D-dimer/albumin ratio is a prognostic marker for patients with aneurysmal subarachnoid hemorrhage-retrospective research

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Research Article

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Abstract

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is a serious neurological disorder with limited treatment options and very little is known about its pathophysiology. And there are few available objective tools for predicting the clinical prognosis of aSAH patients and further aiding in directing clinical therapeutic programs. This study aimed to evaluate whether the raised serum D-dimer/albumin ratio (DAR) could reflect disease severity and predict clinical outcomes after aSAH.

Methods: A total of 178 patients with aSAH were included in this retrospective study. Collected data included demographics; clinical severity of aSAH (WFNS scale and Hunt-Hess scale), levels of D-dimer, albumin, c-reactive protein (CRP), leukocyte counts, mRS on admission; and three-month prognosis. Clinical prognosis was dichotomized into favorable outcome (mRS $\leq$ 2) and unfavorable outcome (mRS $\geq$ 3). And the predictive ability of DAR for aSAH prognosis was determined by Receiver Operating Characteristic (ROC) Curve analysis.

Results: The serum DAR showed a strong positive correlation with disease severity. Univariate analysis revealed that DAR, WFNS grade, Hunt-Hess grade, delayed cerebral infarction (DCI), age, neutrophil-to-lymphocyte ratio (NLR), and c-reactive protein/albumin ratio (CAR) were associated with unfavorable clinical outcome. Multivariate regression analysis further revealed that elevated DAR could predict poor prognosis after correcting for WFNS grade, Hunt-Hess grade, DCI, age, NLR, and CRP/albumin ratio. The receiver operating characteristic curve result demonstrated that DAR was a comparable predictor for clinical outcome of aSAH in comparison with NLR and CAR.

Conclusion: DAR was d promising objective tool for aSAH patients. Hight content DAR was associate with disease severity and unfavorable short-term prognosis.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating neurological disorder known for high mortality and morbidity [1]. While the hitherto limited understanding for the pathophysiology hampered the development of effective therapeutics. The scarcity of treatment options warrants novel methods for evaluating the severity of aSAH and possible therapeutic candidates. Currently, there are many classification systems used to evaluate the severity and prognosis of aSAH patients upon hospital admission, such as the World Federation of Neurological Societies (WFNS) scale and the Hunt-Hess (HH) classification. These rating scales are primarily based on subjective judgements from medical staff, creating bias, and they have limited value in clinical prognoses[2]. An objective indicator to assess disease severity and aid in the prognosis of aSAH patients is needed. With the ease and accessibility of blood tests[3], researchers have examined numerous blood factors in aSAH patients, including D-dimer, of which high levels have indicated a poor prognosis in aSAH patients[4], and albumin, of which low levels have been associated with poor prognoses in aSAH patients[5]. Additionally, the D-dimer/albumin ratio (DAR) has been identified as an independent predictor of poor outcome in patients suffering from

infection, malignancy and critical illness[6, 7]. However, the prognostic value of combined detection of D-dimer and albumin has not been evaluated in aSAH patients. Therefore, this study aimed to validate the prognostic ability of DAR in the clinical outcomes of aSAH patients.

Methods

Patients

This is a single-center, retrospective study of all aSAH patients admitted to the Department of Neurosurgery at Nanjing Drum Tower Hospital (affiliated hospital of Nanjing University School of Medicine) from March 2020 to December 2021. Inclusion criteria were: ≥18 years; admitted within 24 hours of aSAH onset; and serum D-dimer and albumin measurements completed upon hospital admission. Exclusion criteria were: subarachnoid hemorrhage associated with autoimmune disease, inflammatory disease, liver disease, renal impairment, malnutrition, trauma, arteriovenous malformation, or moyamoya disease. Selection of appropriate treatment modality (clipping or coiling) was consistent with current guidelines[8,9].

Data collection

Data collected included patient demographics, baseline characteristics at hospital admission, and clinical outcomes of patients. Patient demographics included age, sex, and medical history. aSAH at hospital admission was diagnosed by computed tomography (CT) or digital subtraction angiography (DSA). Clinical presentation of aSAH was evaluated by WFNS scores, HH grades[10], and modified Rankin Scale (mRS) scores. The occurrence of acute hydrocephalus and delayed cerebral ischemia (DCI) was determined by clinical presentation and radiological examination. Blood levels of D-dimer, c-reactive protein (CRP), albumin, neutrophils, and lymphocytes were recorded. DAR, CRP/albumin ration (CAR), and neutrophil/lymphocyte ration (NLR) were calculated. At a follow-up time of 3 months, patient outcomes were assessed by mRS scores, with mRS≤2 representing a good outcome and mRS≥3 indicating a poor outcome.

Statistical Analysis

To assess the prognostic potential of DAR and other blood factors, patients were dichotomized into two groups (good outcome and poor outcome) based on the 3-month follow-up mRS scores. Continuous variables were reported as means with standard deviations (SD) or median with interquartile according to normality test. Inter-group comparisons were conducted using the two-tailed Student's t test or Mann–Whitney U test. Categorical variables were reported as counts. Comparisons between groups were carried out using chi-squared or Fisher exact tests. The Spearman's Rank correlation test was used to test the correlation of DAR and the WFNS score. Analyses of the receiver operating characteristic (ROC) curves and the area under the ROC curves (AUC) were performed to evaluate predictive performance. Collinearity was examined with the variance inflation factor, with the value of variables used for logistic analysis <5. Data were analyzed using the SPSS 21.0 statistical package (SPSS Inc., Chicago, IL), with the exception

of the comparison of ROC curves, which was carried out using MedCalc statistical software version 18.9 (MedCalc Software, Mariakerke, Belgium). For all tests, $p<0.05$ was considered statistically significant.

Results

A total of 190 patients were enrolled in the study, and 12 patients were excluded for not meeting inclusion criteria. In the final analysis, 178 patients were included. Patient baseline characteristics are detailed in Table 1. Mean patient age was 58.19±10.27 years and 55.6% (99/178) were male. A total of 8/178 (4.5%) patients had a history of diabetes mellitus and 85/178 (47.8%) had hypertension. Upon hospital admission, most patients presented with HH classification scores of 1 (53/178 [29.8%]) and 2 (59/178 [33.1%]), and the most common WFNS scores were 1 (63/178 [35.4%]) and 2 (47/178 [26.4%]). Baseline mRS≤2 was measured in 131/178 (73.6%) patients and mRS≥3 was in 47/178 (26.4%). The most common aneurysm location was in the anterior part of the brain (120/178 [67.4%]). Acute hydrocephalus and DCI occurred in 20/178 (11.2%) and 9/178 (5.1%) of patients, respectively. Initial D-dimer and albumin levels were 185.5 (98.75–324.25) and 39.15 (37.175–40.624), respectively, with a DAR level of 4.868(2.642–8.133).

Clinical outcomes at 3-month follow-up after aSAH were 131/178 (73.6%) patients with mRS≤2, defined as a good outcome, and 47/178 (26.4%) with mRS≥3, defined as a poor outcome (**Table 1**). All measured blood factors were significantly different between the good and poor outcome groups ($p<0.01$). The good outcome group had significantly higher levels of albumin and lymphocytes compared to those with a poor outcome (39.6 [38.2-40.8] vs. 36.8 (35.1-41.6) and 1.1 (0.8-1.5) vs. 0.8 (0.7-1.1), respectively). The good outcome group had significantly lower levels of D-dimer (158 [87-222] vs. 396 [203-716]), CRP (5.7 [3.2-16.6] vs. 25.1 [10.9-69.5]), and neutrophils (7.6 [5.4-9.3] vs. 10.2 [8.0-14.3]) compared to the poor outcome group. The DAR, CAR, and NLR were all significantly lower for the good outcomes group compared to those with poor outcomes (4.04 [2.2-5.8] vs. 11.03 [5.3-18.5], 0.14 [0.09-0.41] vs. 0.67 [0.28-1.83], and 6.3 [4.31-10] vs. 12.5 [8.36-18.2], respectively).

Table 2 shows the correlation between aSAH patient baseline data and clinical outcomes. DAR was shown to have a significant correlation with clinical outcomes (OR: 1.287 [1.138, 1.491], $p<0.01$). Higher DAR value was significantly associated with unfavorable prognosis. Besides, patients with higher WFNS score tended to have undesirable outcome with exceptionally high OR value. D-dimer/albumin ratio was significantly correlated with WFNS grade at admission (**Figure 1**). In order to further clarify the predictive value of DAR for patient prognosis, a ROC curve was used. As shown in **Figure2,** the area under the curve for DAR was greater than that of D-dimer, albumin, neutrophils, lymphocytes, NLR, or CAR. indicating that DAR was of better predictive value than single indicators or the other ratios did.

A binary logistic regression analysis was used to analyze independent risk factors that were associated with prognosis in univariate analysis. After adjustment for age, WFNS grade, HH grade, DCI, and NLR, binary logistic regression identified DAR as an independent risk factor for poor 3-month outcomes in patients with aSAH. (**Table 2**, $p<0.05$)

Discussion

An accurate prognosis for aSAH patients is critical in determining the appropriate therapeutic strategy. This study is the first to explore the significance of DAR in predicting the prognosis of patients with aSAH. These results demonstrated that high DAR was associated with aSAH severity and clinical prognosis of patients after adjusting for age, WFNS grade, HH grade, CAR, and DCI. These data suggested that DAR could be potentially used as a predictive tool for aSAH clinical outcomes.

Hypoalbuminemia are common in patients with aSAH and are independently associated with a poor prognosis[5].Similarly, we had observed a negative correlation between albumin concentration and clinical outcome, which was in consistent with former studies[11, 12]. Hypoproteinemia in patients with aSAH may be caused by systemic inflammation, malnutrition and active catabolic metabolism. Additionally, emerging evidence has suggested that albumin had neuroprotective effects via promotion of neurovascular remodeling and attenuation of brain damage[13]. Preclinical studies had confirmed that intravenously-administered albumin could ameliorate neurological impairment of patients suffering from intracranial hemorrhage[13]. Furthermore, one study suggested that 1.25 g/kg/day albumin treatment might have neuroprotective effects in patients with aSAH[14]. In addition, intravenously administered albumin has been shown to modify cerebral vascular integrity, impact cerebral vasospasm, and even modulate neuroinflammation and microglia functions[14].Collectively, albumin might be a promising therapeutic candidate for aSAH patients.

D-dimer, as another blood factor, has been widely investigated in many diseases, such as deep vein thrombosis, cerebral hemorrhage, and acute aortic dissection.[15] Elevation of D-dimer indicated an enhanced fibrinolysis activity, which could be used as a biomarker of hypercoagulative state or subsequent fibrinolysis in patients with aSAH[16]. Previous studies have shown that aSAH patients with high D-dimer levels tended to have poor prognosis[16], which was consistent with the results reported here. Following hemorrhagic stroke, blood vessel integrity is ravaged and an endogenous coagulation system is activated following tissue factor exposure. Free blood can enter the subarachnoid space, further initiating the coagulation process and promoting microthrombosis, which explains the elevation of D-dimer. It has been suggested that microthrombosis is associated with blood brain barrier (BBB) disfunction, neuronal injury, and the occurrence of DCI[17]. Additionally, emerging evidence has focused on thromboinflammation—a hyper-coagulative state promoted by the occurrence of microthrombosis in response to hemorrhagic ictus or disturbed micro-circulation. This could favor the adhesion of migrating immune cells and further exaggerate inflammation, thus disrupting the integrity of the BBB, and leading to an unfavorable clinical prognosis, even without occurrence of vasospasm or DCI[17].

DAR has been shown as an independent prognostic marker in patients with infection, malignancy, and other disease[6, 7], so it is not surprising that multivariate analysis in this study showed that DAR was an independent predictor of poor prognosis in aSAH patients, better than D-dimer or albumin alone.

Other blood factors have also been assessed in aSAH patients. One characteristic feature of aSAH injury is the destruction of the BBB, and the subendothelial space damaged by neutrophil infiltration plays an

important role in the increase of BBB permeability[18]. Disruption of the vessel wall can lead to leakage of plasma and molecules into the extravascular space, thereby exacerbating cerebral edema[19]. In our study, the poor-prognosis aSAH patients had a higher neutrophil count, similar to previous reports[18]. High CRP levels have been shown to correlate with the severity of aSAH, and though the underlying mechanism remains obscure, CRP could be used as a reliable prognostic factor in aSAH patients[20]. Moreover, previous studies have also demonstrated that NLR and CAR had a predictive value for poor prognosis in aSAH[11, 18]. Here, a significant correlation between the predictive value of NLR and CAR on patient outcomes was also observed. In this study, we have proved that the predictive power of DAR ratio was at least comparable, if not better than that of neutrophil/lymphocyte ratio or c-reactive protein/albumin ratio. Taken together, DAR could be used as an independent predictor of poor prognosis in aSAH patients.

While the present study has several limitations. This is a single-center, retrospective study with limited enrolled patients. Additional studies are warranted with a larger patient population. Besides, the follow-up period was a short-term visit, long-term follow-up studies are needed to further evaluate the prognostic potential of DAR.

Conclusion

This study has demonstrated that high DAR is associated with the severity of aSAH in patients and that DAR had a significant correlation with patient outcomes, indicating its use as a potential prognostic aid in aSAH patients.

Abbreviations

aSAH: Aneurysmal subarachnoid hemorrhage

mRS: Modified Rankin Scale

WFNS: World Federation of Neurosurgical Societies

DCI: Delayed cerebral infarction

NLR: Neutrophil-to-lymphocyte ratio

CRP: C-reactive protein

CAR: C-reactive protein/albumin ratio

DAR: D-dimer/Albumin ratio

ROC: Receiver operating characteristic

Declarations

Ethics approval and consent to participate

This study was approved by local ethics committee. According to national regulations, written informed consent for participation was not required for this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Author's Contribution

Chun Hua Hang, Ding Ding Zhang, Wei Li designed and revised the manuscript Xun Zhi Liu, Xiang Xin Chen, Wei Wu, Bin Sheng collected the data; Wei wu, Xun Zhi Liu, Bin Sheng, Jia Tong Zhang performed date analysis, Wei Wu and Xun Zhi Liu wrote the manuscript. All authors read and approved the final manuscript.

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Not applicable

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Tables

Table 1

Demographic characteristics of patients

	All patients (178)	mRs 1-2（131）	mRs 3-5（47）	P-Value
Sex				0.096
Male	99（55.6%）	68(51.9%)	31(66%)	
Female	79（44.4%）	63(48.1%)	16(34%)	
Age	58.19±10.27	57.10±9.48	61.23±11.78	0.034
Diabetes mellitus	8(4.5%)	6(4.6%)	2(4.3%)	0.644
Hypertension	85(47.8%)	64(48.9%)	21(44.7%)	0.623
HH				<0.01
1	53（29.8%）	52(39.7%)	1(2.1%)	
2	59（33.1%）	56(42.7%)	3(6.4%)	
3	26（14.6%）	15(11.5%)	11(23.4%)	
4	34（19.1%）	7(5.3%)	27(57.4%)	
5	6（3.4%）	1(0.8%)	5(10.6%)	
	178(100%)	131(100%)	47(100%)	
WFNS				<0.01
I	63（35.4%）	62(47.3%)	1(2.1%)	
II	47（26.4%）	45(34.4%)	2(4.3%)	
III	18（10.1%）	11(8.4%)	7(14.9%)	
IV	34（19.1%）	12(9.2%)	22(46.8%)	
V	16（9%）	1(0.8%)	15(31.9%)	
	178（100%）	131(100%)	47(100%)	
Aneurysm location				0.69
Anterior	120（67%）	86(65.6%)	34(72.3%)	
Posterior	46（25.8%）	36(27.5%)	10(21.3%)	
Multiple	12(6.7%)	9(6.9%)	3(6.4%)	
	178(100%)	131(100%)	47(100%)	
Repair procedure（WFNS IV-V）				0.2
Clipping	28(56%)	10(76.9%)	18(48.6%)	

Coiling	20(40%)	3(23.1%)	17(45.9%)	
None	2(4%)	0(0%)	2(5.4%)	
	50(100%)	13(100%)	37(100%)	
Acute hydrocephalus	20(11.2%)	15(11.5%)	5(10.6%)	0.56
DCI	9(5.1%)	2(1.5%)	7(14.9%)	<0.01
Intraventricular hemorrhage	30(16.9%)	22(16.8%)	8(17%)	0.566
D-dimer(ug/dL)	185.5 (98.75–324.25)	158(87-222)	396(203-716)	<0.01
CRP(mg/L)	39.15 (37.175–40.624)	5.7(3.2-16.6)	25.1(10.9-69.5)	<0.01
Alb(g/L)	39.15 (37.175–40.624)	39.6(38.2-40.8)	36.8(35.1-41.6)	<0.01
DAR	4.868(2.642–8.133)	4.04(2.2-5.8)	11.03(5.3-18.5)	<0.01
CAR	0.215（0.0996-0.6598）	0.14(0.09-0.41)	0.67(0.28-1.83)	<0.01
Neutrophil(×10^9/L)	7.9（5.975-10.4）	7.6(5.4-9.3)	10.2(8.0-14.3)	<0.01
Lymphocyte（×10^9/L）	1（0.8-1.5）	1.1(0.8-1.5)	0.8(0.7-1.1)	<0.01
NLR	7.875（4.8-12.81）	6.3(4.31-10)	12.5(8.36-18.2)	<0.01

Table 1 Values are displayed as mean (SD), median (IQR), count (%); WFNS, World Federation of Neurological Surgeons scale; DCI, Delayed cerebral ischemia; CAR, c-reactive protein/albumin; NLR, Neutrophils/lymphocytes ratio; DAR, d-dimer/albumin.

Table 2

Binomial logistic regression analysis of 3-month outcome.

Object	Adjust OR	95% CI		P-value
		Lower Limit	Upper Limit	
Age	0.992	0.934	1.054	0.787
DCI	2.623	0.305	2.551	0.380
DAR	1.287	1.138	1.491	<0.01
CAR	1.692	0.682	3.909	0.265
NLR	1.054	0.985	1.126	0.233
WFNS I	Ref	Ref	Ref	-
WFNS II	1.334	0.093	19.005	0.832
WFNSIII	26.306	2.525	274.043	0.006
WFNSIV	51.338	4.877	540.451	0.001
WFNSV	179.919	8.114	3989.350	0.001

Table 2 CI, Confidence interval; OR, Odds ratio; WFNS, World Federation of Neurological Surgeons Scale; DCI, Delayed cerebral ischemia; CAR, c-reactive protein/albumin ratio; NLR, Neutrophil/lymphocyte ratio; DAR, d-dimer/albumin ratio. P<0.05 was deemed as statistically significant.

Figures

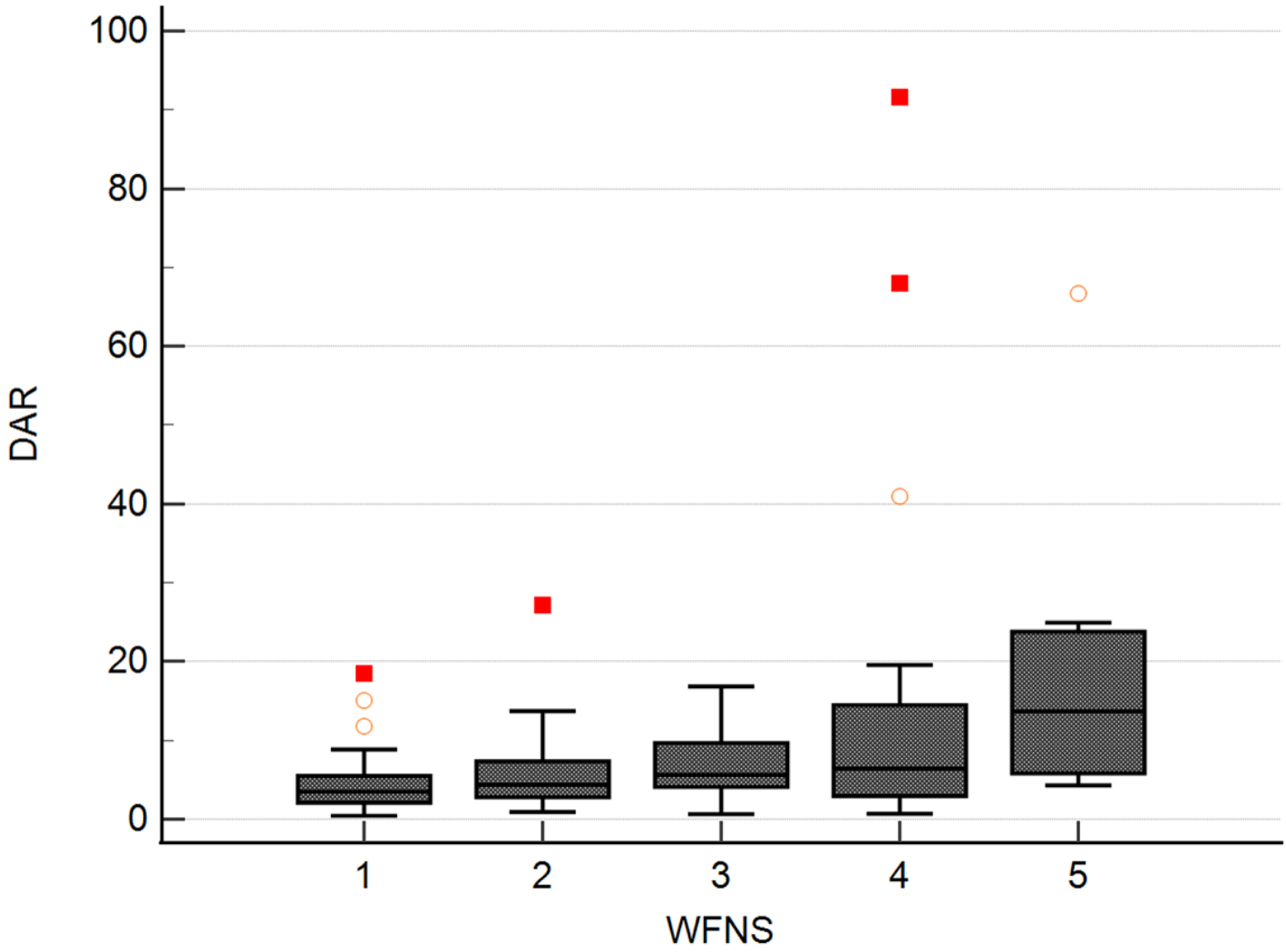

Figure 1

Correlation of the DAR with WFNS grade of aSAH patients on admission.

Correlation of the DAR with World Federation of Neurological Surgeons Scale (WFNS) grade of aneurysmal subarachnoid hemorrhage(aSAH) patients on admission ($r=0.397$, $p<0.001$).

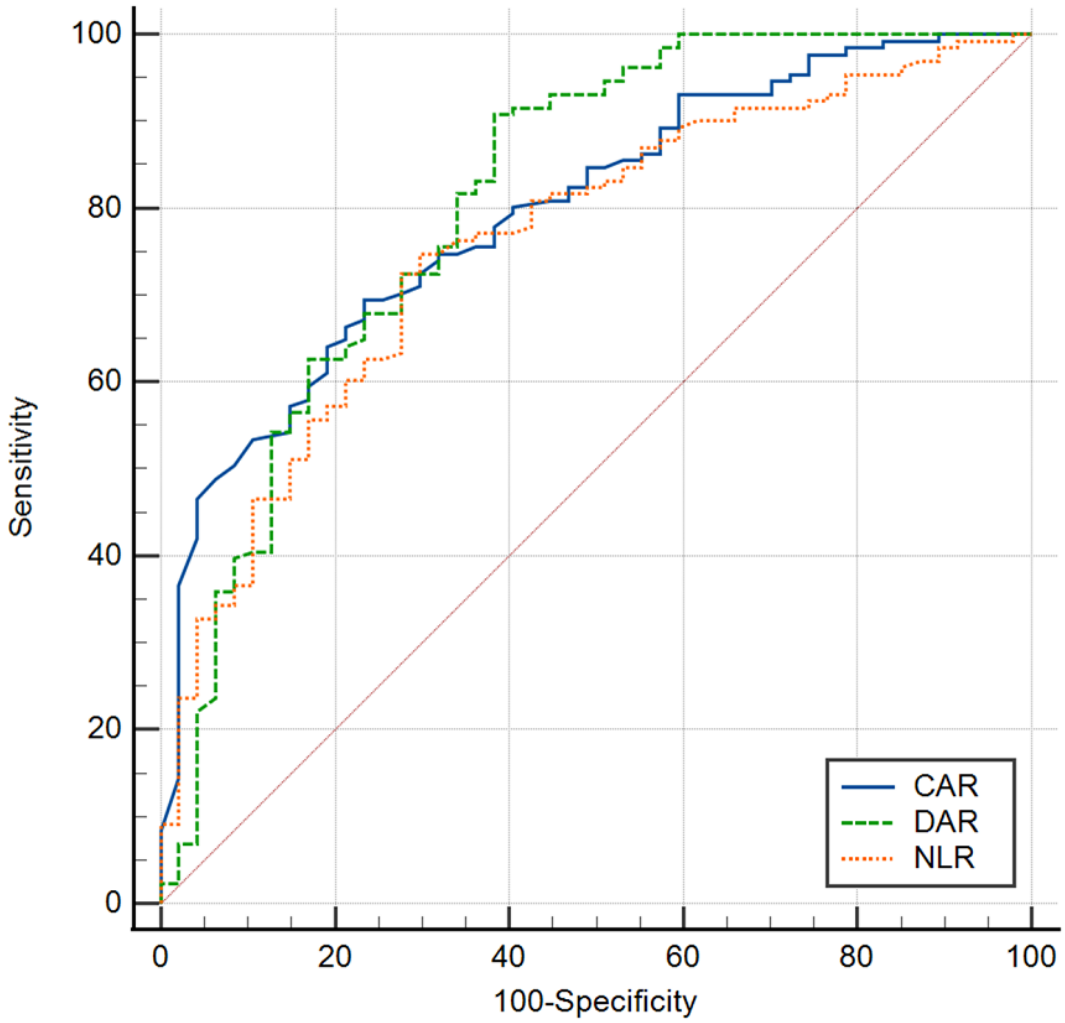

Figure 2

Receiver operating characteristics curves of DAR, CAR and NLR.

Receiver operating character□ROC□curves of DAR, CAR, and NLR for predicting 3-month clinical outcomes in aneurysm subarachnoid hemorrhage(aSAH□patients. The area under the curve was 0.81 for DAR, 0.797 for CAR, and 0.764 for NLR.