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Risk stratification of delayed causative aneurysm detection and long-term outcome in angiographically negative spontaneous subarachnoid haemorrhage

Jie Wang, Jian-Feng Meng, Shuo Wang, Ji-Zong Zhao, Yong Cao

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JW and J-FM contributed equally.

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Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Correspondence to
Dr Yong Cao; caoyong@bjtth.org

ABSTRACT

Background The risk factors of aetiology and poor outcome in angiographically negative subarachnoid haemorrhage (anSAH) were unclearly.

Methods The authors performed a retrospective review of a prospectively maintained database for anSAH patients between 2014 and 2018. AnSAH was defined as SAH presents in CT with no underlying vascular abnormality on initial digital subtraction angiography (DSA) within 72 hours of admission. Baseline and follow-up information, including medical history, bleeding pattern (perimesencephalic angiogram-negative SAH (PAN-SAH) and non-PAN-negative SAH (NPAN-SAH)), modified Fisher Scale (mFS), Glasgow Coma Score (GCS), Hunt-Hess grade, repeated imaging and causative vascular lesions and follow-up modified Rankin Scale (mRS) were reviewed. Poor outcome was defined as mRS scored 3–6 at last clinical follow-up.

Results Among 303 enrolled patients, 272 patients underwent at least once repeated imaging examination (median follow-up time, 3.0 months). Twenty-one (7.7%) aneurysms were detected. Multivariate logistic analysis showed that NPAN-SAH and mFS 3–4 were associated with a high rate of aneurysm detection in anSAH patients. Based on risk stratification, the aneurysm detection rate in the high-risk group (both NPAN-SAH and mFS 3–4) was as high as 20.370 per 100 person-years. Furthermore, of 251 non-aneurysm anSAH patients, after a total follow-up time of 1265.83 patient-years, poor outcome occurred in 18 (7.2%) patients. Multivariate Cox analysis found that NPAN-SAH and GCS 3–12 were associated with a high rate of poor outcome of anSAH. The cumulative 5-year incidence rate for poor outcome in the non-aneurysm anSAH patients in the high-risk group (both NPAN-SAH and GCS 3–12) was as high as 75.302 per 100 person-years.

Conclusions Even in anSAH confirmed by initial DSA, patients with NPAN-SAH and mFS 3–4 should be monitored for delayed causative aneurysm detection, meanwhile in non-aneurysm anSAH patients, NPAN-SAH and initial functional impairment are associated with poor prognosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies reported that approximately 10% causative aneurysms were detected in angiographically negative subarachnoid haemorrhage (anSAH) patients, and anSAH patients had a benign outcome. However, the risk factors of aetiology and poor outcome in anSAH were unclearly.

WHAT THIS STUDY ADDS

⇒ We identified that although in anSAH confirmed by initial digital subtraction angiography, patients with non-perimesencephalic angiogram-negative (NPAN)-SAH and modified Rankin Scale 3–4 should be monitored for delayed causative aneurysm detection, meanwhile in non-aneurysm anSAH patients, NPAN-SAH and initial functional impairment are associated with poor prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may assist neurologist in the clinical determination of whether to perform repeated imaging and predict the long-term outcome in anSAH patients.

INTRODUCTION

Spontaneous subarachnoid haemorrhage (SAH) affects approximately 10–15 per 100 000 population per year[1 2] and is most commonly caused by intracranial aneurysms.[3] Aneurysmal SAH leads to a high risk of morbidity and mortality.[3–5] Previous studies have reported that the overall fatality and morbidity rates caused by aneurysmal SAH were over 50% and 50%, respectively.[4 6] Furthermore, rebleeding of aneurysms leads to a much higher rate of morbidity and mortality.[7 8] The early detection of the causative aneurysm using digital subtraction angiography (DSA) followed by appropriate treatment has great significance in preventing rebleeding in SAH patients.

However, the cause of the spontaneous SAH in approximately 15%–20% patients cannot be detected, even with extensive diagnostic imaging studies, including DSA, and these are termed angiographically negative SAH (anSAH).[2 9] Usually, detecting causative vascular lesions by repeated imaging, including any imaging modalities of CT angiography (CTA), DSA, MR angiography (MRA), should be necessary in the clinic.[10–12]

Prior studies have reported that 2%–17% of causative vascular lesions, mainly aneurysms, were identified in initial anSAH patients by follow-up radiological imaging examinations.[13–15] However, the rebleeding of causative aneurysms poses a life-threatening risk prior to repeated imaging, while additional DSA examination on patients without causative vascular lesions may lead to extra DSA-related complications and a non-negligible medical burden.[16–18] Therefore, discriminating a suspicious aneurysm in these anSAH patients is crucial. However, to the best of our knowledge, there are no clear risk factors associated with delayed causative aneurysm detection and poor functional outcome in anSAH patients because of the limited number of cases and follow-up duration.

In our current study, we analysed the follow-up data of 303 enrolled patients with anSAH confirmed by DSA to investigate risk factors associated with positive detection of causative aneurysms and explore the risk factors associated with poor functional outcome with anSAH. Our study suggested definite risk stratification by initial imaging examination for causative aneurysm recognition and long-term poor prognosis in anSAH patients.

METHODS

Data availability disclosure

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study design

This study was a retrospective review of a prospectively maintained database for all patients with anSAH who were enrolled between January 2014 and December 2018.

Patients and data collection

Patients diagnosed with anSAH were consecutively enrolled between January 2014 and December 2018. AnSAH was defined as SAH present in a plain CT scan with no underlying vascular abnormality on the first DSA within 72 hours of admission.[9 19 20] Patients with aneurysms, arteriovenous malformations, arterial dissections and other vascular lesions detected in follow-up neurovascular imaging were excluded to evaluate the long-term outcome. Baseline demographics, angiographic features and hospitalisation course were carefully reviewed. Baseline demographics, including age, sex, personal medical history, medication history, smoking history and modified Rankin Scale (mFS), were recorded. Angiographic features, including bleeding pattern (perimesencephalic angiogram-negative (PAN)-SAH and non-PAN (NPAN)-SAH) and mFS, were reviewed. The Glasgow Coma Score (GCS), Hunt-Hess (HH) grade and mFS were used for evaluation on admission.[21] PAN-SAH was defined as blood present anterior to the midbrain with or without extension to the anterior ambient cistern or basal Sylvian fissure and without complete filling of the interhemispheric fissure or extension to the lateral Sylvian fissure, and NPAN-SAH was defined as acute blood seen on the CT scan that was not confined to the PAN-SAH territory.[19 20 22] Vasospasm was defined as a reduced level of consciousness and/or neurological deficit occurring after a SAH with confirmed angiographic vasoconstriction.[23 24] Based on previous studies, HH grade was categorised into two groups: 1–2 and 3–5 groups; GCS was divided into two groups: 3–12 and 13–15 groups; and mFS was grouped into two groups: 1–2 and 3–4 groups.[4 21 25 26] The length of hospital stays (LOS) and in-hospital complications comprising hydrocephalus, cerebral vasospasm, cerebral infarction, rebleeding, pulmonary infection, electrolyte imbalance, acute gastric ulcer, deep venous thrombosis and death were compared between NPAN-SAH and PAN-SAH. Bleeding pattern, GCS, HH grade and mFS were examined by two neurosurgeons (J-FM and JW). Discrepancies were resolved by a senior neurosurgeon (YC).

Repeated imaging and outcomes by follow-up

All anSAH patients were given recommendations for undergoing imaging and clinical follow-up. Imaging follow-up, any imaging modality, including DSA, CTA and MRA, was suggested to proceed within 6 months after hospital discharge. Clinical follow-up was performed every 6 months within the first 2 years and then annually. The modified Rankin Scale (mRS) at the last clinical follow-up was used to assess functional outcome. Poor functional outcome was defined as mRS scores of 3–6 during the follow-up.[4 9]

Statistical analysis

Continuous variables are presented as the means±SDs or as medians and IQRs, and categorical variables are expressed as percentages. Wilcoxon rank-sum tests, t-tests and χ^2 tests were used accordingly. The associations between causative anomalies for SAH and pertinent risk factors were evaluated by univariate logistic regression analysis. Covariates including NPAN-SAH and mFS were entered into the multivariate logistic regression analysis. The associations between poor functional outcome and pertinent risk factors were evaluated by univariate Cox regression analysis. Covariates including NPAN-SAH, HH grade and GCS score were entered into the multivariate Cox regression analysis. Multivariate logistic and Cox analyses using the forwards stepwise selection method were used. The incidence rate (IR) for causative vascular lesion events and poor functional outcome events were calculated by dividing the numbers of events by person-years at risk, with 95% CIs estimated using a Poisson model. The cumulative incidence of poor outcome events is presented with Kaplan-Meier curves. The analyses were performed with the statistical software SPSS V.24.0 (IBM) and STATA V.15.0 (StataCorp). A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics and hospitalisation complications

Three hundred and thirty patients with anSAH were reviewed retrospectively in a prospectively maintained

Table 1 Baseline characteristics and hospitalisation complications of all anSAH patients

Variables	Overall (n=303)	PAN-SAH (n=110)	NPAN-SAH (n=193)	P value
Age mean (years)	54.7±11.2	52.7±11.5	55.7±11.1	0.027†*
>60 years, no (%)	104 (34.3)	24 (21.8)	80 (41.5)	0.001‡*
Female, no (%)	159 (52.5)	59 (53.6)	100 (51.8)	0.760‡
Smoking history, no (%)	64 (21.1)	23 (20.9)	41 (21.2)	0.993‡
Medical history, no (%)				
Hypertension	118 (38.9)	35 (31.8)	83 (43.0)	0.055‡
Hyperlipidaemia	136 (44.9)	53 (48.2)	83 (43.0)	0.384‡
Diabetes mellitus	50 (16.5)	15 (13.6)	35 (18.1)	0.310‡
Coronary heart disease	22 (7.3)	7 (6.4)	15 (7.8)	0.650‡
Ischaemic cerebrovascular disease	18 (5.9)	5 (4.5)	13 (6.7)	0.410‡
Antithrombotic drugs, no (%)	19 (6.3)	8 (7.3)	11 (5.7)	0.587‡
HH grades 3–5	20 (6.6)	0	20 (10.4)	<0.001‡*
mFS 3–4	76 (25.1)	17 (15.0)	59 (30.6)	0.004‡*
GCS 3–12	12 (4.0)	2 (1.8)	10 (5.2)	0.255‡
Complications				
Rebleed, no (%)	2 (0.7)	0	2 (1.0)	0.536§
Ictal infarction, no (%)	2 (0.7)	1 (0.9)	1 (0.5)	0.999§
Delayed cerebral infarction, no (%)	6 (2.0)	2 (1.8)	4 (2.1)	0.999§
Vasospasm, no (%)	6 (2.0)	1 (0.9)	5 (2.6)	0.423§
Hydrocephalus, no (%)	50 (16.5)	5 (4.5)	45 (23.3)	<0.001‡*
CSF drainage, no (%)	5 (1.7)	0	5 (2.6)	0.163§
Pulmonary infection, no (%)	20 (6.6)	1 (0.9)	19 (9.8)	0.001‡*
Electrolyte imbalance, no (%)	171 (56.4)	45 (40.9)	126 (65.3)	<0.001‡*
Acute gastric ulcer, no (%)	19 (6.3)	2 (1.8)	17 (8.8)	0.016‡*
Deep venous thrombosis, no (%)	14 (4.6)	6 (5.5)	8 (4.1)	0.602‡
Death, no (%)	3 (1.0)	0	3 (1.6)	0.556§
LOS mean (days)	12.9±5.8	12.0±5.0	13.4±6.2	0.041†*

*p<0.05.
†T-test.
‡χ^2 test.
§Fisher's exact test.
anSAH, angiogram-negative subarachnoid haemorrhage; CSF, cerebrospinal fluid; GCS, Glasgow Coma Score; HH grade, Hunt-Hess grade; LOS, length of stay; mFS, modified Fisher Scale; NPAN-SAH, non-perimesencephalic angiogram-negative SAH; PAN-SAH, perimesencephalic angiogram-negative SAH.

database between January 2014 and December 2018. Twenty-seven (8.2%) patients were lost to follow-up. Of 303 patients, 193 (63.7%) displayed a haemorrhagic pattern consistent with NPAN-SAH, and 110 (36.3%) displayed a PAN-SAH pattern. The baseline clinical characteristics of the 303 patients are presented in table 1. The mean age of all patients was 54.7±11.2 years; 104 (34.3%) patients were older than 60 years and women comprised 52.5% of the population. Sixty-four (21.1%) patients had a smoking history. The comorbid diseases were hypertension in 118 (38.9%), diabetes mellitus in 50 (16.5%), hyperlipidaemia in 136 (44.9%), ischaemic cerebrovascular disease in 18 (5.9%) and heart disease in 22 (7.3%) patients. Antithrombotic drugs were reported in 19 (6.3%) patients. HH grades 3–5 occurred in 20 (6.6%) patients, mFS 3–4 occurred in 76 (25.1%) patients and GCS 3–12 was found in 12 (4.0%) patients. The patients in the NPAN-SAH group were older than those in the PAN-SAH group (p=0.027), and higher HH grade and mFS were more likely to occur in the NPAN-SAH group (p<0.05).

The LOS in the patients with anSAH was 12.9±5.8 days, and that in the NPAN-SAH group was longer than that in the PAN-SAH group (13.4±6.2 vs 12.0±5.0, p=0.041). The clinical hospitalisation complications were shown in table 1. Of all patients, rebleeding occurred in 2 (0.7%),

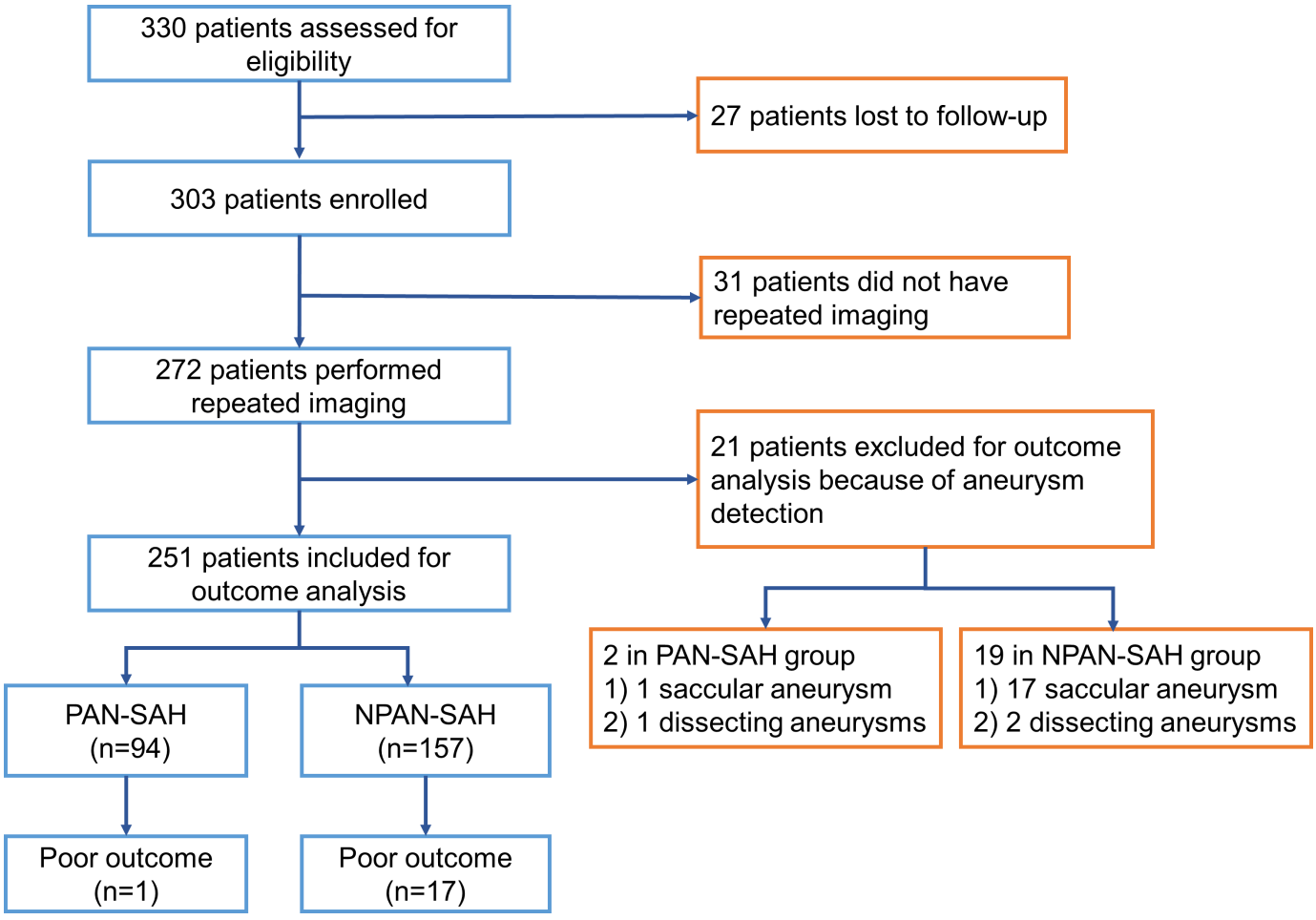

Figure 1 The flow chart of the study patient. NPAN-SAH, non-perimesencephalic angiogram-negative SAH; PAN-SAH, perimesencephalic angiogram-negative subarachnoid haemorrhage.

ictal infarction in 2 (0.7%), delayed cerebral infarction in 6 (2.0%), vasospasm in 6 (2.0%), hydrocephalus in 50 (16.5%), pulmonary infection in 20 (6.6%), electrolyte imbalance in 171 (56.4%), acute gastric ulcer in 19 (6.3%) and deep venous thrombosis in 14 (4.6%). Patients with NPAN-SAH showed a higher proportion of hydrocephalus, pulmonary infection, electrolyte imbalance and acute gastric ulcer than the PAN-SAH patients ($p<0.05$). Three patients (1.0%) died in the hospital, all of whom were from the NPAN-SAH group.

Repeated imaging investigation and causative aneurysm detection risks

Among the 303 patients, 272 (89.8%) patients underwent at least once repeated imaging follow-up. Twenty-one (6.9%) aneurysms were detected during follow-up (median follow-up time, 3.0 months), including 18 (6.6%) saccular aneurysms and 3 (1.1%) dissecting aneurysms (figure 1). Nine internal carotid artery aneurysms (ophthalmic artery, choroidal artery and paraclinoid), four anterior communicating artery aneurysms, four posterior circulation aneurysms (posterior inferior cerebellar artery, basilar artery and superior cerebellar artery), three posterior communicating artery aneurysms and one middle cerebral artery aneurysm were detected by follow-up imaging. According to previous study,[27] the location of ruptured aneurysms was middle cerebral artery (32.0%), anterior communicating artery (32.0%), posterior communicating artery (14.0%), followed by posterior circulation (8.0%, posterior inferior cerebellar artery, basilar artery and superior cerebellar artery), internal carotid artery (6.0%) and others (8.0%). Compared with this study, our results demonstrated that initially occult aneurysms might have a predilection for location of internal carotid artery (42.9%) and posterior circulation (19.0%). Among the 272 patients, 152 underwent only CTA, 30 underwent only DSA and 90 underwent both CTA and DSA, and the detection number of causative aneurysms in the only CTA group, only DSA group, and CTA plus DSA group was 7, 5 and 9, respectively (p=0.061). The detection rate in the CTA group and DSA group was 6.6% (16/242) and 11.7% (14/120), respectively, while the p value was 0.101 between the two groups (χ^2 test). Of the 90 patients who underwent both CTA and DSA, the 9 aneurysms were detected by both CTA and DSA, while no aneurysm was found in the left 81 patients. By a χ^2 test, aneurysms were more likely to be

Table 2 Diagnosis of causative vascular lesions by repeated imaging in anSAH patients

	Overall (n=303)	PAN-SAH (n=110)	NPAN-SAH (n=193)	P value
Repeated imaging, no (%)	272 (89.8)	96 (87.3)	176 (91.2)	0.279†
CTA	242 (89.0)	85 (88.5)	157 (89.2)	0.868†
DSA	120 (44.1)	41 (42.7)	79 (44.9)	0.525†
MRA	9 (3.3)	6 (6.3)	3 (1.7)	0.085†
Diagnosis, no (%)	21 (7.7)	2 (2.1)	19 (10.8)	0.010†*
Saccular aneurysm	18 (6.6)	1 (1.0)	17 (9.7)	
Dissecting aneurysm	3 (1.1)	1 (1.0)	2 (1.1)	

*p<0.05.
†χ^2 test.
anSAH, angiogram-negative subarachnoid haemorrhage; CTA, CT angiography; DSA, digital subtraction angiography; MRA, MR angiography; NPAN-SAH, non-perimesencephalic angiogram-negative SAH; PAN-SAH, perimesencephalic angiogram-negative SAH.

detected in the NPAN-SAH group than in the PAN-SAH group (table 2, p=0.01). The univariate logistic analysis found that NPAN-SAH and mFS 3–4 had a p<0.1. In the multivariate logistic analysis, NPAN-SAH (OR 4.682 (95% CI 1.050 to 20.872); p=0.043, table 3) and mFS 3–4 (OR 3.790 (95% CI 1.502 to 9.566); p=0.005, table 3) were associated with a high rate of aneurysm diagnosis in anSAH.

Furthermore, we stratified the patients into three groups according to the presence of two risk factors (NPAN-SAH and mFS 3–4). The low-risk group did not have any of the two risk factors, the intermediate-risk group had only one risk factor, and the high-risk group had two risk factors. The rate of low-risk, intermediate-risk and high-risk patients in CTA group is 29.3% (71/242), 52.5% (127/242) and 18.2% (44/242), respectively; the rate of low-risk, intermediate-risk and high-risk patients in DSA group is 26.7% (32/120), 45.0% (54/120) and 28.3% (34/120), respectively, and the distribution of risk groups between CTA group and DSA group had no statistical difference (χ^2 test, p=0.085). The aneurysm detection

Table 3 Logistic analyses of risk factors associated with detection of causative aneurysm by repeated imaging†

		Univariate analysis		Multivariate analysis	
Variable	n	OR (95% CI)	P value	OR (95% CI)	P value
NPAN-SAH	19	5.688 (1.296 to 24.968)	0.021*	4.682 (1.050 to 20.872)	0.043*
Age >60 years	8	1.315 (0.524 to 3.330)	0.559		
Female	11	0.945 (0.388 to 2.305)	0.901		
Smoker	3	0.477 (0.136 to 1.672)	0.247		
Hypertension	11	1.661 (0.680 to 4.056)	0.265		
Hyperlipidaemia	10	0.581 (0.251 to 1.343)	0.987		
Diabetes mellitus	4	1.279 (0.408 to 4.005)	0.673		
Coronary heart disease	1	1.553 (0.184 to 13.075)	0.686		
Ischaemic cerebrovascular disease	2	1.927 (0.405 to 9.174)	0.410		
HH grades 1–2‡	20				
HH grades 3–5	1	0.688 (0.087 to 5.442)	0.723		
mFS 1–2 ‡	9				
mFS 3–4	12	4.437 (1.781 to 11.053)	0.001*	3.790 (1.502 to 9.566)	0.005*
GCS 13–15‡	19				
GCS 3–12	2	2.830 (0.570 to 14.044)	0.203		
Hydrocephalus	5	1.601 (0.555 to 4.613)	0.384		

*p<0.05.
†Thirty-one patients without repeated imaging were excluded for the logistic analysis.
‡Reference.
GCS, Glasgow Coma Score; HH grade, Hunt-Hess grade; mFS, modified Fisher Scale; n, number of events; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid haemorrhage.

Table 4 The incidence rate for aneurysm detection in different risk groups

Group	Aneurysm detection	
	n/N	IR (95% CI)
Low risk*	1/80	1.250 (0.176 to 8.874)
intermediate risk*	9/138	6.522 (3.393 to 12.534)
high risk*	11/54	20.370 (5.034 to 36.783)
Overall	21/272	7.721 (5.034 to 11.841)

*The patients were stratified into three groups according to the presence of two risk factors (NPAN-SAH and mFS 3–4): the low-risk group was without any of the two risk factors, the intermediate-risk group only had one risk factor, and the high-risk group had >1 risk factor.
IR, incidence rate; mFS, modified Rankin Scale; N, total number in the corresponding group; n, number of events; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid haemorrhage.

rate of anSAH was 7.721 (95% CI 5.034 to 11.841) per 100 person-years. The aneurysm detection rates in the low-risk and intermediate-risk groups were 1.250 and 6.522 per 100 person-years, respectively, whereas the cumulative aneurysm detection rate in the high-risk group was 20.370 (95% CI 5.034 to 36.783) per 100 person-years (table 4).

Long-term outcome

In our study, 330 patients with anSAH were included. Of 330 patients, 27 were lost to follow-up and 272 of the 303 patients had undergone repeated imaging. In these 272 patients, 21 causative aneurysms were detected. In the rest of 251 patients with non-aneurysm, we performed outcome analysis (figure 1). After a total follow-up time of 1265.83 patient-years, poor functional outcome occurred in 18 (7.2%) patients with a median follow-up time of 60.0 months, including a case in PAN-SAH group and 17 cases in NPAN-SAH group, respectively. The mean durations of follow-up for the patients with poor outcomes and non-poor outcomes were 60.0±16.5 and 61.8±15.4 months (p=0.635), respectively. The IR for poor functional outcome was 1.422 (95% CI 0.896 to 2.257) per 100 person-years (figure 2A). The univariate Cox analysis found that NPAN-SAH, HH grades 3–5 and GCS 3–12 had p values <0.1. In the multivariate Cox analysis, NPAN-SAH (HR 8.792 (95% CI 1.162 to 66.528); p=0.035, table 5; figure 2B) and GCS 3–12 (HR 6.090 (95% CI 1.744 to 21.258); p=0.005, table 5; figure 2C) were associated with a high rate of poor functional outcome of anSAH.

Furthermore, the patients were also divided into three groups according to two risk factors (NPAN-SAH and GCS 3–12). The low-risk group had no risk factors, the intermediate-risk group had only one risk factor, and the high-risk group had two risk factors. The cumulative 5-year IR for poor outcome of anSAH per 100 person-years in the low-risk group and intermediate-risk group were 1.875 (95% CI 0.264 to 13.310) and 10.744 (95% CI 4.630 to 27.573), respectively; however, the cumulative 5-year IR for poor outcome of anSAH per 100 person-years in the high-risk group was 75.302 (95% CI 10.607 to 534.573, table 6).

DISCUSSION

Approximately 10%–20% of patients with non-traumatic SAH have no structural cause for bleeding on initial DSA. According to 2019 special report and 2023 guidelines for the management of patients with aneurysmal SAH, DSA should be repeated days to weeks later regardless of negative CTA results, because small aneurysms or other occult vascular lesions may not be fully defined on CTA imaging owing to limitations in spatial resolution.[5 12] The detection rate of causative aneurysm is 10%.[10 11 15 28] However, there is no consensus on risk factors associated with the detection of causative aneurysms in these patients. Meanwhile, the patients with anSAH were considered to have a better outcome, but a proportion of the patients still had a poor functional outcome.[2 4 9 29] Thus, the risk factors associated with poor functional outcome in anSAH patients need to be investigated. In our current study, patients with NPAN-SAH and mFS 3–4 will be monitored for the development of delayed causative aneurysm; meanwhile, in non-aneurysm patients, NPAN-SAH and initial functional impairment are associated with long-term poor outcome.

At present, there is no clear consensus regarding the need for repeated imaging in patients with anSAH. According to the 2019 special report for the management of patients with SAH, patients with PAN-SAH and initial negative CTA, DSA or MRA were suggested to proceed with no further imaging investigation,[12] whereas several studies showed that even in PAN-SAH group, some causative vascular lesions were detected by repeated imaging during follow-up.[30–35] Moreover, repeated DSA or CTA may be needed in cases of PAN-SAH with haematoma and vasospasm in which there is significant suspicion of occult vascular lesions.[26] In our current study, according to initial CT characteristics, NPAN-SAH and mFS 3–4 were associated with a high rate of aneurysm detection. Moreover, based on risk factor stratification, the aneurysm detection rate in the high-risk group (20.370 per 100 person-years) was significantly higher than that in the low-risk group (1.250 per 100 person-years) and intermediate-risk group (6.522 per 100 person-years). Therefore, we suggest that repeated imaging is strongly advised in the intermediate-risk group and high-risk group. This study may assist in the clinical determination of whether to perform repeated imaging.

To date, there is still no consensus regarding risk factors for poor functional outcome of anSAH because of the limited patient data and short follow-up duration. A study has shown that the functional outcome in PAN-SAH patients was not different from that in NPAN-SAH patients,[9] whereas some studies have demonstrated that NPAN-SAH patients had a worse outcome than PAN-SAH patients.[4 25 36 37] In our current study, we consecutively enrolled patients with anSAH. After a median follow-up

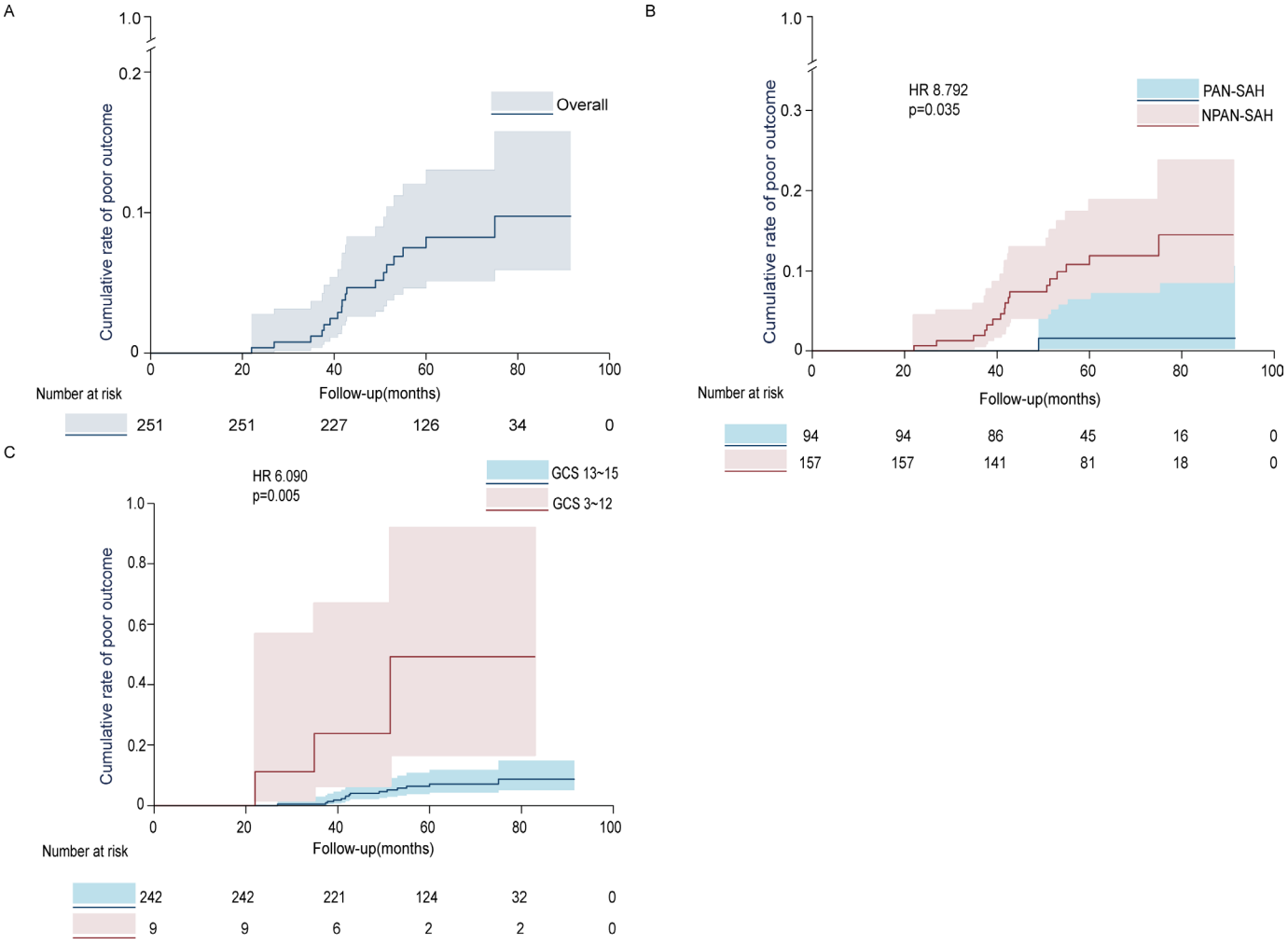

Figure 2 Kaplan-Meier curves showing the poor outcome rates in different subgroups. (A) Kaplan-Meier curve analysis showing the overall poor outcome rates; (B) Kaplan-Meier curve analysis (log-rank test) showing the different cumulative poor outcome rates between NPAN-SAH and PAN-SAH; (C) Kaplan-Meier curve analysis (log-rank test) showing the different cumulative poor outcome rates between GCS 13–15 and GCS 3–12. NPAN-SAH, non-perimesencephalic angiogram-negative SAH; PAN-SAH, perimesencephalic angiogram-negative subarachnoid haemorrhage.

time of 60.0 months, we found that a lower GCS and NPAN-SAH were independent risk factors associated with poor functional outcome in anSAH. Furthermore, based on concomitant risk factor stratification, the cumulative poor functional outcome rate in the high-risk group (NPAN-SAH and GCS 3–12) was 75.302 per 100 person-years; therefore, we suggest that neurologists should pay more attention to high-risk patients.

Limitations

The limitations of this study need to be noted. First, this study was a single-centre retrospective design study, which may be limited by potential bias, but the data were collected systematically with prospective follow-up. Further randomised and prospective studies are still needed to mitigate this selection bias. Second, in our study, only 44.1% of the patients underwent at least one repeated DSA, which may be due to the concern about neurological complications caused by invasive DSA.[16–18] Therefore, 89.0% of the patients underwent repeated CTA. Previous studies showed that CTA is a reliable replacement for DSA because of its high sensitivity and specificity.[12 34 35] Our study showed that although the aneurysm detection rate in DSA group was higher than CTA group, there was no significantly statistical difference between two groups, which might be attributed to small sample size with only 21 aneurysms. Whether CTA is a reliable replacement for DSA requires further larger cohort studies. Third, the rate of high-risk patients in DSA group (28.3%, 34/120) was higher than that in CTA group (18.2 %, 44/242), and the aneurysm detection rate in DSA group (11.7%, 14/120) was higher than CTA group (6.6%, 16/242). Whether certain groups preferentially received a particular follow-up imaging modality needs further larger cohort studies. Finally, vasospasm can lead to cerebral ischemia with significant neurological deficits and/or death.[23 24 38] Our study indicated that cerebral vasospasm was not common in non-aneurysm SAH patients (2.4%), which was consistent with a recent

Table 5 Univariate and multivariate Cox analyses of risk factors associated with poor outcome†

		Univariate analysis		Multivariate analysis	
Variable	n	HR (95% CI)	P value	HR (95% CI)	P value
NPAN-SAH	17	9.931 (1.321 to 74.670)	0.026*	8.792 (1.162 to 66.528)	0.035*
Age >60 years	9	0.855 (0.305 to 2.401)	0.767		
Female	12	1.059 (0.418 to 2.684)	0.904		
Smoker	3	1.211 (0.431 to 3.402)	0.716		
Hypertension	9	0.809 (0.303 to 2.155)	0.671		
Hyperlipidaemia	4	0.467 (0.166 to 1.311)	0.148		
Diabetes mellitus	4	0.753 (0.173 to 3.276)	0.705		
Coronary heart disease	3	2.028 (0.466 to 8.832)	0.346		
Ischaemic cerebrovascular disease	2	2.994 (0.685 to 13.084)	0.145		
Antithrombotic drugs	1	0.802 (0.107 to 6.033)	0.830		
HH grades 1–2‡	16				
HH grades 3–5	2	2.879 (0.830 to 9.985)	0.096		
mFS 1–2‡	3				
mFS 3–4	15	2.207 (0.823 to 5.917)	0.116		
GCS 13–15‡	14				
GCS 3–12	4	8.218 (2.362 to 28.590)	0.001*	6.090 (1.744 to 21.258)	0.005*
Hydrocephalus	2	2.229 (0.794 to 6.254)	0.128		
Pulmonary infection	2	0.924 (0.123 to 6.947)	0.939		
Deep venous thrombosis	1	3.258 (0.747 to 14.216)	0.116		

*p<0.05.
†Thirty-one patients without repeated imaging and 21 patients with aneurysm detection were excluded for the Cox analysis.
‡Reference.
GCS, Glasgow Coma Score; HH grade, Hunt-Hess grade; mFS, modified Fisher Scale; n, number of events; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid haemorrhage.

Table 6 Annual and 5-year incidence rates of poor outcome in the different groups

			Cumulative IR (95% CI)
Group	n/N	Annual IR (95% CI)	5 years
Low risk*	1/92	0.215 (0.030 to 1.527)	1.875 (0.264 to 13.310)
Intermediate risk*	14/152	1.817 (1.076 to 3.067)	10.744 (4.630 to 27.573)
High risk*	3/7	9.883 (3.187 to 30.643)	75.302 (10.607 to 534.573)
Overall	18/251	1.422 (0.896 to 2.257)	8.431 (3.352 to 24.405)

*The patients were stratified into three groups according to the presence of two risk factors (NPAN-SAH and GCS 3–12): the low-risk group is without any of the two risk factors, intermediate-risk group only has one risk factor, and high-risk group has >1 risk factor.
GCS, Glasgow Coma Score; IR, incidence rate; N, total number in the corresponding group; n, number of events; NPAN-SAH, non-perimesencephalic angiogram-negative subarachnoid haemorrhage.

study reported that cerebral vasospasm occurred in 4.8% of the non-aneurysm SAH patients.[4] Furthermore, univariate Cox analyses in our study showed that vasospasm was not associated with poor functional outcome of anSAH. The few cases of vasospasm may limit the statistical power and further larger cohort studies were needed to validate the association of vasospasm and outcome.

Conclusions

Even in anSAH confirmed by initial DSA, patients with NPAN-SAH and mFS 3–4 will be monitored for causative aneurysm detection, which strongly suggests that repeated imaging is needed in this group; meanwhile, in the non-aneurysm patients, NPAN-SAH and lower GCS are associated with long-term poor prognosis, warranting intensive attention in this group. Further larger and prospective studies are needed to validate our findings.

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Ethics approval This study involves human participants and was approved by Institutional Review Board of Tiantan Hospital (approval number KY2017-035-02). Participants gave informed consent to participate in the study before taking part.

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ORCID iD

Yong Cao http://orcid.org/0000-0002-8289-1120

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