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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

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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. • 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. • Our estimates of post-test probability for SAH after a negative CT-brain within 24 hours of headache onset were consistently less than 1%. • 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. • This study highlights the importance of distinguishing between aneurysmal and non-aneurysmal SAH in diagnostic studies. • Our results suggest a low post-test probability using CT-brain up to 24 hours from headache onset, which warrants further study.

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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.

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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

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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

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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

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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 >5×10^6/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.

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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%)

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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).

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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

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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%).

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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

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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

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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

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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

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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

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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

Confidential: For Review Only

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

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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

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

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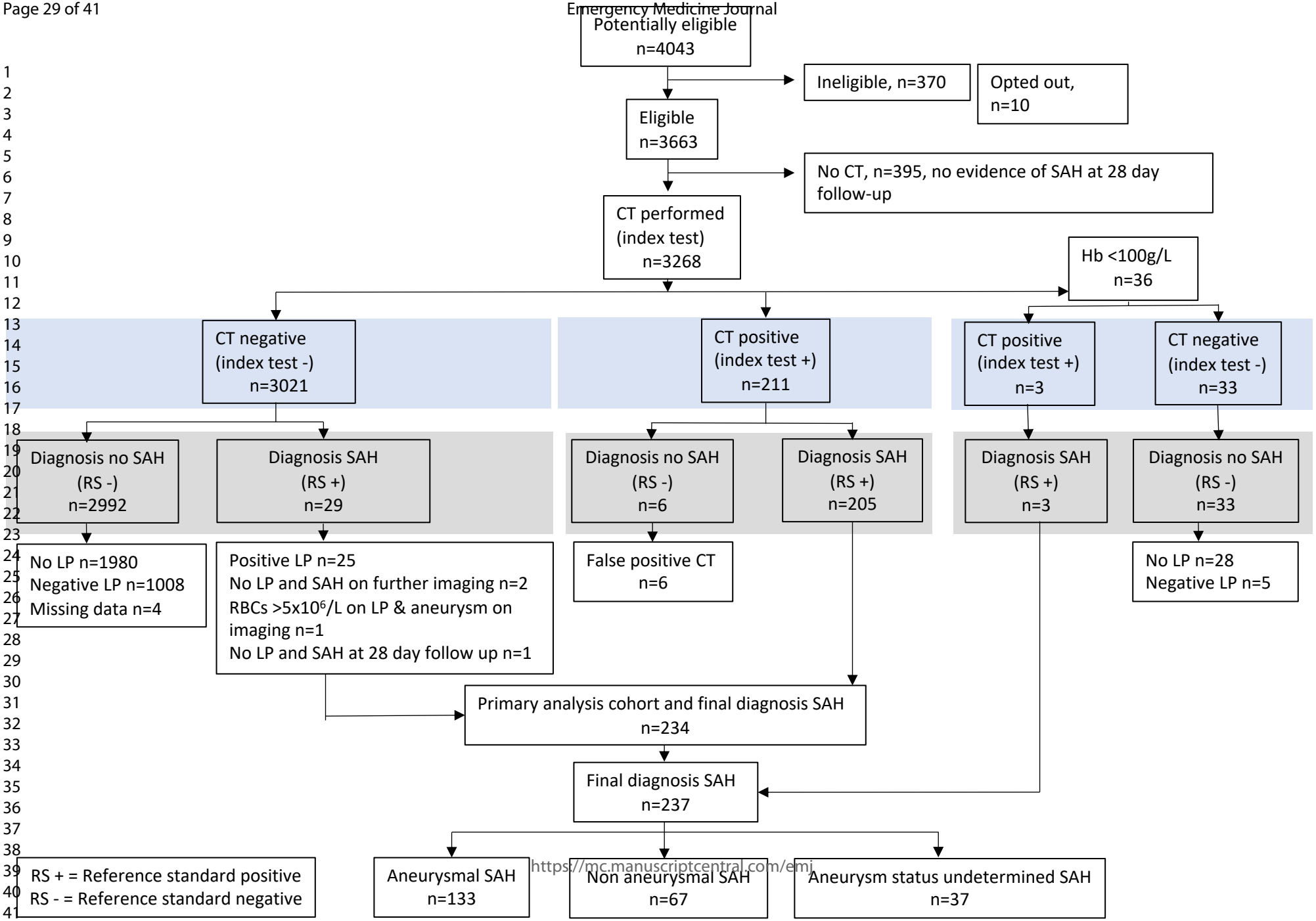

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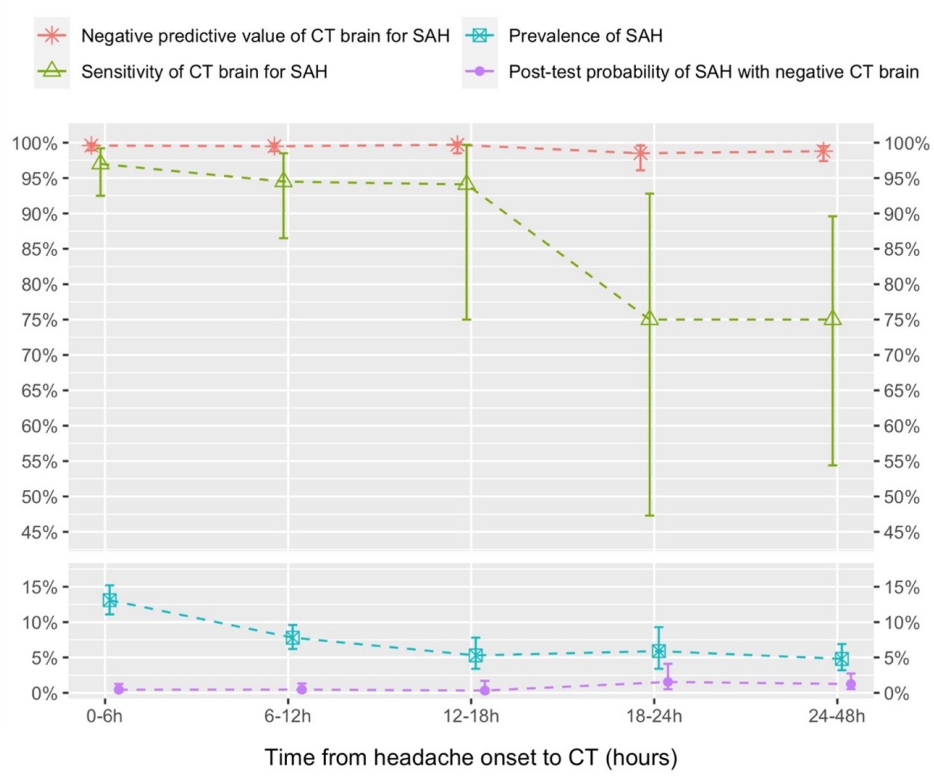

Figure 2. Test characteristics of CT brain for SAH over time.

159x127mm (220 x 220 DPI)

Supplementary material
Online supplement 1. Inclusion checklist

IRAS: 253791
16/10/2020
Study Inclusion Checklist V 1.4

PIS NUMBER_____

Place sticker here. If no sticker, please enter the below:

Name: _____

Date of Birth: _____

Hospital / NHS Number: _____

Inclusion Criteria (please tick)	Yes	No (do not proceed if any "no" ticked)
Is the patient aged 18 or older?		
Do they have an acute severe headache which peaked (reached maximum intensity) within an hour?		

If "Yes" to **both** criteria above, please continue to opt out recruitment and record the below during your initial consultation.

What was the date/time of headache onset?

_____ /__ /_____ (Day/Month/Year) _____ : _____ (HH:MM) 24-hour clock

Prospective Questions (please tick)	Yes	No
Does the patient describe a thunderclap headache? (rapidly reaching maximal intensity over seconds)		
Was the onset of the headache during exertion?		
Does the participant report neck pain or neck stiffness?		
Was there any witnessed loss of consciousness?		
Is there any limited neck flexion on clinical examination?		
Has the patient received the opt-out patient information sheet?		
Have you written the PIS number from the opt-out patient information sheet at the top of this page?		
Full name of person completing checklist (optional – there will be a prize for top recruiter!)		

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Online Supplement 2. Statistical methods.

Empirical 95% confidence intervals for likelihood ratio and post-test probability

For each iteration ($i\ in\ 1, \ldots, 10000$):

1. Simulate the prevalence, sensitivity and specificity from the Bayesian posterior distribution using an uninformative Beta(1,1) prior, i.e. $\theta_i \sim Beta(TP + FN + 1, TN + FP + 1)$ for the prevalence, $\alpha_i \sim Beta(TP + 1, FN + 1)$ for the sensitivity and $\beta_i \sim Beta(TN + 1, FP + 1)$ for the specificity, where TN is the observed number of true positives, FN is the observed number of false negatives, TN is the number of true negatives and FP is the number of false positives.
2. Calculate:
    a. Pre-test odds: $\gamma_{0,i} = \theta_i/(1 - \theta_i)$
    b. Positive likelihood ratio: $LR_i^+ = \alpha_i/(1 - \beta_i)$
    c. Negative likelihood ratio: $LR_i^+ = (1 - \alpha_i)/\beta_i$
    d. Positive post-test odds: $\gamma_{1,i}^+ = \gamma_{0,i} \times LR_i^+$
    e. Negative post-test odds: $\gamma_{1,i}^- = \gamma_{0,i} \times LR_i^-$
    f. Positive post-test probability: $p_i^+ = \gamma_{1,i}^+/(1 + \gamma_{1,i}^+)$
    g. Negative post-test probability: $p_i^- = \gamma_{1,i}^-/(1 + \gamma_{1,i}^-)$

The empirical 95% confidence intervals are then provided by the 2.5th and 97.5th percentiles calculated (using the quantile function in R) from the 10000 values for the metric of interest (S), e.g. the 2.5th and 97.5th percentiles of S are given by

$$Q(2.5, S) = 0.025 \times S^{(250)} + 0.975 \times S^{(251)},$$

$$Q(97.5, S) = 0.975 \times S^{(9750)} + 0.025 \times S^{(9751)},$$

where $S^{(j)} = jth$ order statistic of S, and $S\ \epsilon\ \{LR^+, LR^-, p^+, p^-\}$.

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Online Supplement 3. Process followed to ensure accurate timings for key events.

The date-times of onset, arrival and the CT scan request, performance and result were reviewed for errors. Any dates that were not in chronological order were reviewed. Additionally, all patients that had differences of more than 3 days between onset and arrival were reviewed. The following strategies were applied:

1. Where a non-chronological date was sandwiched by dates that were the same, it was replaced by this date. Where a non-chronological date was sandwiched but multiple days were between, the earliest date was selected.
2. Years were reviewed for probable typos and replaced where deemed appropriate.
3. Months were reviewed for probable typos and replaced where deemed appropriate.
4. Instances where the times were recorded past midnight but the date was not changed were overridden to be the following date.
5. Hour of time was reviewed for typos
6. Order of digits for dates and times were reviewed for typos (e.g. 03 instead of 30)
7. Non-chronological timings were reviewed and replaced by the latest hour before the next time
8. Non-chronological timings were reviewed and the hour was replaced by the earliest hour after the previous time

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Online Supplement 4. Serious pathology other than SAH.

Diagnosis	Number of patients	Proportional incidence by total sample (3663)
AV malformation	1	0.00%
Cavernoma	2	0.00%
Encephalitis	3	0.00%
Glaucoma	3	0.00%
Idiopathic intracranial hypertension	16	0.44%
Intracerebral mass	12	0.33%
Malignancy	1	0.00%
Meningitis	1	0.00%
Meningitis (bacterial)	9	0.25%
Meningitis (viral)	53	1.44%
Other intracranial haemorrhage	11	0.30%
Stroke	45	1.22%
Subdural	7	0.19%
Temporal Arteritis	1	0.00%
Trigeminal Neuralgia	9	0.25%
Vascular dissection	1	0.00%
Venous sinus thrombosis	8	0.22%

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Online Supplement 5. Criteria by which SAH made by aneurysm status.

		Criteria by which SAH diagnosis made						
		1	2	3a	3b	3c	4	
Time window	Type of SAH							
0-6h	Aneurysmal SAH	66	0	0	1	0	0	
	Non-aneurysmal SAH	23	0	2	0	0	0	
	Aneurysmal status undetermined SAH	12	0	0	0	0	0	
6-12h	Aneurysmal SAH	30	0	0	0	0	0	
	Non-aneurysmal SAH	10	0	1	2	0	0	
	Aneurysmal status undetermined SAH	12	0	0	0	0	0	
12-18h	Aneurysmal SAH	7	0	0	0	0	0	
	Non-aneurysmal SAH	4	0	0	1	0	0	
	Aneurysmal status undetermined SAH	5	0	0	0	0	0	
18-24h	Aneurysmal SAH	4	0	0	0	1	0	
	Non-aneurysmal SAH	4	0	2	0	0	0	
	Aneurysmal status undetermined SAH	1	0	0	0	0	0	
24-48h	Aneurysmal SAH	10	0	0	0	0	0	
	Non-aneurysmal SAH	4	1	3	1	0	0	
	Aneurysmal status undetermined SAH	1	0	0	0	0	0	
2-7d	Aneurysmal SAH	10	0	1	1	0	0	
	Non-aneurysmal SAH	1	2	2	3	0	0	
	Aneurysmal status undetermined SAH	3	0	0	1	0	1	
7-30d	Aneurysmal SAH	1	1	0	0	0	0	
	Non-aneurysmal SAH	0	0	1	0	0	0	
	Aneurysmal status undetermined SAH	0	0	1	0	0	0	
Totals		208*	4	13	10	1	1	237

Criteria by which SAH diagnosis made	
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	Cerebrospinal fluid (CSF) findings consistent with SAH according to the 2008 national reporting guideline for the analysis of CSF in SAH. [23]
3b	Visible xanthochromia on LP, reported by clinical chemistry.
3c	Red blood cells (>5_106/L) in the final tube of cerebrospinal fluid collected and an aneurysm identified on cerebral angiography (digital subtraction, computed tomography or magnetic resonance angiography)
4	28 day follow-up

- Includes 3 patients positive on CT brain but who had Hb less than 100 g/L

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Online Supplement 6. Diagnostic test characteristics of CT over incremental time from headache onset.

Time to CT	n =	SAH	Sensitivity	Specificity	PPV	NPV	Negative LR	Negative Post-test probability
0-6h	772	101 (13.1%)	97% (92.5%-99.2%)	100% (99.6%-100%)	100% (97%-100%)	99.6% (98.9%-99.9%)	0.03 (0.01-0.08)	0.4% (0.2%-1.3%)
0-12h	1480	156 (10.5%)	96.2% (92.6%-98.3%)	99.8% (99.4%-99.9%)	98% (95%-99.5%)	99.5% (99.1%-99.8%)	0.04 (0.02-0.08)	0.5% (0.2%-1.0%)
0-18h	1803	173 (9.6%)	96% (92.5%-98.1%)	99.8% (99.5%-99.9%)	98.2% (95.5%-99.5%)	99.6% (99.2%-99.8%)	0.04 (0.02-0.08)	0.4% (0.2%-0.9%)
0-24h	2008	185 (9.2%)	94.6% (91.0%-97.0%)	99.8% (99.6%-100%)	98.3% (95.7%-99.5%)	99.5% (99.1%-99.7%)	0.05 (0.03-0.1)	0.5% (0.3%-1.0%)
0-48h	2426	205 (8.5%)	92.7% (89%-95.4%)	99.9% (99.7%-100%)	98.4% (96%-99.6%)	99.3% (99%-99.6%)	0.07 (0.05-0.12)	0.7% (0.4%-1.1%)
0-7d	3079	230 (7.5%)	88.7% (84.7%-92%)	99.8% (99.6%-99.9%)	97.1% (94.4%-98.7%)	99.1% (98.7%-99.4%)	0.11 (0.08-0.16)	0.9% (0.6%-1.3%)
0-30d	3230	234 (7.2%)	87.6% (83.5%-91%)	99.8% (99.6%-99.9%)	97.2% (94.5%-98.8%)	99% (98.7%-99.3%)	0.12 (0.09-0.17)	1% (0.7%-1.4%)
>6h	2458	133 (5.4%)	80.5% (73.9%-85.9%)	99.7% (99.5%-99.9%)	94.7% (89.8%-97.7%)	98.9% (98.5%-99.2%)	0.2 (0.14-0.27)	1.1% (0.8%-1.6%)
>24h	1222	49 (4%)	61.2% (48.5%-72.9%)	99.7% (99.3%-99.9%)	90.9% (78.1%-97.5%)	98.4% (97.7%-99%)	0.39 (0.27-0.53)	1.6% (1%-2.4%)

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Online Supplement 7. Diagnostic test characteristics of CT brain for diagnosis of aneurysmal SAH (aSAH). Patients whose SAH could not be determined as aneurysmal or not were assigned as not aSAH.

Time from headache onset to CT	n	aSAH present (prevalence)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	NLR (95% CI)	Post-test Probability of SAH after negative CT (95% CI)
All patients	3232	130* (4.0%)	96.2% (92.1%-98.5%)	97.2% (96.7%-97.7%)	59.2% (53.4%-64.9%)	99.8% (99.7%-99.9%)	0.04 (0.02-0.09)	0.2% (0.1%-0.4%)
0-6 hrs	772	64 (8.3%)	98.4% (92.8%-99.9%)	95.1% (93.5%-96.3%)	64.3% (55.6%-72.3%)	99.9% (99.3%-100%)	0.02 (0-0.09)	0.2% (0.0%-0.8%)
6-12 hrs	708	30 (4.2%)	100% (90.5%-100%)	96.3% (94.9%-97.4%)	54.5% (42.6%-66.1%)	100% (99.5%-100%)	0.00 (0.00-0.12)	0.0% (0.0%-0.6%)
12–18 hrs	323	7 (2.2%)	100% (65.2%-100%)	97.2% (95.1%-98.5%)	43.8% (22.7%-66.7%)	100% (99.0%-100%)	0.00 (0.00-0.39)	0.0% (0.0%-1.1%)
18-24 hrs	205	5 (2.4%)	80% (34.3%-99%)	97.5% (94.8%-99%)	44.4% (16.9%-74.9%)	99.5% (97.6%-100%)	0.21 (0.04-0.67)	0.5% (0.1%-2.5%)
24-48 hrs	419	10 (2.4%)	100% (74.1%-100%)	98.8% (97.4%-99.5%)	66.7% (42.3%-85.8%)	100% (99.3%-100%)	0.00 (0.00-0.29)	0% (0%-0.8%)
2-7 days	653	12 (1.8%)	83.3% (56.2%-97.0%)	98.9% (98%-99.5%)	58.8% (36.4%-78.8%)	99.7% (99.0%-99.9%)	0.17 (0.05-0.46)	0.3% (0.1%-1.1%)
7-30 days	151	2 (1.3%)	50.0% (2.5%-97.5%)	100% (98%-100%)	100% (5.0%-100%)	99.3% (96.9%-100%)	0.50 (0.10-0.92)	0.7% (0.1%-3%)
Missing	1							

*Note: 3/133 aSAH were patients with hb<100, hence were excluded from this table to be consistent with CT performance metrics evaluated for all SAH. All were identified as SAH on CT within 6 hrs of headache onset.

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Online Supplement 7 continued: Diagnostic test characteristics of CT for aneurysmal SAH (aSAH) over incremental time from headache onset. Patients whose SAH could not be determined as aneurysmal or not were assigned as not aSAH.

Time to CT	n =	aSAH	Sensitivity	Specificity	PPV	NPV	Negative LR	Negative Post-test probability
0-6 hrs	772	64 (8.3%)	98.4% (92.8%-99.9%)	95.1% (93.5%-96.3%)	64.3% (55.6%-72.3%)	99.9% (99.3%-100%)	0.02 (0.00-0.09)	0.1% (0.0%-0.8%)
0-12 hrs	1480	94 (6.4%)	98.9% (95.1%-99.9%)	95.7% (94.7%-96.5%)	60.8% (53.8%-67.4%)	99.9% (99.6%-100%)	0.01 (0.00-0.06)	0.1% (0.0%-0.4%)
0-18 hrs	1803	101 (5.6%)	99.0% (95.4%-99.9%)	95.9% (95.1%-96.7%)	59.2% (52.6%-65.5%)	99.9% (99.7%-100%)	0.01 (0.00-0.06)	0.1% (0.0%-0.3%)
0-24 hrs	2008	106 (5.3%)	98.1% (94.2%-99.7%)	96.1% (95.3%-96.8%)	58.4% (52.0%-64.6%)	99.9% (99.7%-100%)	0.02 (0.01-0.07)	0.1% (0.0%-0.4%)
0-48 hrs	2427	116 (4.8%)	98.3% (94.7%-99.7%)	96.6% (95.9%-97.2%)	59.1% (52.9%-65.0%)	99.9% (99.7%-100%)	0.02 (0.01-0.06)	0.1% (0.0%-0.3%)
0-7 days	3080	128 (4.2%)	96.9% (93%-98.9%)	97.1% (96.5%-97.6%)	59% (53.2%-64.7%)	99.9% (99.7%-100%)	0.03 (0.01-0.08)	0.1% (0.1%-0.3%)
0-30 days	3231	130 (4.0%)	96.2% (92.1%-98.5%)	97.2% (96.7%-97.7%)	59.2% (53.4%-64.9%)	99.8% (99.7%-99.9%)	0.04 (0.02-0.09)	0.2% (0.1%-0.4%)
>6 hrs	2459	66 (2.7%)	93.9% (86.7%-97.9%)	97.9% (97.3%-98.3%)	54.9% (46.7%-62.8%)	99.8% (99.6%-99.9%)	0.06 (0.03-0.15)	0.2% (0.1%-0.4%)
>24 hrs	1223	24 (2.0%)	87.5% (70.8%-96.5%)	99% (98.4%-99.4%)	63.6% (47.8%-77.5%)	99.7% (99.3%-99.9%)	0.13 (0.05-0.32)	0.3% (0.1%-0.7%)

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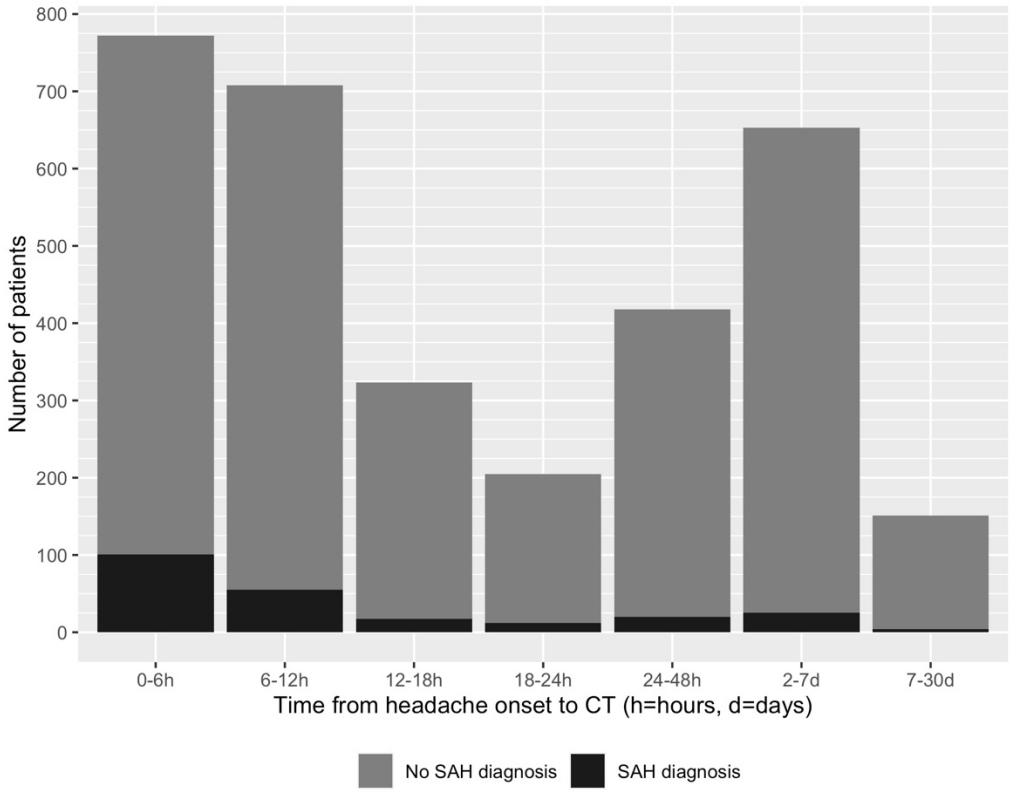
Online supplement 8. Breakdown of the grade of reporting radiologist and whether the imaging was outsourced to a telemedicine service for patients that were identified with SAH that underwent CT and did not have Hb<100g/l

Grade of radiologist	Service	CT False negatives (n=29)	CT True positives (n=205)	Sensitivity
Consultant	Local	15	92	86.0%
Consultant	Telemedicine	9	52	85.2%
Consultant	Missing	0	2	100.0%
Registrar	Local	4	46	92.0%
Registrar	Telemedicine	1	0	0.0%
Registrar	Missing	0	3	100.0%
Missing	Local	0	8	100.0%
Missing	Telemedicine	0	2	100.0%

Online Supplement 9. Final diagnosis of SAH vs no SAH by time from onset to CT – bar plot.



Dear Ellen and David,

Thank you very much indeed the opportunity to submit another revision to this manuscript.

We have addressed Ellen's comments and accepted all of the suggested changes alongside some significant editing to reduce word count. The manuscript now has a word count of 3426 and the references have been reduced to 34.

In response to Ellen's comments

- I hate to be the hatchet-man but the paper is considerably over the word limit and I do need to ask you to reduce it, by approximately 900 words- 1000 words and reduce the references to closer to 30 (Our word limit is 3000 but we can go to 3300-3400. If the additional references are essential--i.e. not cut out by the accompanying text changes--, we can leave those.)

As above – the word count has been reduced to 3426 and the number of references to 34.

- I have reviewed in depth and have put some suggestions in the attached ms. In addition, I have suggested a change in the ordering f the results and removal there of the sentences about the SAH's in those excluded due to Hgb status as the placement was confusing.

We have accepted the changes made, thank you.

In general I think that the potential places for considerable reduction are - 1) the detailed description of the non-CT diagnoses of SAH, if they are already in a table. You also describe these in the context of the timing of the CT scan and it is more relevant there to see how the diagnoses were made during the different time frames.

- We have managed to considerably reduce the word count without changing this paragraph. We do feel this provides a useful summary to readers who will be interested to hear how diagnoses were reached without needing to reference the supplementary material.

2) The strengths of the study can be reduced. . I think that the study was conducted by TERN and allowed you to do research in community settings which also potential improves representation is important but could be shortened a bit. Some of the other strengths are simply standard - such as data cleaning and statistical analysis-- and by adding these you dilute the strength of the TERN aspect. Moreover, the strengths of the study is clear by what you have done and that is has passed through peer review!

- Thank you, we have reduced this section in line with your recommendations.

3) The directions for future research should either be removed, or considerably condensed. (You might consider a future "In Perspective" article which takes into

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account your findings, prior findings, perhaps cost-effectiveness modeling data to tell us what we should do clinically and where future work is needed and put this in that.).

- This section has been considerably shortened. We will consider a subsequent In Perspective article, thank you for the suggestion.

Other potential options are to shorten the beginning of the introduction by not repeating (or summarizing ore briefly) the findings in the section on context. Smaller ways to reduce word counts here and there is to not use a full sentence to point out a table but rather describe the results and after the first sentence of description put in (Table X). Similarly after you describe enrollment you can just add: (Figure 1). Again, see suggestions in the attached.

- Thank you – we have followed these suggestions to considerably reduce word count.

The statistician refers to adjustment but to my reading, there is only one comparison, which is about the age groups. I think that the statistical testing there should simply be removed as your goal was not to assess risk factors. I may have missed it but I don't see this done in the Table or with any other variables.

- This has been removed.

I did have a bit of confusion about the concept of secondary analyses. You state that you removed those with HGB in the primary analysis, but its not clear what is the primary analysis and the secondary analyses - are any of the secondary analyses described in the main paper? Could you clarify which these are? I am suggesting removing the sentences about the results for those with low Hbg from the initial results as whether they have a positive or Negative CT at this point is confusing. You only need to say that they were excluded at this point. But then we do need to know where they were included.

- We have removed reference to secondary analysis and, as suggested, removed the sentences about those with a low Hb from the initial results.

In response to reviewer 1's comments:

-Please report for each of the 5 points that you include in the definition of gold standard how many patients underwent the test required and how many were positive. Please discuss this in order to expand/refine the weakness

- The number of patients diagnosed by each of the criteria is reported in the supplementary material. The number of patients undergoing LP is included in the study flowchart - figure 1.

Please evaluate if worth to adjust for prognostic factors on the statistical analyses

- Thank you for suggesting this, it was not however part of the planned analysis and we don't intend to include it.

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Many thanks indeed for further considering this manuscript and your help in revising it.

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