clipped	24	13	11	0.153	11	13	0.166
Coiled	160	114	46	**0.008**	100	60	**0.032**
Outcomes							
mRS (3–6)					116 (5)	81 (60)	**<0.001**
DCI	197 (81)	132 (21)	65 (60)	**<0.001**			
Hospital LOS	22 (16,25)	19 (16,22)	28 (19,30)	**<0.001**	18 (15,21)	27 (18,30)	**<0.001**
Rebleeding	197 (19)	132 (4)	65 (15)	**<0.001**	116 (6)	81 (13)	**0.012**
Hydrocephalus	197 (54)	132 (8)	65 (46)	**<0.001**	116 (4)	81 (50)	**<0.001**
Intracranial infection	197 (5)	132 (3)	65 (3)	0.368	116 (4)	81 (1)	0.28
Pneumonia	197 (165)	132 (103)	65 (62)	**0.002**	116 (90)	81 (75)	**0.005**

Data are presented as either Median (interquartile range) or Total (number). GCS, Glasgow score; HHS, Hunt Hess Scale; mFS, modified Fisher Scale; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; DCI, delayed cerebral ischemia; LOS, length of stay. P-values that are statistically significant are in bold.

< 0.001], higher HH grade [18 (20.1%) vs. 3 (2.6%), P < 0.001], and higher mFS scores [40 (49.4%) vs. 20 (17.2%), P < 0.001] had more DCI, Subjects developed DCI had higher proportion of IVH [46 (56.8%) vs. 31 (26.7%),P < 0.001], worse outcomes [mRS ≥3: 60 (74.1%) vs. 5 (4.3%), P < 0.001], longer hospitalization time [27 days (IQR 18, 30) vs. 18 days (15, 21), P < 0.001]. higher rate of rebleeding [13 (16%) vs. 6 (5.2%), P = 0.012], higher rate of hydrocephalus [50 (61.7%) vs. 4 (3.4%), P < 0.001] while higher probability of pneumonia [75 (92.6%) vs. 90 (77.6%), P = 0.005]. Subjects received intravascular embolization had a lower rate of DCI [No treatment 8 (61.5%), clipped 13 (54.2%), coiled 60 (37.5%), P = 0.032].

3.2. Blood cell trends

Overall trends in blood cells of outcomes were shown in Fig. 1. Neutrophils reached their peak on the first day after SAH and decreased until the seventh day in both good and poor outcomes. While neutrophils were consistently higher in poor outcomes than good outcomes (Fig. 1A). This same trend occurred for leukocytes (Fig. 1E). Lymphocytes decreased from first day to third day, then increased and reached their peak on seventh day in poor outcomes while increased from day 1 to day 7 in good outcomes. Lymphocytes in good outcomes were higher than poor outcomes at day 5 and 7 (Fig. 1B). NLR was also highest on day 1 and decreased until day 7 in both good and poor outcomes. NLR in poor outcomes was higher than good outcomes from day 3 to day 7 (Fig. 1C). After SAH, monocytes gradually increased and reached their peak on the seventh day in good outcomes and increased reaching a peak at day 3, gradually decreased to day 7 in poor outcomes (Fig. 1D). Platelets decreased from first day to fifth day, and then peaked on seventh day in both groups (Supplementary Fig. 2). Erythrocytes rapidly decreased from day 1 to day 3 and maintained no statistical difference from day 5 to day 7 compared to day 3 in poor outcomes while slowly increased from day 3 to day 7 in good outcomes. Erythrocytes in good outcomes were higher than poor outcomes from day 3 to day 7 (Fig. 1F).

Overall trends in blood cells of DCI are shown in Fig. 2. Neutrophils were highest on day 1 and decreased until day 7 in both groups. While neutrophils were higher in DCI than no DCI from day 3 to day 7 (Fig. 2A). This same trend occurred for leukocytes but leukocytes were consistently higher in DCI than no DCI from day 1 to day 7 (Fig. 2E). Lymphocytes decreased from day 1 to day 3, gradually increased from fifth day to seventh day in DCI, and increased from first day to seventh day in the absence of DCI. Lymphocytes in no DCI were higher than DCI at day 5 and day 7 (Fig. 2B). NLR was also highest on day 1 and decreased until day 7 in both groups. NLR in no DCI group was lower than DCI group from day 3 to day 7 (Fig. 2C). After SAH, monocytes gradually increased and reached their peak on the seventh day without DCI and increased reaching a peak at day 3, maintained stability to day 7 in DCI (Fig. 2D). Platelets also decreased from first day to fifth day, and then reached their peak on seventh day in both groups (Supplementary Fig. 3). Erythrocytes also rapidly decreased from day 1 to day 3 and maintained no statistical difference from day 5 to day 7 compared to day 3 in DCI while slowly increased from day 3 to day 7 in no DCI. Erythrocytes in no DCI were higher than DCI from day 3 to day 7 (Fig. 2F).

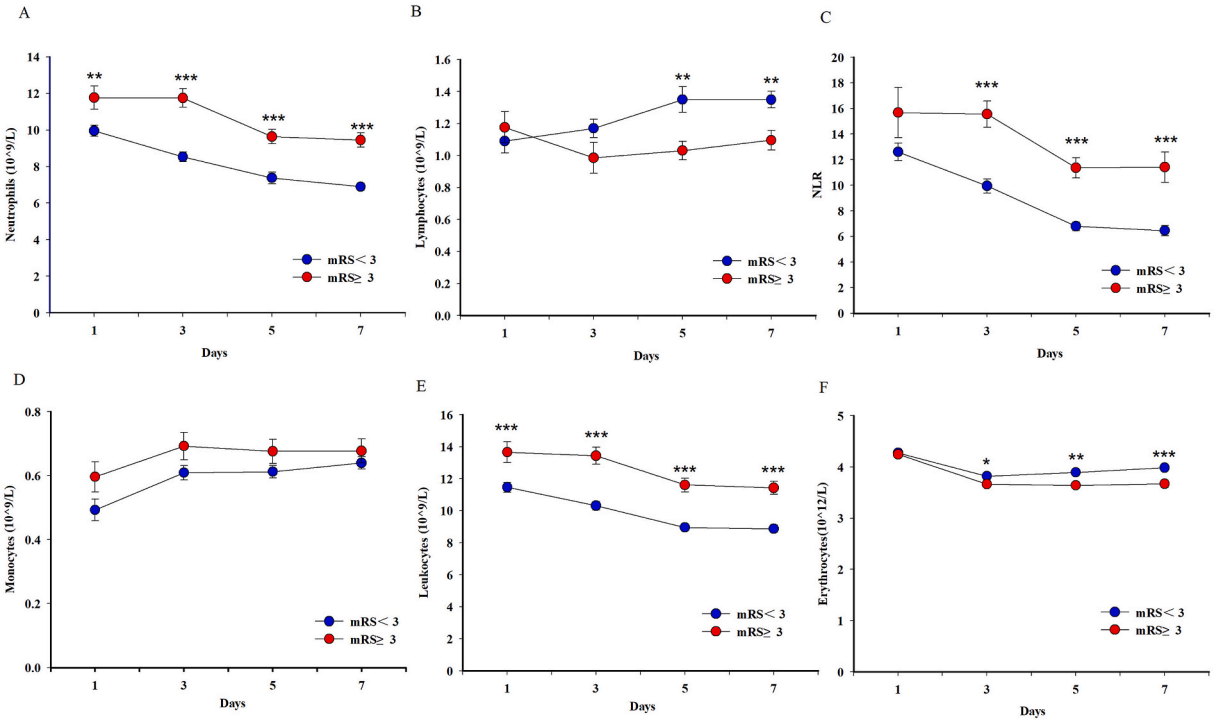

Fig. 1. Blood cell counts stratified by outcomes. Neutrophils (A), lymphocytes (B), NLR (C), monocytes (D), leukocytes (E) and erythrocytes (F) (mean and standard error) are shown from day 1 of SAH through day 7. Outcome is dichotomized according to mRS good (≤2) or poor (≥3). *P < 0.05, **P < 0.01, ***P < 0.001. Abbreviations: mRS, modified Rankin Scale; NLR, neutrophil-to-lymphocyte ratio.

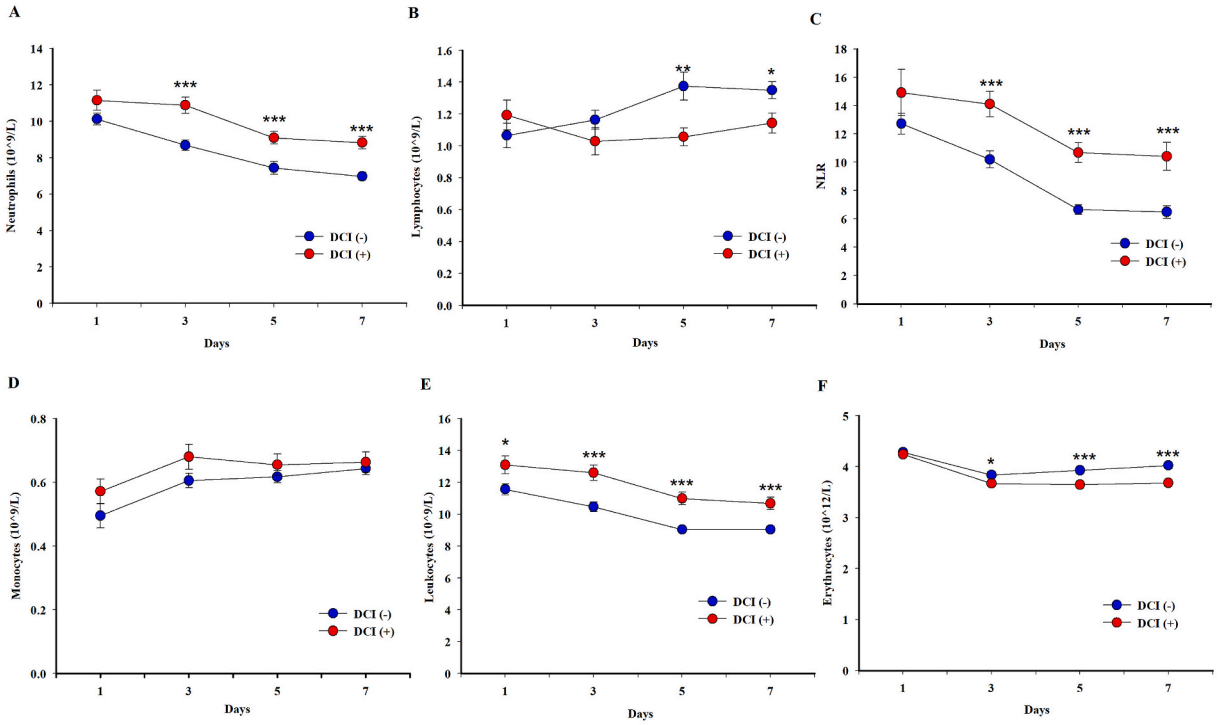

Fig. 2. Blood cell counts stratified by occurrence of delayed cerebral ischemia (DCI). Neutrophils (A), lymphocytes (B), NLR (C), monocytes (D), leukocytes (E) and erythrocytes (F) (mean and standard error) are shown from day 1 of SAH through day 7. DCI is dichotomized according to DCI (+) or DCI (−). *P < 0.05, **P < 0.01, ***P < 0.001. Abbreviations: delayed cerebral ischemia (DCI), neutrophil-to-lymphocyte ratio (NLR).

3.3. Outcome models

We constructed MLR models daily to evaluate the correlation between cell count and clinic outcomes (Table 2). Age, IVH and lymphocytes were correlated to poor outcomes on first day. IVH and neutrophils were associated with poor clinic outcomes on third day. IVH was associated with poor clinic outcomes on fifth and seventh day.

MLR models were also constructed on each day to evaluate the relationship between blood cell counts and DCI as shown in Table 3. Pneumonia and GCS were associated with DCI on day 1 and day 3. GCS, pneumonia, lymphocytes and erythrocytes were associated with DCI on fifth day. GCS, pneumonia, and erythrocytes were associated with DCI on seventh day.

3.4. Receiver operating characteristics (ROC) curves

We created receiver operating characteristics curves every day and found the optimal critical value of lymphocytes for predicting poor prognosis was 0.91*10^9/L and the sensitivity was 60% while specificity was 56.1%, the optimal critical value of age for predicting poor prognosis was 64.5 and the sensitivity was 52.3% while specificity was 75% on first day (AUC: 0.831, 95% CI 0.765–0.897) (Fig. 3A). The optimal critical value for predicting poor results of neutrophils was 9.5*10^9/L and the sensitivity was 32.3% while specificity was 71.2% on third day (AUC: 0.849, 95% CI 0.791–0.907) (Fig. 3B).

The optimal critical value for predicting DCI of lymphocytes was 1*10^9/L and the sensitivity was 60.5% while specificity was 66.4%, the optimal cutoff value for predicting DCI of erythrocytes was 3.44*10^12/L and the sensitivity was 38.3% while specificity was 87.1% on fifth day (AUC: 0.908, 95% CI 0.863–0.954) (Fig. 3C). The optimal critical value for predicting DCI of erythrocytes was 3.69*10^12/L and the sensitivity was 56.8% while specificity was 71.6% on seventh day (AUC: 0.903, 95% CI 0.854–0.952) (Fig. 3D).

4. Discussion

Our study is the first to demonstrate that the dynamic changes in peripheral blood cell count strongly distinguish between outcomes after SAH, with elevated neutrophils or decreased lymphocytes, and red blood cells predicting DCI and poor clinical outcomes.

The ischemic injury of the carotid bodies, which regulates blood pH, causes acidosis [22] and may aggravate blood cells destruction secondary to the injury to blood cells and vascular endothelium in SAH. Choroid plexus damage caused by SAH may change the cerebrospinal fluid supply and chemistry [23], which may lead to disruptions in the circulation of the cerebral arteries running in the subarachnoid space. Reduction of cerebrospinal fluid volume caused by choroid plexus degeneration leads to cerebral thromboembolism after SAH [24]. After aSAH, blood spreads to the whole brain and goes into the subarachnoid space. Red blood cells degrade and

Table 2
Relationship between functional outcome and blood cells.

		Day1			Day3			Day5			Day7		
Outcomes	Factors	Results	95% CI	P value	Results	95% CI	P value	Results	95% CI	P value	Results	95% CI	P value
	Age	OR = 1.664	(1.089–2.541)	**0.018**	OR = 1.43	(0.956–2.139)	0.082	OR = 1.502	(0.987–2.284)	0.057	OR = 1.259	(0.818–1.939)	0.296
	GCS	OR = 0.946	(0.567–1.579)	0.832	OR = 0.883	(0.542–1.437)	0.616	OR = 0.909	(0.546–1.514)	0.714	OR = 0.845	(0.508–1.406)	0.517
	HHS	OR = 1.84	(0.782–4.33)	0.163	OR = 1.475	(0.637–3.416)	0.365	OR = 1.301	(0.567–2.985)	0.535	OR = 1.153	(0.507–2.62)	0.734
mRS≥3	mFS	OR = 1.813	(0.78–4.213)	0.167	OR = 1.257	(0.513–3.083)	0.617	OR = 2	(0.836–4.786)	0.119	OR = 1.95	(0.844–4.504)	0.118
	IVH	OR = 3.431	(1.565–7.521)	**0.002**	OR = 2.931	(1.329–6.463)	**0.008**	OR = 2.35	(1.045–5.285)	**0.039**	OR = 2.755	(1.24–6.117)	**0.013**
	Pneumonia	OR = 2.828	(0.746–10.722)	0.126	OR = 3.643	(0.816–16.254)	0.09	OR = 3.118	(0.756–12.861)	0.116	OR = 3.758	(0.906–15.583)	0.068
	Neutrophils	OR = 1.766	(0.802–3.892)	0.158	OR = 3.003	(1.28–7.046)	**0.012**	OR = 1.806	(0.818–3.987)	0.143	OR = 1.844	(0.793–4.288)	0.155
	Lymphocytes	OR = 0.457	(0.217–0.964)	**0.04**	OR = 0.603	(0.25–1.459)	0.262	OR = 0.924	(0.39–2.185)	0.856	OR = 0.775	(0.322–1.862)	0.568
	NLR	OR = 0.786	(0.205–1.727)	0.321	OR = 0.823	(0.437–1.549)	0.546	OR = 1.446	(0.701–2.982)	0.318	OR = 1.072	(0.526–2.186)	0.847
	Monocytes	OR = 0.88	(0.608–1.274)	0.498	OR = 0.745	(0.514–1.079)	0.119	OR = 0.712	(0.449–1.13)	0.149	OR = 0.843	(0.524–1.074)	0.067
	Leukocytes	OR = 1.493	(0.576–3.869)	0.409	OR = 1.239	(0.538–2.857)	0.615	OR = 1.981	(0.728–5.388)	0.181	OR = 2.107	(0.722–6.146)	0.172
	Erythrocytes	OR = 0.899	(0.419–1.927)	0.784	OR = 0.595	(0.253–1.395)	0.232	OR = 0.681	(0.292–1.585)	0.372	OR = 0.461	(0.193–1.102)	0.081

Abbreviations: CI: confidence interval; mRS, modified Rankin scale; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio, GCS, Glasgow score; HHS, Hunt Hess Scale; mFS, modified Fisher Scale; IVH, intraventricular hemorrhage; P-values that are statistically significant are in bold.

Table 3
Relationship between DCI and blood cells.

		Day1			Day3			Day5			Day7		
Outcomes	Factors	Results	95% CI	P value	Results	95% CI	P value	Results	95% CI	P value	Results	95% CI	P value
DCI (+)	Age	OR = 1.419	(0.905–2.225)	0.127	OR = 1.448	(0.921–2.274)	0.109	OR = 1.214	(0.761–1.937)	0.415	OR = 1.205	(0.75–1.936)	0.441
	GCS	OR = 0.419	(0.227–0.774)	**0.005**	OR = 0.432	(0.239–0.779)	**0.005**	OR = 0.407	(0.225–0.737)	**0.003**	OR = 0.419	(0.23–0.762)	**0.004**
	HHS	OR = 0.96	(0.384–2.396)	0.93	OR = 0.823	(0.332–2.04)	0.674	OR = 0.955	(0.371–2.458)	0.923	OR = 0.811	(0.316–2.079)	0.662
	mFS	OR = 1.36	(0.538–3.438)	0.515	OR = 1.128	(0.432–2.95)	0.805	OR = 1.121	(0.424–2.962)	0.818	OR = 1.334	(0.505–3.525)	0.561
	IVH	OR = 0.934	(0.359–2.425)	0.888	OR = 0.776	(0.301–2.002)	0.6	OR = 0.664	(0.252–1.747)	0.406	OR = 0.989	(0.374–2.614)	0.982
	Pneumonia	OR = 54.244	(14.947–196.857)	**<0.001**	OR = 43.301	(12.042–155.705)	**<0.001**	OR = 41.874	(11.477–152.78)	**<0.001**	OR = 47.73	(12.951–175.906)	**<0.001**
	Neutrophils	OR = 0.948	(0.396–2.272)	0.905	OR = 1.074	(0.412–2.798)	0.884	OR = 1.39	(0.549–3.518)	0.487	OR = 0.982	(0.376–2.567)	0.971
	Lymphocytes	OR = 0.704	(0.29–1.705)	0.436	OR = 0.616	(0.248–1.531)	0.297	OR = 0.388	(0.154–0.981)	**0.045**	OR = 1.256	(0.546–2.89)	0.592
	NLR	OR = 0.798	(0.402–1.58)	0.517	OR = 0.94	(0.461–1.918)	0.865	OR = 0.622	(0.266–1.454)	0.273	OR = 1.522	(0.705–3.284)	0.285
	Monocytes	OR = 0.645	(0.413–1.009)	0.055	OR = 1.025	(0.656–1.601)	0.913	OR = 0.618	(0.37–1.032)	0.066	OR = 0.751	(0.489–1.151)	0.189
	Leukocytes	OR = 1.216	(0.409–3.613)	0.725	OR = 1.571	(0.59–4.184)	0.366	OR = 1.797	(0.557–5.8)	0.327	OR = 0.875	(0.258–2.962)	0.83
	Erythrocytes	OR = 1.018	(0.428–2.422)	0.968	OR = 0.784	(0.305–2.012)	0.613	OR = 0.335	(0.112–1.008)	**0.050**	OR = 0.242	(0.08–0.734)	**0.012**

Abbreviations: CI: confidence interval; mRS, modified Rankin scale; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio, GCS, Glasgow score; HHS, Hunt Hess Scale; mFS, modified Fisher Scale; IVH, intraventricular hemorrhage; P-values that are statistically significant are in bold.

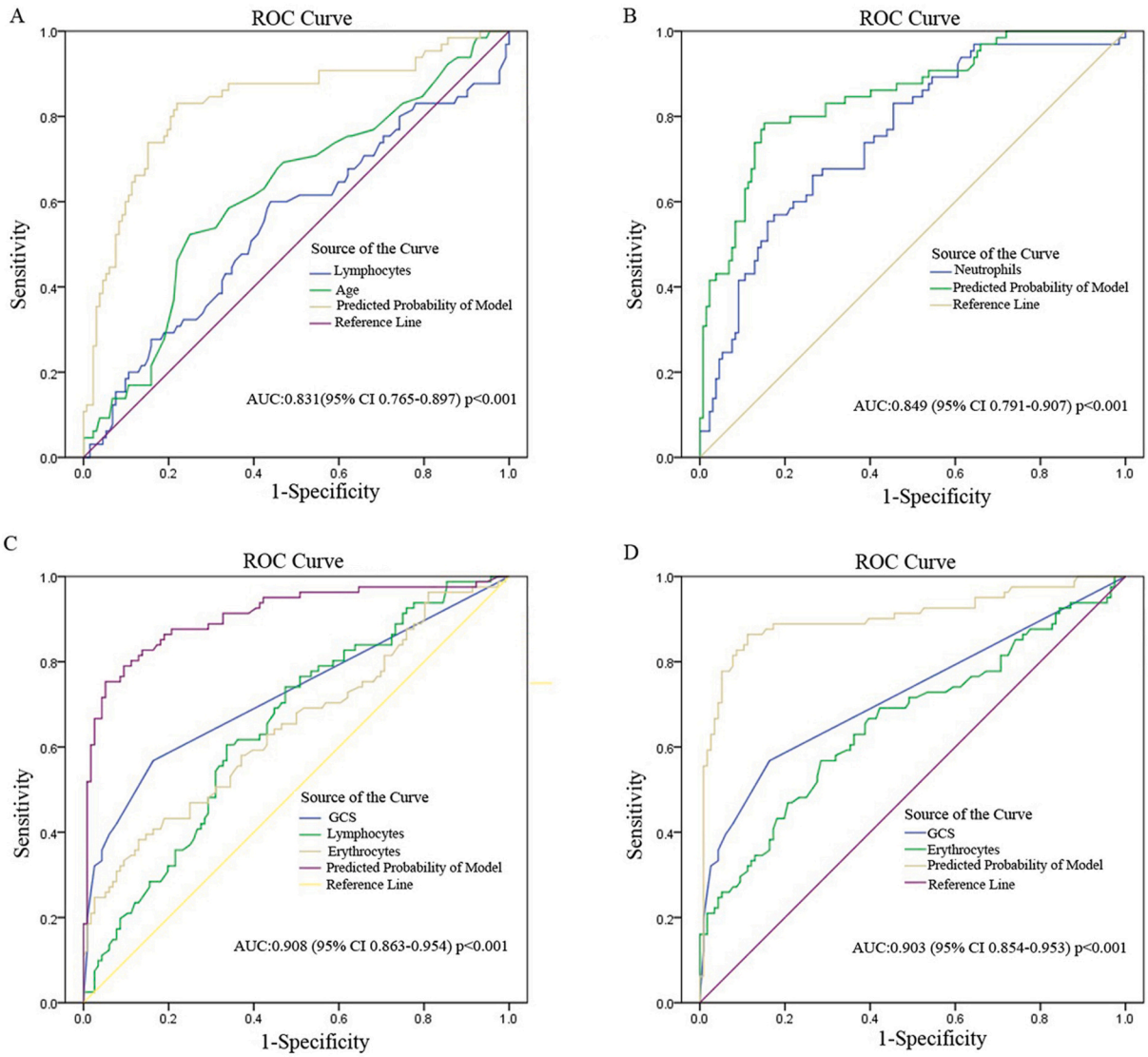

Fig. 3. ROC curves for mRS and DCI. ROC curves were generated for the discrimination of poor discharge mRS, with mRS dichotomized into good (0–2) and poor (3–6) outcomes at day 1 (A), and day 3 (B). ROC curves were generated for the discrimination of DCI at day 5 (C), day 7 (D). AUC and 95%CI interval were calculated for each ROC curve. DCI, delayed cerebral ischemia; mRS, modified Rankin Scale; AUC, area under the curve.

release a large amount of potential toxic materials [25], then destruct blood vessels of brain, trigger inflammatory cascade reactions [26]. Various of pathways induced inflammation and inflammation plays a crucial role in nerve destruction and damage [27].

Endoplasmic reticulum (ER) stress has been shown to be related to the increased formation of neutrophil extracellular traps (NETs). The stress induced neuronal apoptosis. Inhibiting the formation of NETs could reduce this stress activation and stress-induced neuronal apoptosis [28]. Neutrophils interact with activated endoplasmic reticulum, exacerbating inflammatory response, leading to blood-brain barrier disruption, brain edema, hypoperfusion, and neurological injury. It could reverse cerebral hypoperfusion, reduce neuronal cell death and decrease secondary brain injury by targeting neutrophil function [29–31]. Neutrophils can exacerbate microcirculation disorders and exhibit significant procoagulant effects [32]. Previous studies have demonstrated, within 10 min after SAH, neutrophils infiltrate the cerebral vasculature. It could improve vascular integrity and outcomes by reducing neutrophil levels or activity in animal models [33,34]. Pro-inflammatory cytokines were produced by neutrophils. Neutrophils also generated a large amount of oxidative stress by releasing myeloperoxidase and so on. Impaired vasodilation could be result from hypochlorous acid and consume nitric oxide produced by myeloperoxidase [35]. Isoproterenol produced by oxidative stress induced by neutrophil also leads to vasoconstriction [36]. In addition, early cerebral hypoperfusion can be caused by neutrophils after SAH [37]. We found neutrophils were higher in poor outcomes from day 1 to day 7 while in DCI from day 3 to day 7 and neutrophils could predict poor outcomes on day 3 suggesting neutrophils contribute to cerebral destruction after SAH. Neutrophils produce pro-inflammatory cytokines, oxidative stress resulting in vasoconstriction and contribute to early cerebral hypoperfusion, which induce DCI and poor outcome after aSAH. It

can guide us to provide early intervention to reduce the incidence of poor outcome by detecting dynamic changes of neutrophils at early stage after aSAH.

Lymphocytes play complex roles in the injured brain and need further elucidation. After aSAH, researchers have found lymphocytes in the central nervous system (CNS) [38]. Regulatory T cells (Tregs) are the leading important immunomodulator and play a vital role in eliminating inflammatory media [39–41]. The peripheral CD4 (+)CD25 (+)FOXP3 (+)Tregs level of cerebral hemorrhage patients is significantly increased [42]. While the dynamic and unique activation patterns of CD4+T cell subsets were found after SAH. There is significant increase of HLA-DR-CD38^{+} Tregs during delayed brain injury phase compared with early brain injury phase in SAH subjects developing cerebral vasospasm (CVS), infections and seizures. There is significant decrease of HLA-DR-CD38-Tregs during early brain injury stage in subjects with cerebral ischemia compared with none cerebral ischemia. There is significant increase of HLA-DR-CD38-Th2 cells during early brain injury stage. There are significant reductions of HLA-DR-CD38 + Th17/Tregs ratios and Th17/Tregs in SAH patients. While HLA-DR- CD38^{-} Th1/Th2 ratios and HLA-DR- CD38^{-} Th17/Tregs decrease during early brain injury stage [43]. The profound loss of total lymphocytes is defined as pathophysiological immunosuppression, which has complex mechanisms and can last for some weeks. Lymphocytes play a key role for host in protecting from pathogens. while it can increase susceptibility to systemic infection accompanied by immunosuppression [27]. A previous study found lymphocytes was significantly higher in good clinic outcomes group than in bad clinic outcomes while lymphocytes could not predict the outcomes at admission day [20]. Another study showed lymphocytes significantly reduced in good clinic outcomes group than in bad clinic outcomes at admission day but not statistically different at following 8 days [13] Lymphocytes were higher at day 5 and 7 in good outcomes and no DCI groups. Lymphocytes were associated with poor outcomes on day 1 (OR = 0.457) indicating higher lymphocytes predicted good outcomes, with DCI on day 5 (OR = 0.388) indicating higher lymphocytes predicted no DCI in our study. The difference of our results from previous research reports perhaps due to different definition of poor outcome, regions and sample sizes. It seems contradictory lymphocytes were higher at day 5 and 7 in good outcomes and no DCI groups. but associated with poor outcomes on day 1 not day 5 or 7, with DCI on day 5 not day 7 or other days, perhaps because the statistical differences and causal relationships have not been further reflected due to limited sample size in our study.

Anemia is common in subjects with aSAH. There are strong reasons to assume that ruptured intracranial aneurysms or intra-operative blood loss can lead to hemorrhagic anemia and a decrease in erythrocytes count. After aSAH, normal compensatory mechanisms to respond to anemia may be diminished that could increase cerebral hypoxia [44]. Although there is no direct evidence to demonstrate hypoxia induces cerebral vasospasm, but hypoxia could induce coronary vasospasm [45]. CVS further exacerbates DCI and poor outcomes. Patients of aSAH face a clear risk of cerebral ischemia and vascular spasm in the weeks following bleeding. The risk of sustained ischemia may reduce their tolerance to anemia. Rebleeding, upregulated leukocytosis or inflammation also aggravates anemia and induced poor outcomes. Existing data suggest that anemia is related with adverse outcomes after SAH [18]. We found erythrocytes rapidly decreased from day 1 to day 3 and maintained no statistical difference from day 5 to day 7 compared to day 3 in poor outcomes and DCI groups while slowly increased from day 3 to day 7 in good outcomes and no DCI groups. Erythrocyte could predict DCI at day 5 and 7 indicating erythrocyte is a beneficial factor after SAH.

Peripheral monocytes show a critical role in inflammatory response after brain injury, such as neurodegenerative disease, status epilepticus and intracerebral hemorrhage (ICH) [46–48]. Monocytes expressing programmed death-1 (PD-1) and CD14^{+}CD16^{-} monocytes are believed to play a vital role in the development of vasospasm. Because blocking these monocytes entry into the CNS after SAH could attenuate vasospasm [49]. It has recently been confirmed that monocytes could predict DCI and poor clinic outcomes after SAH in several studies [13,17]. However, there was no significant association of monocytes with DCI or poor outcomes in our study, perhaps because of limited subjects.

In previous studies, NLR was suggested to assist clinicians in evaluating the prognosis of aSAH patients and identifying potential serious subjects [20,27,50]. It has been observed that admission NLR predicted DCI and poor outcomes following aSAH [51–56]. Admission NLR has also been demonstrated to predict rebleeding following aSAH [57]. We found NLR was lower from day 3 to day 7 in good outcomes and no DCI but not predicted the DCI or poor outcomes perhaps because of limited patients and excluding patients who died within 7 days in our study. Other blood cell count ratio such as admission platelets to lymphocytes ratio also predicted poor clinical outcomes after aSAH [55], We additionally confirmed that platelets to lymphocytes ratio was higher in poor outcomes than good outcomes from day 3 to day 7 (Supplementary Fig. 4A). Interestingly, we also found monocytes to neutrophils ratio was higher in good outcomes than poor outcomes from day 3 to day 7 (Supplementary Fig. 4B) and monocytes to lymphocytes ratio was higher in poor outcomes than good outcomes from day 1 to day 7 (Supplementary Fig. 4C). The similar results about DCI were also found. Platelets to lymphocytes ratio was higher in DCI than no DCI from day 5 to day 7 (Supplementary Fig. 5A). Monocytes to neutrophils ratio was lower in DCI than no DCI from day 5 to day 7 (Supplementary Fig. 5B) while monocytes to lymphocytes ratio was higher in DCI than no DCI from day 3 to day 7 (Supplementary Fig. 5C). Unfortunately, due to sample size limitations, we were unable to perform MLR models about monocytes/neutrophils ratio, platelets/lymphocytes ratio and monocytes/lymphocytes ratio. Other inflammatory indicators such as CRP [58], coagulation indicators such as fibrinogen [59] and imaging indicator [60] have also been suggested to predict clinical outcomes after aSAH.

Animal experimental and human SAH could induce microvascular platelet thrombosis and aggregation. aSAH platelets show prolonged increases in activation and aggregation [61]. Platelet counts showed no significant changes after aSAH in our study. Continuous research on the dynamic alteration of platelet activation and aggregation after aSAH is encouraged.

Generally, after aSAH, there is a large amount of blood in the subarachnoid space and the whole brain. Erythrocytes degrade and release lots of toxic materials, then destroy blood vessels and initiate inflammatory cascade. Neutrophils infiltrate the cerebral vasculature quickly after aSAH. Neutrophils produce pro-inflammatory cytokines, oxidative stress which result in vasoconstriction and neutrophils also contribute to early cerebral hypoperfusion. The loss of total lymphocytes is defined as pathophysiological

immunosuppression, that could last for some weeks and has complex mechanisms after aSAH. Lymphocytes play a key role for host in protecting from pathogens. while it can increase susceptibility to systemic infection accompanied by immunosuppression. Ruptured intracranial aneurysms and intraoperative blood loss can lead to hemorrhagic anemia and erythrocytes count loss. After aSAH, the loss of erythrocytes count could increase cerebral hypoxia, further induce cerebral vasospasm. The increase of neutrophils and decrease of lymphocytes or erythrocytes further exacerbate DCI and poor outcomes. The human body has regulatory mechanisms to prevent the increase of neutrophils and decrease of lymphocytes or erythrocytes after aSAH, striving for a good prognosis. But if the regulatory functions are decompensated, DCI and poor outcomes will occur. If we can detect these decompensation phenomena at early stage and take timely intervention to reverse the decompensation phenomena, these will help patients get good outcomes.

There are several important limitations in this study. It is a single center study and limited sample size, that limits its generalizability. As this is a retrospective study, selection bias easily happens. As our study is limited to clinically available differences, the pathophysiological basis of the relationship between blood cell counts and clinic outcomes need be further elucidated. Future experiments will be conducted to investigate the relevant mechanisms.

We suppose that after SAH, increased level of neutrophils or decreased level of lymphocytes plays a vital role in inducing risk of infection, while decreased level of erythrocytes is key factor resulting into risk of vasospasm and cerebral ischemia, with these serving as important determinants of outcomes.

5. Conclusions

Despite there have been some previous reports on blood cell count and ratios to predict clinical prognosis after aSAH. Dynamic changes in mean platelet volume and peripheral leukocytosis after aSAH have also been studied [12–19]. Our study determined the time course about blood cell counts (leukocytes, neutrophils, lymphocytes, monocytes, erythrocytes and platelets) after aSAH in an independent research project for the first time. We found that elevated neutrophils, leukocytes, NLR, and decreased lymphocytes, erythrocytes were accompanied by DCI and poor outcome. Neutrophils, lymphocytes and erythrocytes counts could help clinical workers predict DCI and clinic outcomes after aSAH and can be regarded as targets for treatment pathways.

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Ethics approval and consent to participate

The ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 was conducted in our study. The study was approved by the ethics committee of the First People's Hospital of Jing zhou (LL2023121). Because the study was a retrospective nature study. it was allowed to be conducted by board without patients' consent.

Data availability statement

All data are available from the corresponding author on request.

CRediT authorship contribution statement

Yi Luo: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation. **Jian Zhao:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation.

Declaration of competing interest

The authors declare there is none financial interests/personal relationships which may be considered as potential competing interests.

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Declared none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29763.

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