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# Subarachnoid haemorrhage in the emergency department (SHED): a prospective observational multicentre cohort study

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## Abstract

### Background

People presenting to the Emergency Department (ED) with acute severe headache often undergo investigation to exclude subarachnoid haemorrhage (SAH). International guidelines propose that brain imaging within six hours of headache onset can exclude SAH, in isolation. The safety of this approach is debated. We sought to externally validate this strategy and evaluate the test characteristics of CT-brain beyond six hours.

### Methods

A prospective, multi-centre, observational cohort study of consecutive adult patients with non-traumatic acute headache presenting to the ED within a United Kingdom National Health Service setting. Investigation, diagnosis and management of SAH were all performed within routine practice. All participants were followed for 28 days using medical records and direct contact as necessary. Uncertain diagnoses were independently adjudicated.

### Results

Between March 2020 and February 2023, 3663 eligible patients were enrolled from 88 EDs (mean age 45.8 (SD 16.6), 64.1% female). 3268 patients (89.2%) underwent CT-brain imaging. There were 237 cases of confirmed SAH, a prevalence of 6.5%. CT within six hours of headache onset (n=772) had a sensitivity of 97% (95% CI 92.5%-99.2%) for the diagnosis of SAH and a negative predictive value of 99.6% (95% CI 98.9%-99.9%). The post-test probability after a negative CT within 6 hours was 0.5% (95% CI 0.2%-1.3%). The negative likelihood ratio was 0.03 (95% CI 0.01-0.08). CT within 24 hours of headache onset (n=2008) had a sensitivity of 94.6% (95% CI 91.0%-97.0%). Post-test probability for SAH was consistently less than 1%. For *aneurysmal* SAH post-test probability was 0.1% (95% CI 0.0%-0.4%) if the CT was performed within 24 hours of headache onset.

### Conclusion

Our data suggests a very low likelihood of SAH following a negative CT-brain scan performed early after headache onset. These results can inform shared decision making on the risks and benefits of further investigation to exclude SAH, in ED patients with acute headache.

| **What is already known on this topic** |
| --- |
| • CT-brain has been reported as highly sensitive for the exclusion of SAH if performed within six hours of acute headache onset. |
| **What this study adds** |
| • In our validation cohort, CT-brain was highly sensitive for the diagnosis of SAH when performed within six hours of headache onset.<br>• Up to 24 hours, sensitivity of CT remained high and the majority of SAH cases 'missed' by initial CT imaging were non-aneurysmal. All non-aneurysmal SAH were conservatively managed without neurosurgical intervention.<br>• Our estimates of post-test probability for SAH after a negative CT-brain within 24 hours of headache onset were consistently less than 1%.<br>• Our estimates for post-test probability for *aneurysmal* SAH after a negative CT-brain within 24h were 0.1% (95% CI 0.0%-0.4%). |
| **How this study might affect research, practice, or policy** |
| • These data will inform clinicians and patients about the risks and benefits of further investigation for SAH after a negative CT-brain.<br>• This study highlights the importance of distinguishing between aneurysmal and non-aneurysmal SAH in diagnostic studies.<br>• Our results suggest a low post-test probability using CT-brain up to 24 hours from headache onset, which warrants further study. |

## Introduction

Acute headache accounts for between 1–2% of all Emergency Department (ED) attendances, estimated at >350,000 United Kingdom (UK) patients per year. [1] Serious intracranial pathology is found in approximately 10% of such patients. [2] Subarachnoid haemorrhage (SAH) is the most frequently identified serious pathology. [3]

Subjective clinical headache features and examination findings are unreliable discriminators of pathology in headache. Emergency clinicians therefore pursue high rates of invasive investigation to definitively exclude SAH. [4] However, incidental findings on CT imaging can cause significant anxiety for patients and lumbar puncture (LP) can prolong hospital stay. [5]

To address these challenges, the Ottawa SAH Clinical Decision Rule (CDR) was designed to rule out SAH without neuroimaging. A 2020 validation study reported a sensitivity of 100% (95% CI 98.1%-100%). However, the CDR demonstrates poor specificity (12.7% (95% CI 11.7-13.9)) and is yet to be validated in a European population. [6,7]

The majority of patients with suspected SAH still undergo plain CT-brain imaging. If this is performed early after headache onset, diagnostic performance is high. [8–10] Two systematic reviews and meta-analyses in 2016 and 2022 report a pooled diagnostic sensitivity of CT-brain for SAH of 98.7% when performed within six hours of headache onset. [9,10] Sensitivity of CT for *aneurysmal* SAH may remain high up to 24 hours. [11]

National UK and US consensus guidelines recommend avoiding further investigations for SAH in those with a negative CT-brain scan obtained within six hours of headache onset. [12,13] Some experts have raised concerns regarding this diagnostic strategy, citing limited validation studies and the severe clinical consequences of delayed diagnosis. [14,15]

We designed the Subarachnoid Haemorrhage in the Emergency Department (SHED) study to externally validate a diagnostic strategy using negative CT-brain imaging within six hours to exclude SAH. Our secondary aims included an exploration of the diagnostic test characteristics for CT-brain beyond six hours, and external validation of the Ottawa SAH CDR within an unselected UK population.

# Methods

## Design and Setting

A multicentre prospective observational cohort study led by the Trainee Emergency Research Network (TERN) in the UK. Patients were recruited from 88 type-1 EDs or same day emergency care settings between March 2020 and February 2023.

Consecutive patients attending the ED with non-traumatic headache reaching maximal intensity within one hour were eligible for inclusion. The time frame to peak onset was selected based on previous definitions used by Perry *et al* in derivation of the Ottawa CDR and the original six hour CT rule out study. [16] Potential participants were identified by trained ED clinicians and research nurses. Recruitment was paused from April 2020 to September 2021 due to the COVID-19 pandemic.

Key clinical data was collected prospectively by treating teams on a dedicated, one-page inclusion checklist (online supplement 1), including headache onset time, time to peak headache and each component of the Ottawa CDR. Prospective data collection ensured data accuracy for key subjective variables known to be poorly documented in medical records. [5] Imaging review, ancillary investigations, discharge diagnosis and other data points were subsequently extracted from medical records at a later date by direct care and research staff. All patients were followed up for 28 days through case note review, direct contact and/or primary care contact, to determine reattendance patterns and clinical outcome. The study protocol is registered at ISCTRN 18417697 and is freely available online. [17]

The study was approved by the South-West Frenchay Ethics committee (19/SW/0243) and sponsored by the Northern Care Alliance NHS Foundation Trust. A novel opt out consent process is described in full within the published study protocol. [17] Study findings are reported using the EQUATOR guidelines and STARD reporting template. [18]

## Participants

Patients were eligible for inclusion if they were aged 18 years or older, alert (awake and fully orientated or GCS 15/15) and presenting with non-traumatic acute headache reaching

maximal intensity within one hour. Patients were excluded from the study if they met any of the following criteria: direct head trauma in the previous seven days; returning for reassessment of the same headache within the recruitment period; established prior diagnosis of SAH; known brain neoplasm; known ventricular shunt or hydrocephalus prior to attendance at the ED; focal neurological deficit; headache with onset >14 days prior to attendance; recurrent headaches (three or more headaches of similar character and intensity as presenting headache); transfer from another hospital with confirmed SAH; prisoners and patients currently detained under the Mental Health Act.

## Outcome Measures

There is no universally agreed definition for SAH; we therefore adapted the criteria suggested by Perry *et al* as below*,* with any one positive criteria occurring within 28 days of headache onset resulting in a reference standard diagnosis of SAH: [8]

1. Subarachnoid blood present on unenhanced CT-brain reported by a qualified radiologist.
2. Subarachnoid blood present on CT-Angiogram or MR-Angiogram reported by a qualified radiologist.
3a. Spectrophotometry cerebrospinal fluid (CSF) findings consistent with SAH according to the 2008 national reporting guideline for the analysis of CSF in SAH. [19]
3b. Visible xanthochromia on LP, reported by clinical chemistry.
3c. Red blood cells (>$5\times10^6$/L) in the final tube of cerebrospinal fluid collected **and** an aneurysm identified on cerebral angiography (digital subtraction, computed tomography or magnetic resonance angiography).

Where necessary, any inconclusive or contradictory diagnostic evaluations were adjudicated as SAH positive or negative by a panel of clinicians independent to the study team. The panel consisted of a consultant neurosurgeon, consultant neurointensivist, consultant acute medical physician and a consultant in emergency medicine. This panel did not review original imaging but did have access to key data uploaded to the study database by participating sites. We classed any mention of potential SAH by a reporting radiologist as a positive initial CT report, in line with routine practice. If future investigations discounted the

possibility of SAH (determined within the context of routine expert care or via adjudication committee), we subsequently classed the initial CT report as false positive.

The Ottawa SAH CDR is a rule out tool and only needs a single positive integer to fail (i.e. cannot exclude). As such, we considered the CDR to be sufficiently complete when at least one positive component was recorded, or all components were recorded as negative.

## Statistical Analysis

An independent statistician performed all data evaluation, presentation and analysis. Diagnostic test characteristics are presented alongside Clopper-Pearson 95% confidence intervals (CIs). Empirical 95% CIs for likelihood ratios and post-test probabilities were obtained using Monte Carlo simulation. Uninformative *Beta* (1,1) priors for the sensitivity and specificity were utilised to produce 10,000 random draws that were used to estimate the likelihood ratio and post-test probability. Full details are provided in the online supplement 2-3. All analyses were performed using R v4.3.2.

### Sample size calculation

Prevalence figures for SAH in alert patients with atraumatic headache attending the ED range from 2% to 7.5%; we assumed a prevalence of 5%. [6,8,9,20] We initially aimed to recruit 9000 patients, to give a lower 95% confidence interval for the sensitivity of CT-brain imaging within six hours of headache onset above 98%, with at most three missed cases. Further detail on the sample size calculation is described in the protocol. [17]

### Pre-planned subgroup analyses

Patients with a haemoglobin (Hb) of <100g/L were excluded from the primary analysis considering the diagnostic test characteristics of CT-brain due to published concerns regarding CT detection of blood at lower Hb thresholds. [6,21]

### Missing data

Diastolic blood pressure values below 30 and systolic blood pressure values below 50 were considered erroneous and treated as missing. Values of 0 for haemoglobin were considered missing. The central study team made extensive contact with local site teams to support the

completion of missing/incorrect data. Where data is missing this is reported.

## Results

We enrolled 3663 eligible patients, of whom 3268 (89.2%) had CT-brain imaging (Figure 1).

The mean age was 45.8 (SD 16.6) years and 64.1% were female (Table 1). Of the 3268 patients who underwent CT-brain imaging, 36 (1.1%) had a Hb <100g/l. After removal of these patients, 3232 participants were eligible for the primary analysis; 772 (23.9%) had a CT performed within six hours of headache onset; 708 (21.9%) between six to 12 hours from onset; 323 (10.0%) between 12-18 hours from onset; 205 (6.3%) between 18-24 hours from onset and 1223 (37.8%) beyond 24 hours from onset.

237 participants were diagnosed with SAH, a prevalence of 6.5% within the full cohort. 183 patients were diagnosed with serious pathology other than SAH (online supplement 4). 208 (87.8%) confirmed SAH cases were diagnosed by initial CT-brain and 29 met other diagnostic criteria: 23 had an independently positive LP, one case had RBC $>5\times10^6$/L and an aneurysm on further imaging, four had evidence of SAH on further imaging without LP and one patient had a subsequent diagnosis of SAH at 28-day follow-up. Of the 3021 patients with initial negative CT-brain imaging, 1039 (34.4%) had an LP performed; 1008 (97.0%) LP results were negative for SAH, there was missing data for four patients.

Table 1 participant demographics and clinical features

| | **Total** | **CT performed** | | **CT not performed*** |
|---|---|---|---|---|
| | | **No SAH** | **SAH** | |
| | n = 3663 | n = 3031 | n = 237 | n = 395 |
| **Gender, n (%)** | | | | |
| Female | 2349 (64.1%) | 1948 (64.3%) | 132 (55.7%) | 269 (68.1%) |
| Male | 1285 (35.1%) | 1061 (35%) | 103 (43.5%) | 121 (30.6%) |
| Missing | 29 (0.8%) | 22 (0.7%) | 2 (0.8%) | 5 (1.3%) |
| **Age** | | | | |
| Mean (SD) | 45.8 (16.6) | 46.0 (16.6) | 55.4 (13.3) | 38.5 (14.6) |
| Missing, n (%) | 2 (0.1%) | 1 (0%) | 0 (0%) | 1 (0.3%) |
| **Time from headache onset to peak, n (%)** | | | | |
| Thunderclap | 2280 (62.2%) | 1920 (63.3%) | 167 (70.5%) | 193 (48.9%) |
| <1 min | 347 (9.5%) | 291 (9.6%) | 20 (8.4%) | 36 (9.1%) |
| 1-5 mins | 290 (7.9%) | 238 (7.9%) | 24 (10.1%) | 28 (7.1%) |
| 5-10 mins | 140 (3.8%) | 113 (3.7%) | 9 (3.8%) | 18 (4.6%) |
| 10-30 mins | 195 (5.3%) | 163 (5.4%) | 6 (2.5%) | 26 (6.6%) |
| 30-60 mins | 339 (9.3%) | 246 (8.1%) | 8 (3.4%) | 85 (21.5%) |
| Missing | 72 (2%) | 60 (2%) | 3 (1.3%) | 9 (2.3%) |
| **Neck pain or stiffness, n (%)** | | | | |
| No | 2186 (59.7%) | 1855 (61.2%) | 84 (35.4%) | 247 (62.5%) |
| Yes | 1456 (39.7%) | 1162 (38.3%) | 151 (63.7%) | 143 (36.2%) |
| Missing | 21 (0.6%) | 14 (0.5%) | 2 (0.8%) | 5 (1.3%) |
| **Loss of consciousness, n (%)** | | | | |
| No | 3408 (93%) | 2830 (93.4%) | 208 (87.8%) | 370 (93.7%) |
| Yes | 209 (5.7%) | 164 (5.4%) | 25 (10.5%) | 20 (5.1%) |
| Missing | 46 (1.3%) | 37 (1.2%) | 4 (1.7%) | 5 (1.3%) |
| **Onset during straining or exertion, n (%)** | | | | |
| No | 3287 (89.7%) | 2731 (90.1%) | 195 (82.3%) | 361 (91.4%) |
| Yes | 376 (10.3%) | 300 (9.9%) | 42 (17.7%) | 34 (8.6%) |
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Onset during sexual activity, n (%)** | | | | |
| No | 3486 (95.2%) | 2872 (94.8%) | 225 (94.9%) | 389 (98.5%) |
| Yes | 147 (4%) | 136 (4.5%) | 9 (3.8%) | 2 (0.5%) |
| Missing | 30 (0.8%) | 23 (0.8%) | 3 (1.3%) | 4 (1%) |

| | | | | |
|---|---|---|---|---|
| **Vomiting since headache onset, n (%)** | | | | |
| No | 2521 (68.8%) | 2116 (69.8%) | 97 (40.9%) | 308 (78%) |
| Yes | 1062 (29%) | 852 (28.1%) | 136 (57.4%) | 74 (18.7%) |
| Missing | 80 (2.2%) | 63 (2.1%) | 4 (1.7%) | 13 (3.3%) |
| **Arrived by ambulance, n (%)** | | | | |
| No | 2673 (73%) | 2222 (73.3%) | 125 (52.7%) | 326 (82.5%) |
| Yes | 930 (25.4%) | 765 (25.2%) | 108 (45.6%) | 57 (14.4%) |
| NA | 60 (1.6%) | 44 (1.5%) | 4 (1.7%) | 12 (3%) |
| **Heart Rate (BPM), n (%)** | | | | |
| Mean (SD) | 81.7 (15.7) | 81.7 (15.7) | 78.3 (15.4) | 83.8 (16.4) |
| Missing, n (%) | 100 (2.7%) | 80 (2.6%) | 3 (1.3%) | 17 (4.3%) |
| **Systolic Blood Pressure** | | | | |
| Mean (SD) | 142.4 (25.7) | 142.1 (25.5) | 155.4 (27.4) | 136.9 (23.1) |
| Missing | 89 (2.4%) | 71 (2.3%) | 3 (1.3%) | 15 (3.8%) |
| **Diastolic Blood Pressure** | | | | |
| Mean (SD) | 84.8 (15.3) | 84.7 (15.2) | 88.4 (16.6) | 82.9 (14.7) |
| Missing, n (%) | 93 (2.5%) | 75 (2.5%) | 3 (1.3%) | 15 (3.8%) |
| *All followed up at 28 days, no evidence of SAH | | | | |

Seven cases provided contradictory diagnostic information and required evaluation by the independent adjudication panel. This panel reviewed CT, LP, further imaging and angiogram reports as well as discharge letters and neurovascular MDT notes where relevant. Five cases were subsequently judged to be positive for SAH.

Among all patients with a confirmed diagnosis of SAH, 133 (56.1%) were diagnosed with aneurysmal SAH, 67 (28.3%) had non-aneurysmal SAH and for 37 (15.6%) there were insufficient data to determine aneurysm status (online supplement 5).

## Diagnostic test characteristics of CT-brain

The diagnostic test characteristics of CT-brain imaging for the detection of SAH across all time points are shown in table 2 and figure 2.

1) Diagnostic test characteristics of CT-brain within six hours.

CT-brain was 97.0% sensitive (95% CI 92.5%-99.2%) and 100% specific (95% CI 99.6%-100%) for SAH when performed within six hours of headache onset. For this population, the post-test probability of SAH was 0.5% (95% CI 0.2%-1.3%) and negative likelihood ratio was 0.03 (95% CI 0.01-0.08). There were three patients with a false negative initial CT performed within six hours of headache onset. Each case was diagnosed with SAH via a positive LP. Two were diagnosed as non-aneurysmal SAH following further investigation. The third was found to have two intracranial aneurysms that were both coiled. This latter patient presented with a thunderclap headache and a strong family history of aneurysmal disease. The treating emergency clinician performed a CT-angiogram as the initial investigation on arrival. There were no patients with a false positive initial CT-brain within 6 hours of onset.

2) Diagnostic test characteristics for CT-brain beyond six hours

CT-brain imaging was 94.5% sensitive (95% CI 86.5%-98.5%) and 99.5% specific (95% CI 98.8%-99.9%) for SAH when performed between six to 12 hours of headache onset. The sensitivity in those undergoing CT-brain at 12-18 hours was 94.1% (95% CI 75.0%-99.7%) and the specificity was 100% (95% CI 99.0%-100.0%). The sensitivity in those undergoing CT-brain at 18-24 hours from onset was 75.0% (95% CI 47.3%-92.8%) and the specificity was 100% (95% CI 98.5%-100.0%). Further test characteristics are shown in table 2 and figure 2.

In patients undergoing CT-brain between six to 12 hours there were three false negative results. Between 12-18 hours there was one false negative and between 18–24 hours there were three false negatives. Only one false negative case was later confirmed as aneurysmal SAH, with initial CT-brain performed between 18-24 hours.

There were three false positive results at 6-12 hours (CT report suggestive of SAH but diagnosis refuted by specialist teams after further assessment). There were no false

positives between 12-24 hours. Test characteristics for CT-brain by incremental time from headache onset are reported in online supplement 6. Up to 24h, the post-test probability for *aneurysmal* SAH after a negative CT-brain was 0.1% (95% CI 0.0%-0.4%). Test characteristics for *aneurysmal* SAH are reported in online supplement 7.

### External validation of the Ottawa SAH CDR within an unselected UK population.

The CDR was fully complete in 3467 (94.6%) patients and sufficiently complete (at least one positive component) in a further 171 (4.7%) patients. We observed a sensitivity of 98.3% (95% CI 96.2%-99.4%) and a specificity of 8.1% (95% CI 7.3%-8.9%) for the diagnosis of SAH. The CDR demonstrated a negative predictive value of 98.6% (95% CI 96.7%-99.5%) and negative likelihood ratio of 0.21 (95% CI 0.08-0.53). For the overall cohort the post-test probability of SAH was 6.9% (95% CI 6.1%-7.7%) with a positive CDR and 1.4% (95% CI 0.6% - 3.6%) with a negative CDR. The pre-test probability (prevalence) of SAH in those with a potentially negative CDR based on age (< 40) was 2.0% (n=1527 95% CI: 1.4%-2.7%), for those 40 or older it was 9.7% (n=2136 95%CI 8.7%-10.8%).

Table 2: Diagnostic test characteristics of CT-brain for diagnosis of SAH

| Time from headache onset to CT | n | SAH present (prevalence) | Sensitivity (95% CI) (n=TP/TP+FN) | Specificity (95% CI) (n= TN/TN+FP) | PPV (95% CI) | NPV (95% CI) | NLR (95% CI) | Post-test probability of SAH after negative CT (95% CI) |
|---|---|---|---|---|---|---|---|---|
| **All patients** | 3232 | 234 (7.2%) | 87.6% (83.5%-91%) (n=205/234) | 99.8% (99.6%-99.9%) (n=2992/2998) | 97.2% (94.5%-98.8%) | 99% (98.7%-99.3%) | 0.12 (0.09-0.17) | 1.0% (0.7%-1.4%) |
| **0-6 hrs** | 772 | 101 (13.1%) | 97% (92.5%-99.2%) (n=98/101) | 100% (99.6%-100%) (n=671/671) | 100% (97%-100%) | 99.6% (98.9%-99.9%) | 0.03 (0.01-0.08) | 0.5% (0.2%-1.3%) |
| **6-12 hrs** | 708 | 55 (7.8%) | 94.5% (86.5%-98.5%) (n=52/55) | 99.5% (98.8%-99.9%) (n=650/653) | 94.5% (86.5%-98.5%) | 99.5% (98.8%-99.9%) | 0.06 (0.02-0.15) | 0.5% (0.2%-1.3%) |
| **12–18 hrs** | 323 | 17 (5.3%) | 94.1% (75%-99.7%) (n=16/17) | 100% (99%-100%) (n=306/306) | 100% (82.9%-100%) | 99.7% (98.5%-100%) | 0.06 (0.01-0.27) | 0.3% (0.1%-1.7%) |
| **18-24 hrs** | 205 | 12 (5.9%) | 75.0% (47.3%-92.8%) (n=9/12) | 100% (98.5%-100%) (n=193/193) | 100% (71.7%-100%) | 98.5% (96.1%-99.6%) | 0.25 (0.09-0.54) | 1.5% (0.5%-4.1%) |
| **24-48 hrs** | 419 | 20 (4.8%) | 75.0% (54.4%-89.6%) (n=15/20) | 100% (99.3%-100%) (n=399/399) | 100% (81.9%-100%) | 98.8% (97.4%-99.5%) | 0.25 (0.11-0.47) | 1.2% (0.5%-2.7%) |
| **2-7 days** | 653 | 25 (3.8%) | 56.0% (37.9%-73%) (n=14/25) | 99.5% (98.8%-99.9%) (n=625/628) | 82.4% (60.4%-95%) | 98.3% (97.2%-99%) | 0.44 (0.27-0.63) | 1.7% (0.9%-3.0%) |
| **7-30 days** | 151 | 4 (2.6%) | 25.0% (1.3%-75.1%) (n=1/4) | 100% (98.0%-100%) (n=147/147) | 100% (5.0%-100%) | 98% (94.9%-99.5%) | 0.75 (0.28-0.95) | 2.0% (0.5%-5.1%) |
| **Missing** | 1 | | | | | | | |

CT = Computed Tomography, hrs = hours, SAH = subarachnoid haemorrhage, CI = confidence interval, TP = true positive, FN = false negative, TN = true negatives, FP = false positives, PPV = positive predictive value, NPV= negative predictive value, NLR = negative likelihood ratio

# Discussion

## Principal Findings

In this large UK cohort of unselected patients attending the ED with non-traumatic headache peaking within 60 minutes, our key findings were as follows:

1) CT-brain imaging performed within six hours of headache onset and reported as normal by a trained radiologist had a high sensitivity and conveyed a very low post-test probability for the diagnosis of SAH.
2) Although the sensitivity of CT-brain imaging in isolation for the diagnosis of SAH reduced over time between six to 24 hours, the post-test probability of a negative CT remained low at 0.5% (95% CI 0.3%-1.0%) up to 24h from headache onset. The post-test probability for *aneurysmal* SAH after a negative CT up to 24 hours was lower at 0.1% (95% CI 0.0%-0.4%).
3) The Ottawa CDR showed high sensitivity but very low specificity. The rule conveyed minimal impact on post-test probability, given the low baseline pre-test probability.

## Findings in context

Our data demonstrate that non-contrast CT-brain imaging remains the commonest initial diagnostic test used by UK emergency physicians in cases of unselected acute headache. When performed within six hours of headache onset, CT-brain imaging alone had a high sensitivity for exclusion of SAH and conferred a low post-test probability. These findings are in keeping with previous work on the topic. [10] Furthermore, both the negative predictive value and the post-test probability estimates following CT imaging up to 24 hours from headache onset raise questions about the six hour threshold recommended by international guidelines. [12,13]

A previous survey found that Emergency Medicine Consultants and Consultant Neurosurgeons, Neurologists and Neuroradiologists would accept a post-test probability of SAH after non-invasive work up of up to 2.8% (SD 3.3) and up to 1.1% (SD 1.9), respectively. [22] Our post-test probability estimates are below these values up to 18 hours, although we acknowledge the upper limits of 95% CI above 1.1% (table 2). Tolerance of the post-test

probability of all SAH and *aneurysmal SAH* could be re-explored with clinicians and patients, informed further by these findings. In addition, it may be helpful to consider whether improvements in sensitivity result from improvements in technology, reporting environments or wider availability of neuroradiology expertise. We report the grade of reporting radiologist and outsourcing in online supplement 8.

Our findings of a decrease in the sensitivity of CT-brain over time are consistent with previous literature and the pathophysiology of SAH. [10] Following an acute bleed, SAH in the CSF is broken down and diluted, becoming more isodense within the CSF, increasing the chance of false negative reporting. [23] We also found a dependent relationship between prevalence, negative predictive value and post-test probability. Although the sensitivity of CT-brain for SAH decreased over time, the prevalence (or *pre*-test probability) also decreased in those patients undergoing CT-brain at a later stage. As a result, the post-test probability remained stable (figure 2). These findings may be influenced by the established concept of self-triage in acute headache; patients with severe initial 'thunderclap' symptoms are more likely to present rapidly to EDs via self-conveyance or ambulance, and those patients with less severe symptoms more likely to attend at later timepoints. [24]

Although previous studies have reported 100% sensitivity for the Ottawa CDR, [25] our findings suggest the tool lacks generalisability to an NHS setting, with very low specificity and clinical impact in only a small number of patients. The latter finding is in keeping with previous work. [10] We found that the CDR did not impact the post-test probability of SAH if negative, and only slightly increased post-test probability if positive. Further health economic analysis is required to understand any future role for the CDR in UK practice.

### Strengths and weaknesses

Our study is one of the largest conducted on acute severe headache in the UK and recruited participants from almost half of all type 1 UK Emergency Departments, including research in underserved communities. This is a significant strength of our trainee network approach which reduces health inequalities. Our prospective data collection points and outcome definitions were predefined and robust, with additional independent multi-specialty adjudication for cases where diagnosis was uncertain. We achieved a high rate of 28 day

follow up enabling capture of downstream 'missed' SAH cases and reporting of false positive cases, where initial CT-brain imaging suggesting SAH was subsequently refuted. The latter cases have not previously been described in the emergency medicine literature.

Our observational study has several potential weaknesses. The index test under investigation for our primary study aim (CT-brain within six hours of headache onset) was also part of the reference standard diagnosis for SAH. This may have led to verification bias and result in overestimation of sensitivity in our reported diagnostic test characteristics. We attempted to mitigate this bias through 28 day follow-up, which is an excellent proxy for missed SAH diagnosis. Re-attendance to the ED following a 'missed' SAH has been reported to occur within 14 days in 96% cases, and aneurysmal rebleeding (without treatment) within 3 days. [26] It is clearly unethical to compare any non-invasive diagnostic pathway in suspected SAH to a gold standard of digital subtraction angiography/invasive cerebral angiography for all.

We allowed clinical teams to investigate suspected SAH in accordance with usual care pathways, which allowed flexibility and subjectivity in diagnostic approach. A high rate of additional investigations in those patients presenting after six hours may have affected our estimates of CT sensitivity.

It is established practice in the UK to use spectrophotometry for the analysis of CSF samples. We included this within our adapted diagnostic criteria for SAH. However, there is evidence to suggest spectrophotometry increases the number of false positive SAH results without meaningful patient benefit. [27] As such, our diagnostic criteria could be regarded as overdiagnostic for SAH, leading to inaccurate estimations of test characteristics for CT. This point is contentious; many experts support the use of spectrophotometry for the diagnosis of SAH. [28] Nevertheless, only 5.5% of our diagnoses were made via spectrophotometry.

By asking clinicians to calculate the Ottawa CDR initially at the point of assessment, we may have lowered the threshold for CT-brain imaging in the context of routine care. However, our imaging rate approaching 90% is not unexpected in the context of acute severe headache and our SAH prevalence rate was in keeping with previous literature. The study

was closed prior to recruiting the pre-specified sample size of 9000 patients for multiple reasons, including a slower than expected recruitment rate, research reallocation within the context of the pandemic and the impact of rotational training on a long term study involving trainee delivery. This issue is reflected in a lack of precision regarding point estimates and confidence intervals. Finally, we did not collect ethnicity as a demographic parameter. This limits the generalisability of our results as the likelihood of accessing diagnostic imaging is known to be reduced in non-white US ED populations and aneurysmal SAH outcomes are known to differ between ethnic groups. [29,30]

### Unanswered questions and future research

The detection of SAH on CT-brain is dependent on haemorrhage volume, and it is possible that the sensitivity of CT-brain for aneurysmal SAH alone is better when non-aneurysmal cases are excluded. [11] Our data would support this hypothesis. Non-aneurysmal SAH is also reported to convey a lower mortality and morbidity in contrast to aneurysmal SAH, and rarely requires any neurosurgical intervention. [31–33] Further work could explore comparative test performance of different diagnostic strategies to identify *aneurysmal* SAH as a priority. Such work could also evaluate comparative intervention rates and differences in clinical outcome between aneurysmal and non-aneurysmal disease.

### Conclusions

In this UK cohort of people attending the ED with acute headache, a normal CT-brain scan obtained within six hours of headache conferred a post-test probability of 0.5% (95% CI 0.2-1.3%) and 0.1% (95% CI 0.0%-0.8%) for all SAH and aneurysmal SAH respectively. We also provide data on diagnostic performance of plain CT imaging up to 24 hours from headache onset, which can be used to inform shared decision making.

Figure 1: Study flowchart

Figure 2: Diagnostic test characteristics of CT-brain for SAH over time

# Declarations

## Author contributions

This study was conducted by TERN. The writing committee consisted of TR, DH, RH, FB and CP. TR was responsible for the initial concept and design with support from DH. TR designed all study related materials. TR, RH and FB were all responsible for the study delivery. CP conducted all statistical analysis. The writing committee were all involved in authorship of this manuscript and take responsibility for its contents. The TERN collaborators were responsible for the patient level recruitment and local approvals. TR is the guarantor of the data and manuscript.

## Patient and public involvement

There was no study specific patient and public involvement but the research questions were developed following the publication of the 2017 James Lind Alliance Emergency Medicine priority setting exercise. Patient and public involvement was a key component of this process. [34]

## Competing interests

None


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## References:


1 Godwin SA, Cherkas DS, Panagos PD, *et al.* Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache. *Annals of Emergency Medicine*. Published Online First: 2019. doi: 10.1016/j.annemergmed.2019.07.009

2 Kelly AM, Kuan WS, Chu KH, *et al.* Epidemiology, investigation, management, and outcome of headache in emergency departments (HEAD study)—A multinational observational study. *Headache*. 2021;61:1539–52. doi: 10.1111/head.14230

3 Roberts T, Horner DE, *et al.* Thunderclap headache syndrome presenting to the emergency department: an international multicentre observational cohort study. *Emergency Medicine Journal*. Published Online First: 2022. doi: 10.1136/emermed-2021-211370

4 Locker TE, Thompson C, Rylance J, *et al.* The utility of clinical features in patients presenting with nontraumatic headache: An investigation of adult patients attending an emergency department. *Headache*. Published Online First: 2006. doi: 10.1111/j.1526-4610.2006.00448.x

5 Migdal VL, Wu WK, Long D, *et al.* Risk-benefit analysis of lumbar puncture to evaluate for nontraumatic subarachnoid hemorrhage in adult ED patients. *American Journal of Emergency Medicine*. Published Online First: 2015. doi: 10.1016/j.ajem.2015.06.048

6 Perry JJ, Sivilotti MLA, Émond M, *et al.* Prospective Implementation of the Ottawa Subarachnoid Hemorrhage Rule and 6-Hour Computed Tomography Rule. *Stroke*. 2020;51:424–30. doi: 10.1161/strokeaha.119.026969

7 Perry JJ, Stiell IG, Sivilotti MLA, *et al.* Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. *JAMA*. 2013;310:1248–55. doi: 10.1001/jama.2013.278018

8 Perry JJ, Stiell IG, Sivilotti MLA, *et al.* Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: Prospective cohort study. *BMJ (Online)*. Published Online First: 2011. doi: 10.1136/bmj.d4277

9 Dubosh NM, Bellolio MF, Rabinstein AA, *et al.* Sensitivity of Early Brain Computed Tomography to Exclude Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. *Stroke*. Published Online First: 2016. doi: 10.1161/STROKEAHA.115.011386

10 Walton M, Hodgson R, Eastwood A, *et al.* Management of patients presenting to the emergency department with sudden onset severe headache: systematic review of diagnostic accuracy studies. *Emergency Medicine Journal*. 2022;39:818–25. doi: 10.1136/emermed-2021-211900

11 Vincent A, Pearson S, Pickering JW, *et al.* Sensitivity of modern multislice CT for subarachnoid haemorrhage at incremental timepoints after headache onset: a 10-year analysis. *Emerg Med J*. 2022;39:810. doi: 10.1136/emermed-2020-211068

12 Hoh BL, Ko NU, Amin-Hanjani S, *et al.* 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2023;54:e314–70. doi: 10.1161/STR.0000000000000436

13 NICE. Overview | Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management | Guidance | NICE. 2022. https://www.nice.org.uk/guidance/ng228 (accessed 10 January 2023)

14 Mark DG, Christian Sonne D, Jun P, *et al.* False-negative Interpretations of Cranial Computed Tomography in Aneurysmal Subarachnoid Hemorrhage. *Academic Emergency Medicine*. Published Online First: 2016. doi: 10.1111/acem.12941

15 https://twitter.com/BritNeurovasc/status/1595432318495297537.

16 Perry JJ, Stiell IG, Sivilotti MLA, *et al.* High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study. *BMJ*. 2010;341:c5204. doi: 10.1136/bmj.c5204

17 Roberts T, Hirst R, Hulme W, *et al.* External validation of a clinical decision rule and neuroimaging rule-out strategy for exclusion of subarachnoid haemorrhage in the emergency department: A prospective observational cohort study. Emergency Medicine 2021.

18 Bossuyt PM, Reitsma JB, Bruns DE, *et al.* STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. doi: 10.1136/bmj.h5527

19 Cruickshank A, Auld P, Beetham R, *et al.* Revised national guidelines for analysis of cerebrospinal fluid for bilirubin in suspected subarachnoid haemorrhage. *Ann Clin Biochem*. 2008;45:238–44. doi: 10.1258/acb.2008.007257

20 Carpenter CR, Hussain AM, Ward MJ, *et al.* Spontaneous Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis Describing the Diagnostic Accuracy of History, Physical Examination, Imaging, and Lumbar Puncture With an Exploration of Test Thresholds. *Academic Emergency Medicine*. Published Online First: 2016. doi: 10.1111/acem.12984

21 Smith W, Batnitzky S, Rengachary S. Acute isodense subdural hematomas: a problem in anemic patients. *American Journal of Roentgenology*. 1981;136:543–6. doi: 10.2214/ajr.136.3.543

22 Lansley J, Selai C, Krishnan AS, *et al.* Subarachnoid haemorrhage guidelines and clinical practice: a cross-sectional study of emergency department consultants' and

neurospecialists' views and risk tolerances. *BMJ Open*. 2016;6:e012357. doi: 10.1136/bmjopen-2016-012357

23 Edlow JA, Malek AM, Ogilvy CS. Aneurysmal Subarachnoid Hemorrhage: Update for Emergency Physicians. *The Journal of Emergency Medicine*. 2008;34:237–51. doi: 10.1016/j.jemermed.2007.10.003

24 Nemer JA, Tallick SA, O'Connor RE, *et al.* Emergency medical services transport of patients with headache: mode of arrival may indicate serious etiology. *Prehosp Emerg Care*. 1998;2:304–7. doi: 10.1080/10903129808958885

25 Perry JJ, Sivilotti MLA, Sutherland J, *et al.* Validation of the Ottawa Subarachnoid Hemorrhage Rule in patients with acute headache. *CMAJ*. 2017;189:E1379–85. doi: 10.1503/cmaj.170072

26 Vermeulen MJ, Schull MJ. Missed Diagnosis of Subarachnoid Hemorrhage in the Emergency Department. *Stroke*. 2007;38:1216–21. doi: 10.1161/01.STR.0000259661.05525.9a

27 Perry JJ, Sivilotti MLA, Stiell IG, *et al.* Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? *Stroke*. 2006;37:2467–72. doi: 10.1161/01.STR.0000240689.15109.47

28 Beetham R, Lhatoo S. Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? *Stroke*. 2007;38:e86; author reply e87. doi: 10.1161/STROKEAHA.107.486258

29 Schupper AJ, Hardigan TA, Mehta A, *et al.* Sex and Racial Disparity in Outcome of Aneurysmal Subarachnoid Hemorrhage in the United States: A 20-Year Analysis. *Stroke*. 2023;54:1347–56. doi: 10.1161/STROKEAHA.122.041488

30 Ross AB, Kalia V, Chan BY, *et al.* The influence of patient race on the use of diagnostic imaging in United States emergency departments: data from the National Hospital Ambulatory Medical Care survey. *BMC Health Serv Res*. 2020;20:840. doi: 10.1186/s12913-020-05698-1

31 Claassen J, Park S. Spontaneous subarachnoid haemorrhage. *The Lancet*. 2022;400:846–62. doi: 10.1016/S0140-6736(22)00938-2

32 Tarkiainen J, Hovi V, Pyysalo L, *et al.* The clinical course and outcomes of non-aneurysmal subarachnoid hemorrhages in a single-center retrospective study. *Acta Neurochir*. 2023;165:2843–53. doi: 10.1007/s00701-023-05767-4

33 Konczalla J, Platz J, Schuss P, *et al.* Non-aneurysmal non-traumatic subarachnoid hemorrhage: patient characteristics, clinical outcome and prognostic factors based on a single-center experience in 125 patients. *BMC Neurol*. 2014;14:140. doi: 10.1186/1471-2377-14-140

34 https://www.jla.nihr.ac.uk/priority-setting-partnerships/emergency-medicine/top-10-priorities.htm.