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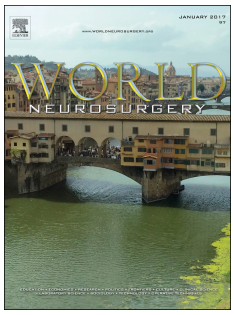

The Prevalence of Cerebral Vascular Abnormalities Detected in Various Diagnostic Subgroups of Spontaneous Subarachnoid Hemorrhage in the Modern Era

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The Prevalence of Cerebral Vascular Abnormalities Detected in Various Diagnostic Subgroups of Spontaneous Subarachnoid Hemorrhage in the Modern Era

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Abstract

Objective: To determine the prevalence of cerebral vascular abnormalities in various diagnostic subgroups of spontaneous subarachnoid hemorrhage (SAH) in a regional neurosurgical center in the modern era.

Methods: Prospective data collection of 609 consecutive patients with spontaneous SAH in a 3-year period (August 2010 to August 2013) was carried out. Patients were divided into three diagnostic subgroups: computed tomography (CT) positive for SAH; CT negative but positive cerebrospinal fluid (CSF) examination by spectrophotometry for SAH; CT negative for SAH and inconclusive CSF examination. All patients fit for intervention then underwent computed tomography angiography (CTA), with or without digital subtraction angiography (DSA) to identify vascular abnormalities for subsequent treatment.

Results: Of the 609 identified patients, 554 were fit for further investigation and consideration of further intervention. 514 patients had confirmed SAH. 61.5% of patients were female. The mean age was 54.0 years. 390 patients (75.9%) showed vascular abnormalities on angiography. 438 patients (85.2%) with confirmed SAH were diagnosed on CT scan (Group 1) and 81.1% had detectable vascular abnormalities. 18.9% of patients with a positive CT scan had no identifiable cause of SAH. 76 patients (14.8%) with confirmed SAH had negative CT but positive LP (Group 2) and 46.1% of patients in this group had vascular abnormalities. 3 patients with inconclusive CSF examination had lesions requiring treatment. The median length of hospital stay in Group 1 patients was longer than the median length of hospital stay in Group 2 patients.

Conclusions: The frequency of vascular abnormalities in spontaneous SAH is lower than the traditionally quoted figure, which would have diagnostic and prognostic implications for patient management.

Introduction

Spontaneous subarachnoid hemorrhage (SAH), makes up 2-9% of all strokes.[1] Historical studies from the 1980s and 1990s showed that 80-85% of spontaneous SAH were secondary to ruptured aneurysm;[2-5] with a mortality of 15% prior to hospitalisation.[2] The in-hospital morbidity and mortality is usually due to re-bleeds and delayed ischemic neurological deficits (DIND). The mortality or morbidity from a re-bleed is 80%.[6] The rate of DIND is 32%.[7] Other rarer causes of SAH include arterial dissection, cerebral arteriovenous malformation (AVM), and dural arteriovenous fistula (dAVF).[8]

In 10-15% of patients with SAH no vascular abnormalities are shown on angiographic studies and this group is commonly termed angio-negative SAH.[4, 9-12] Compared to patients with aneurysmal SAH, patients with angio-negative SAH generally have good outcome.[13-15] Patients with angio-negative SAH have lower rates of DIND compared to patients with aneurysmal SAH, [12] and a lower rate of recurrent hemorrhage.[16]

SAH can be diagnosed using computed tomography (CT) or cerebrospinal fluid (CSF) examination. Modern CT scanners have a sensitivity of 100% in detecting SAH within 6 hours after ictus, when the scan is interpreted by an experienced neuroradiologist.[17] If CT brain is negative for SAH, CSF examination is required to detect SAH.[18] To diagnose SAH via a CSF sample, an oxyhemoglobin (oxyHb) peak with a bilirubin shoulder must be detected in the CSF sample by spectrophotometry analysis. Bilirubin is derived from the degradation of oxyHb,[19] which only occurs in vivo and not in vitro. CSF examination would be inconclusive when spectrophotometric detection of bilirubin in the CSF is impaired by large amounts of oxyHb, often as the result of fresh blood in the CSF.[20, 21]

With increasing sensitivity of multi-detector CT scanners in detecting hemorrhage, and the increasing use of spectrophotometry to detect bilirubin in CSF, we hypothesized that more cases of spontaneous SAH are detected using these techniques. We want to determine the

prevalence of vascular abnormalities identified in patients with spontaneous SAH in our center and compare it to historical data.

Methods

Study design

The Institute of Neurological Sciences, Glasgow, UK is a tertiary referral center for neurosurgery with a catchment population of about 2.6 million. The data was prospectively collected between Aug 2010 and 2013 from consecutive patients referred to the neurosurgical service with SAH, and retrospectively analyzed. The patients who were referred but not transferred for investigation or treatment were identified, usually due to a poor World Federation of Neurosurgical Societies (WFNS) grade.

Study Population

All patients with suspected SAH underwent CT scan as the first line investigation. CT negative patients underwent an LP to obtain CSF to test for bilirubin by spectrophotometry. An inconclusive CSF examination meant that the sample was non-diagnostic and the patient required further investigation to exclude SAH. Patients were stratified into 3 subgroups (Table 1). We grouped patients into Group 1, patients with SAH diagnosed by CT scan; Group 2, patients with SAH diagnosed by positive CSF examination for SAH; Group 3, patients with unconfirmed SAH due to negative CT scan and inconclusive CSF examination (oxyHb masking bilirubin peak).

Imaging

All initial CT imaging was performed at the referring hospitals. All patients accepted for further intervention underwent CT angiography (CTA) with digital three-dimensional reconstruction or CTA followed by four-vessel digital subtraction angiography (DSA). CTA was performed on 64 slice CT scanner. CTA scan parameters were: tube voltage 120kV, tube current 200mAs, CT dose index 38.7, slice thickness 0.625mm and anatomical coverage from

carina to vertex. DSA was performed on a biplane angiography unit with or without 3D reconstruction.

Spectrophotometry

The presence of an oxyhemoglobin absorption peak at 413-415 nm and a bilirubin shoulder at 450-460 nm is diagnostic for SAH.[22] A CSF sample was inconclusive for SAH if oxyhemoglobin was present in a high enough concentration to impair the detection of the bilirubin shoulder.

Statistical analysis

Data were analyzed using the statistical package of the social sciences (SPSS Version 21, IBM). Results were expressed as proportions (%). Fisher's exact test, and Student's t-test were used to compare parametric variables. Mann-Whitney test and Kruskal-Wallis test were used to analyze non-parametric variables. One way analysis of variance (ANOVA) was used to compare means across different groups. Chi squared test of association was used to analyze categorical variables. P values of <0.05 were considered statistically significant.

Results

During the study period 609 patients were referred to neurosurgery with a confirmed or suspected diagnosis of SAH. 554 patients were accepted for transfer and further investigation. 55 patients were not transferred because, patients had either died or were in poor clinical condition at presentation and deemed not fit for intervention following discussion with local doctors and family. Figure 1 describes the flow of patients stratified into subgroups as shown in Table 1. 514 patients had confirmed SAH; 438 patients (85.2%) had SAH diagnosed on CT scan (Group 1). 76 patients (14.8%) had SAH diagnosed on CSF examination due to a negative CT (Group 2). 40 patients with unconfirmed SAH (Group 3) due to negative CT scan and inconclusive CSF examination.

Patients with confirmed spontaneous SAH (Group 1 and Group 2 patients)

The demographic of the study population is in Table 2. The mean age of patients with confirmed SAH was 54.0±12.9 years, 61.5% of patients were female. 390 patients (75.9%) with confirmed SAH showed one or more vascular abnormality. Of these 390 patients, 373 patients (95.6%) showed one or more aneurysms. The rate of multiple aneurysms was 19.8% with 74 patients showing more than one aneurysm. The anatomical location of the aneurysms is shown in Table 3. Other vascular abnormalities were 12 AVMs (3 AVMs were associated with aneurysms), 3 vertebral dissections, 1 reversible cerebral vasoconstriction syndrome (RCVS), 1 dural arteriovenous fistula (dAVF), 1 moya-moya disease, 1 cerebral venous sinus thrombosis, 1 vertebral artery-basilar artery (VA-BA) fenestration. No vascular abnormalities were detected in 124 patients (24.1%) with confirmed SAH. In this cohort, all patients with negative CTA underwent DSA and 7 patients (1.4%) were found to have vascular abnormalities not described in the CTA. For patients with confirmed SAH, the median length of hospital stay was 13 days.

Group 1

438 patients (85.2% of patients with confirmed SAH) had a diagnosis of SAH with CT scan. The mean age of patients with SAH confirmed with CT scan was 54.7±12.7 years, 63.9% of patients were female. 76.5% of patients have good grade SAH (WFNS I-II). The median time from ictus to investigation was 0 days (interquartile range (IR) 0 to 1 day), with 69.5% (304/438) of patients admitted for investigations within 24 hours of ictus. In this cohort, only a small subset of patients (7.5%, 33/438) were investigated over 72 hours of ictus. The rate of vascular abnormality detection was 81.1% (355 patients) in Group 1 patients (Table 4). Of patients with vascular abnormalities, 340 patients (95.8%) have one or more aneurysms. 67 patients (19.7%) had multiple aneurysms. Other vascular abnormalities were, 8 AVMs (1 AVM associated with aneurysms), 3 vertebral dissections, 1 reversible cerebral vasoconstriction syndrome, 1 dAVF, 1 moya moya disease, 1 CVST, 1 VA-BA fenestration. After a first negative CTA or inconclusive CTA, 4 patients (1.0%) were found to have vascular abnormalities on DSA not described in the previous CTA; which included bilateral paraophthalmic aneurysms; dAVF; RCVS; anterior communicating artery aneurysm. In Group 1 patients that have cerebral vascular abnormalities, 85.0% of patients had

endovascular treatment to secure the ruptured aneurysms or vascular lesions, and 10.6% underwent surgical clipping. 1.5% of patients received no surgical intervention due to inoperable aneurysms or death after admission. (Table 5). The median length of hospital stay for Group 1 patients was 14 days (IR 10 to 24 days). At discharge, 78.0% of patients had good clinical outcome (modified Rankin Scale mRS 0-2).

Group 2

76 patients (14.8% of patients with confirmed SAH) had a negative CT scan and a positive CSF examination. The mean age of Group 2 patients was 49.9±13.0 years, 47.4% of patients were female. 98.6% of patients have good grade SAH (WFNS I-II). The median time from ictus to investigation was 3 days (IR 1 to 6 days), with only 15.8% (12/76) of patients investigated within 24 hours of ictus. 46.1% (35/76) of patients presented late and was investigated over 72 hours of ictus. The incidence of vascular abnormalities in Group 2 patients was 46.1% (35 patients). 33 patients (94.3%) had one or more aneurysms. 26 patients (78.8%) had multiple aneurysms. 4 patients had AVMs (2 patients had AVM associated with aneurysms). The difference in the rate of vascular abnormality between Group 1 and Group 2 patients was statistically significant ($p<0.0001$ on two-tailed Fisher's Exact Test). After a first negative CTA or inconclusive CTA, 3 patients (3.9%) were found to have vascular abnormalities not described in the previous CTA. The vascular abnormalities identified by DSA were 2 patients with micro-AVM and 1 patient with small left ICA aneurysm. 77.14% had endovascular treatment to secure the ruptured aneurysms or vascular lesions, and 11.4% underwent surgical clipping. The median length of hospital stay for Group 2 patients was 7 days (IR 4 to 11 days). 95.9% of Group 2 patients had good outcome at discharge (mRS 0-2).

Rebleeding in Group 1 and Group 2 patients

In total 30 patients (5.8%) had rebleeding. 29 patients (6.6%) in Group 1 experienced at least one rebleeding episode. In Group 1, 27 patients (6.2%) experienced one rebleeding episode and 2 patients (0.5%) experienced two rebleeding episodes. 1 patient (1.3%) in Group 2 experienced one rebleed. 26 of the 30 patients that experienced rebleeding received treatment

to secure the ruptured aneurysms, and the median time from ictus to treatment was 3 days (IR 1 to 6 days). The remaining 4 patients died prior to receiving any intervention.

Group 3

There were 40 patients with a negative CT scan and an inconclusive CSF examination. The mean age of Group 3 patients was 44.1±12.5 years. 55.0% of patients were female. The median time from ictus to investigation was 3 days (IR 1 to 5 days), with 17.5% (7/40) of patients investigated within 24 hours of ictus. 42.5% (17/40) of patients presented late and was investigated over 72 hours of ictus. 3 patients had aneurysms detected on CTA. 1 patient underwent surgical clipping of the aneurysm and 2 patients were treated using endovascular techniques. 37 patients had no identifiable vascular abnormalities, and 11 patients had DSA after a first negative or inconclusive CTA and no new vascular abnormality was found. The median length of hospital stay was 4 days in Group 3 patients (IR 1 to 7 days). No patients were readmitted within 6 months of discharge to imply missed vascular anomalies. The median length of hospital stay across the 3 groups were all statistically significant (P=0.000). 100% of Group 3 patients had good mRS at discharge and the proportion of patients with good mRS across the 3 groups were significantly different (P=0.000).

Discussion

The overall rate of identification of vascular abnormalities in patients with confirmed SAH (Groups 1 and 2) in our study is 75.9% (Figure 2). This is lower than the traditionally quoted value of 80-85%.[3] Importantly, 24.1% of patients in our study had SAH with no detectable vascular abnormalities. This is higher than the 10-15% that is traditionally quoted as the proportion of angio-negative SAH.[4, 9-11, 23] This implies that 1 in 4 patients with confirmed SAH could potentially have an excellent prognosis compared to the previously held proportion of 1 in 8 patients. We postulate that the higher proportion of angio–negative SAH in our study is due to several factors, including new generation CT scanners better at detecting low or small blood load SAH. The usage of spectrophotometry instead of xanthochromia might translate into higher sensitivity for detecting SAH[24], furthermore raised CSF bilirubin is not specific for SAH and can be raised in other medical conditions including

meningitis.[25]

If we combine confirmed SAH patients and Group 3 patients the rate of identification of vascular abnormalities is even lower at 70.9%.

The timing from ictus to hospital presentation, and therefore medical investigations for SAH of the various subgroups are different. For group 1 patients, 70% of patients were admitted within 24 hours of ictus, while only 16% and 18% of group 2 and group 3 respectively presented early. Patients in Group 2 had a significantly lower rate (46.1%) of identification of cerebral vascular abnormalities compared to patients in Group 1 (81.1%). Two recent studies from the last 5 years by Chalouhi et al.[26] and Bakker et al.[27], also showed that the rate of vascular abnormality detection for Group 2 patients was 45.7% and 43% respectively. Group 2 patients had a higher proportion of WFNS I-II SAH; required less surgical treatment and had better mRS at discharge compared to Group 1 patients ($P<0.05$). We showed here that patients with SAH confirmed by positive CSF examination (Group 2 patients) had better clinical outcome than patients with SAH confirmed by CT scan.

Questions remained regarding the pickup rate of vascular abnormality after a negative CTA. The common practice is to perform a DSA on patients with negative CTA. Our study found that the pickup rate of vascular abnormalities is low on DSA after a negative CTA. 1.4% of patients with confirmed SAH and negative CTA had positive findings on subsequent DSA, and no further yield was detected for group 3 patients. At first glance, it might appear that group 2 patients had a higher rate (3.9%) of vascular anomalies that were not detected on CTA compared to group 1 (1%), however if we look at the absolute number, 4 patients from group 1 compared to 3 patients in group 2 had subsequent vascular anomalies detected after DSA. Such number is so small, and when calculating the percentages, due to the denominator, despite the differences, this finding is not statistically significant.

19.8% of patients with aneurysms had multiple intracranial aneurysms, and this agreed with multiple large studies including ISAT and BRAT.[28],[29] In this study, most aneurysms were in the anterior circulation and this is in keeping with the published literature.[28,29] Treatment

strategy may differ based on the configuration and location of the aneurysm, and the clinical presentation.[29-32]

In patients with unconfirmed SAH (Group 3), 7% of patients were found to have vascular abnormality after CTA, with no further yield despite DSA. Prior to 2010, we performed delayed DSA and MRI after negative investigations (CTA +/- DSA) for group 3 patients, but departmental audits showed that no further vascular anomalies were picked up despite that practice. Therefore, we no longer subject our group 3 patients to the delayed invasive DSA investigations, but we follow them up clinically. None of the group 3 patients were readmitted within 6 months of discharge to imply missed vascular anomalies.

Group 3 patients do better than Group 1 and Group 2 patients. This is reflected in the statistically significant lower median length of hospital stay and a higher proportion of patients with good mRS at discharge. However we are aware of the limitation with the small sample size in this group to draw any definitive conclusion, although the rate of vascular abnormality might be just slightly higher to the incidence of cerebral aneurysm in the background population.[33] Potentially a group of patients with suspected SAH with a negative CTA can be discharged sooner without the delay of waiting for a DSA, thereby reducing hospital stay. A good history and a careful balancing of the risk and benefits of further investigation for patients with inconclusive LP is essential.

Despite the study from a single regional neurosurgical center, the large study sample size of 609 patients prospectively collected over a 3-year period, we believe would ensure the validity of our results. 55 patients were excluded from analysis and investigation due to poor grade SAH or death and were not transferred to the department. Even if we assume that all these patients have underlying cerebral aneurysms, the rate of vascular anomalies for patients with confirmed SAH would be 78.2% (445/569), which is a difference of 2.3% from the 75.9% (390/514) quoted in our paper and would not alter our conclusion.

Conclusions

This contemporary study in a large UK population challenges the historic studies with regards to the frequency of identification of vascular abnormalities following spontaneous SAH. Our data shows that the frequency of identification of vascular abnormalities is lower when compared to historical data from the 1980s and 1990s, which would have diagnostic and prognostic implications for patient management. Furthermore, patients with SAH diagnosed by CT are more likely to have a lesion requiring treatment than those diagnosed by CSF examination.

Competing interests

Conflicts of interest: none

Author's contribution

MT, NS, JSG were responsible for the conception and design of the study. MT and MYC were responsible for the acquisition of data. MT, MYC, SCM, IP were responsible for the analysis and interpretation of data. All authors were involved in the drafting of the article or revising it for important intellectual content. All authors have given final approval of the version to be submitted.

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Appendix

Figure 1: Flowchart showing the study population

Figure 2: Rate of vascular abnormalities in the different diagnostic subgroups.

Table 1: Stratification of patient subgroups.

Table 2: Comparative table of the patient demographics, admission grade, treatment, and outcome for the 3 groups of patients. Age (mean±SD) and gender distribution of the study population. * statistically significant difference ($P<0.05$)

Table 3. Overall frequency and proportion of anatomical sites of aneurysms

Table 4: Incidence of vascular abnormality in various diagnostic subgroups of SAH

Group	Criteria
1	Confirmed SAH. CT scan positive for SAH.
2	Confirmed SAH. CT scan negative for SAH, bilirubin in CSF.
3	Unconfirmed SAH. CT scan negative for SAH, inconclusive CSF result.

Table 1: Stratification of patient subgroups.

	Confirmed SAH	Group 1	Group 2	Group 3	P values
Number of Patients	514	438	76	40	
Mean Age (years)	54.0±12.9	54.7±12.7*	49.9±13.0*	44.1±12.5*	0.000
Females (%)	61.5	63.9*	47.4*	55.0*	0.017
WFNS Admission Grade (%)					
WFNS I-II	76.1	76.5*	98.6*	NA	0.000
WFNS III-IV	23.9	23.5	1.4	NA	
Median hospital stay (Days)	13	14*	7*	4*	0.000
mRS at discharge (%)					
mRS 0-2 (%)	80.6	78.0*	95.9*	100*	0.000
mRS 3-6 (%)	19.4	22.0	4.1	0	

Table 2: Comparative table of the patient demographics, admission grade, treatment, and outcome for the 3 groups of patients. Age (mean±SD) and gender distribution of the study population. * statistically significant difference (P<0.05)

Aneurysm	Proportion (%)
ACA	5.2
ACom	24.9
ICA	15.7
MCA	20.7
PCom	21.1
Anterior	87.6
PCA	1.0
Basilar	5.0
SCA	2.2
PICA	3.4
AICA	0.4
Vertebral	0.4
Posterior	12.4

Table 3. Overall frequency and proportion of anatomical sites of aneurysms

	Confirmed SAH	Group 1	Group 2	Group 3	P values
Rate of vascular abnormalities	75.9%	81.1%	46.1%	7.5%	0.0001

Table 4: Incidence of vascular abnormality in various diagnostic subgroups of SAH

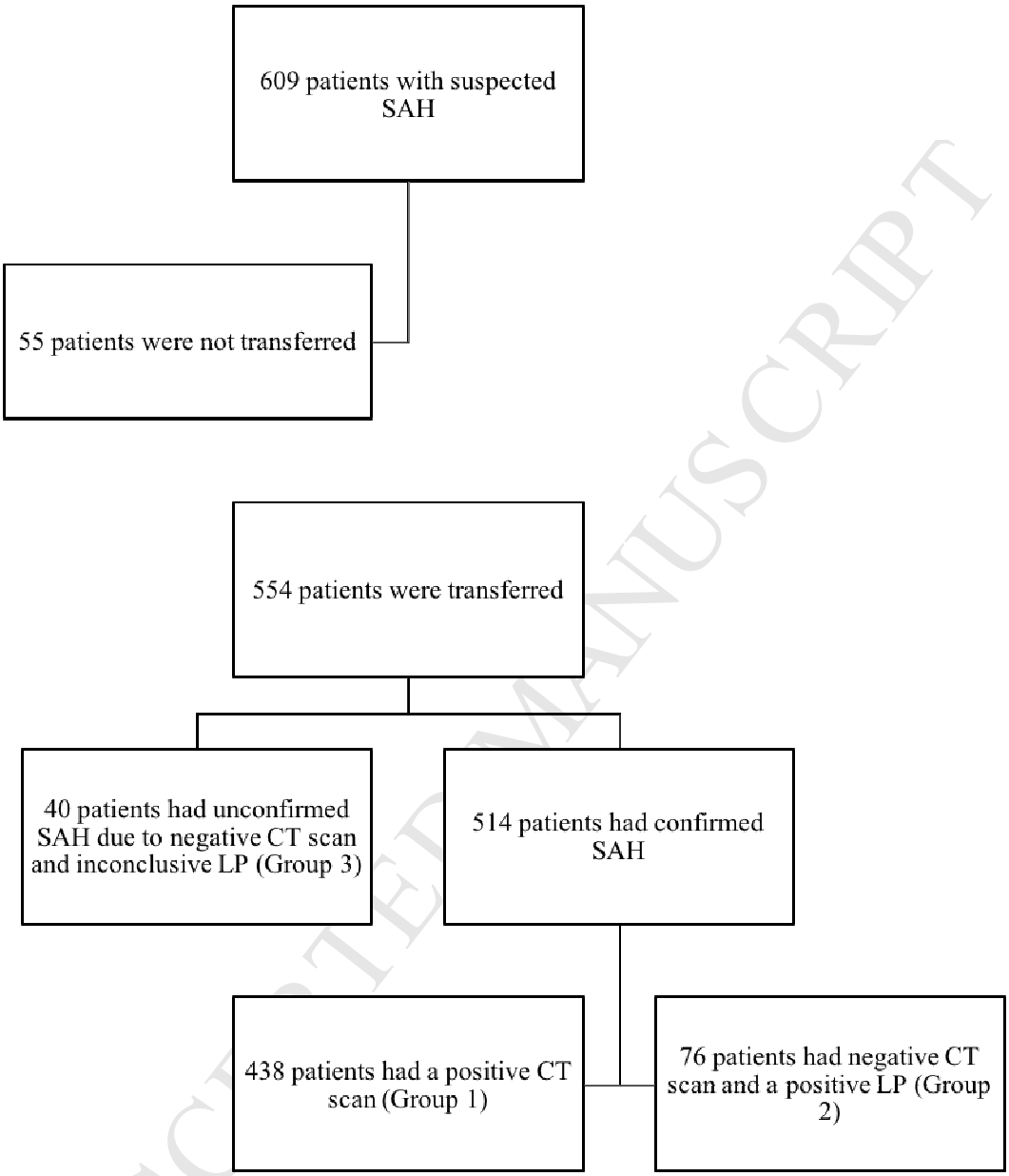

Figure 1: Flowchart showing the study population

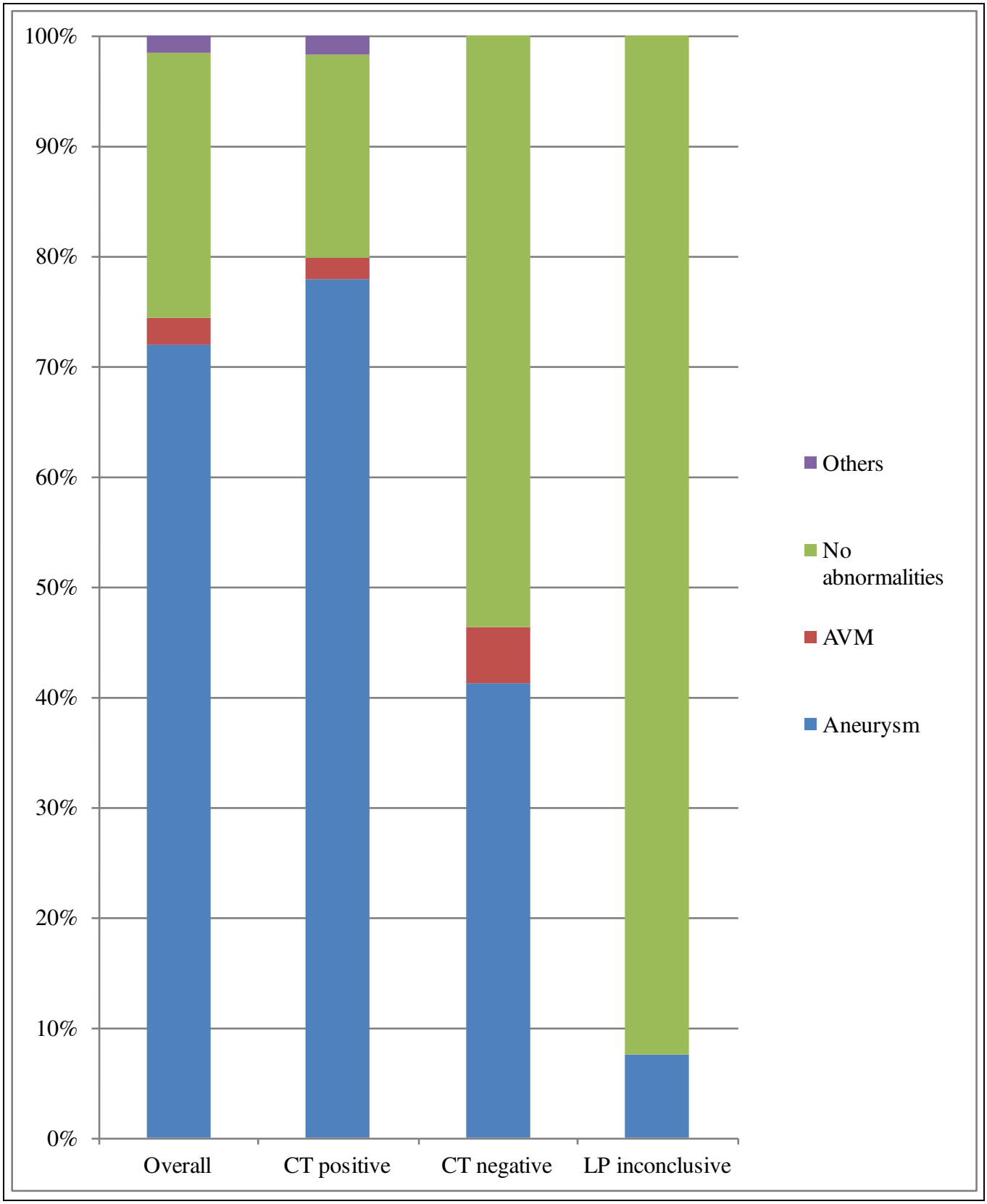

Figure 2: Rate of vascular abnormalities in the different diagnostic subgroups.

Highlights

- The rate of intracranial vascular abnormality in patients with confirmed SAH in the modern era is lower than previous studies from the 1980s and 1990s.
- This finding could have diagnostic and prognostic implications for patients' management.
- Patients with subarachnoid haemorrhage diagnosed by CT are more likely to have an underlying vascular lesion than those diagnosed by LP.

Disclosure

I, Isaac Phang, report no conflict of interest.

The authors alone are responsible for the content and writing of the paper.

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Abbreviation list:

ACA – Anterior Cerebral Artery

AComA – Anterior Communicating Artery

AICA – Anterior Inferior Cerebellar Artery

AVM – Arteriovenous malformation

BRAT – Barrow Ruptured Aneurysm Trial

CSF – Cerebrospinal Fluid

CT – Computed Tomography

CTA – CT Angiography

dAVF – dural Arteriovenous Fistula

DNID – Delayed Neurological Ischemic Disorder

DSA – Digital Subtraction Angiography

ICA – Internal Carotid Artery

INS – Institute of Neurological Sciences

ISAT – International Subarachnoid Aneurysm Trial

LP – Lumbar Puncture

MCA – Middle Cerebral Artery

oxyHb – oxyhemoglobin

PCA – Posterior Cerebral Artery

PComA – Posterior Communicating Artery

PICA – Posterior Inferior Cerebellar Artery

RCVS – Reversible Cerebral Vasoconstriction Syndrome

SAH - Subarachnoid Hemorrhage

SCA – Superior Cerebellar Artery

SPSS – Statistical Package of the Social Sciences

VA-BA – Vertebral Artery-Basilar Artery

WFNS – World Federation of Neurosurgical Societies