Predictive performance of the common red flags in emergency department headache patients: a HEAD and HEAD-Colombia study

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Handling editor Carl Marincowitz

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/emermed-2023-213461).

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Received 27 June 2023
Accepted 25 March 2024

To cite: Chu K, Kelly A-M, Kuan WS, *et al*. *Emerg Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/emermed-2023-213461

ABSTRACT

Objectives Only a small proportion of patients presenting to an ED with headache have a serious cause. The SNNOOP10 criteria, which incorporates red and orange flags for serious causes, has been proposed but not well studied. This project aims to compare the proportion of patients with 10 commonly accepted red flag criteria (singly and in combination) between patients with and without a diagnosis of serious secondary headache in a large, multinational cohort of ED patients presenting with headache.

Methods Secondary analysis of data obtained in the HEAD and HEAD-Colombia studies. The outcome of interest was serious secondary headache. The predictive performance of 10 red flag criteria from the SNNOOP10 criteria list was estimated individually and in combination.

Results 5293 patients were included, of whom 6.1% (95% CI 5.5% to 6.8%) had a defined serious cause identified. New neurological deficit, history of neoplasm, older age (>50 years) and recent head trauma (2–7 days prior) were independent predictors of a serious secondary headache diagnosis. After adjusting for other predictors, sudden onset, onset during exertion, pregnancy and immune suppression were not associated with a serious headache diagnosis. The combined sensitivity of the red flag criteria overall was 96.5% (95% CI 93.2% to 98.3%) but specificity was low, 5.1% (95% CI 4.3% to 6.0%). Positive predictive value was 9.3% (95% CI 8.2% to 10.5%) with negative predictive value of 93.5% (95% CI 87.6% to 96.8%).

Conclusion The sensitivity and specificity of the red flag criteria in this study were lower than previously reported. Regarding clinical practice, this suggests that red flag criteria may be useful to identify patients at higher risk of a serious secondary headache cause, but their low specificity could result in increased rates of CT scanning.

Trial registration number ANZCTR376695.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A small proportion of patients who present to EDs with headache (about 7%) have serious pathology diagnosed. A challenge for ED clinicians is determining which patients (especially those with a normal neurological examination) require further investigation. So-called red flag criteria have been proposed to assist in identification of patients who are at higher risk of serious pathology and to inform decision-making about investigation. There has been limited validation of these criteria in the ED setting with mixed results.

WHAT THIS STUDY ADDS

⇒ Sensitivity of the SNNOOP10 criteria as a group was high, but specificity was very low. The results challenge the predictive utility of some of the red flags. Funduscopy may be a predictor but was rarely performed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Regarding clinical practice, this study suggests that red flag criteria are useful to identify patients at higher risk of a serious secondary headache cause, but their absence alone should not be used to determine whether further investigation is required. The low rate of funduscopy and its reported inaccuracy suggest that new and more accurate ways of examining the optic fundus may be needed.

INTRODUCTION

Only a small proportion of patients presenting to an ED with headache have a serious cause for their headache identified after assessment and investigation—about 7% in recent studies.[1 2] Some with serious pathology are more obvious, such as those presenting with altered conscious state and/or new neurological features (other than headache). The challenge for ED clinicians is to decide which patients without obvious neurological findings require additional investigation to rule out a serious secondary headache cause.

The 'red flags' approach has been promoted and is included in highly respected guidelines.[3] Some years ago, the American Headache Society proposed the SNOOP4 criteria (Systemic signs, Neurological features, Onset sudden, Older age, Progression, Papilloedema, Positional or Pregnancy).[4] More recently, Do *et al* expanded the list to include 15

Systemic symptoms including fever

Neoplasm in history

Neurologic deficit or dysfunction, including decreased consciousness

Onset of headache is sudden or abrupt

Older age (>50 years)

Pattern change or recent onset of headache

Positional headache

Headache precipitated by sneezing, coughing or exercise

Papilloedema

Progressive headache and atypical presentations

Pregnancy or puerperium

Painful eye with autonomic features

Post-traumatic onset of headache

Pathology of the immune system

Painkiller overuse or new drug at onset of headache

Figure 1 SNNOOP10 criteria.[5]

red and orange flags for secondary headache (the so-called SNNOOP10 criteria) (figure 1).[5] These have had limited evaluation in the ED headache population and come from studies with different methodologies and had small sample sizes (fewer than 350 patients in total).[6 7] One of those small studies of 100 patients reported sensitivity of SNNOOP10 list of 100% (95% CI 90.2% to 100%).[7]

The HEAD and HEAD-Colombia studies are multinational studies of patients presenting with headache to ED.[1 2] Their data provide an opportunity to evaluate the common red flags for serious headache in a large, real-world ED population.

The main aim of this study was to explore the association between, and predictive value for serious secondary headache of, 10 commonly accepted red flag criteria (singly and in combination) using a large, multinational cohort of ED patients presenting with headache. A planned secondary objective was to explore this association in the subgroup of patients who did not present with altered conscious state, new confusion or new neurological signs on examination. The rationale for this subgroup is that, for people presenting with new neurological features (in addition to headache), it is usually clear that they require investigation. The group with normal neurology poses the main challenge for ED clinicians with respect to diagnostic decision-making, including selection of investigations.

METHODS

Study design and setting

This was an unplanned analysis of data collected in the HEAD and HEAD-Colombia studies.[1 2] Both were observational studies of adult ED patients with headache. The HEAD study was a multinational study conducted in Australia, New Zealand, Singapore, Hong Kong, UK, France, Belgium, Romania, Turkey and Israel. The HEAD Columbia study was undertaken in Colombia. There were 69 healthcare facilities across 11 countries (online supplemental table 1). Their methodology has been published previously.[1 2]

Data sources

The HEAD and HEAD-Colombia studies used the same protocol and collected the same data with minor variation due to availability of some medications in some countries. (supplemental file 1) Data were collected in 2019 and 2021 for the two studies, respectively. One of the HEAD study authors (A-MK) was involved in the HEAD Columbia study but investigators from the latter were not involved in the planning of the original HEAD study.

We considered that combining the data from these studies was valid because they used the same methodology and the same data collection tool and covered approximately the same time period. Moreover, we analysed pooled patient-level data from the two studies. A meta-analysis, on the other hand, typically analyses study-level results from multiple studies. Our data were thus in keeping with a single multicentre study, and hence were analysed as such and not as a meta-analysis.

Data collected included data on medical history and medications, headache features, examination findings, patterns

Table 1 Population characteristics stratified by serious secondary headaches

	HEAD and HEAD-Colombia studies			HEAD study			HEAD-Colombia study		
	Non-serious secondary headache	Serious secondary headache	Total	Non-serious secondary headache	Serious secondary headache	Total	Non-serious secondary headache	Serious secondary headache	Total
	N=4970 (93.9%)	N=323 (6.1%)	N=5293	N=4276 (94.3%)	N=260 (5.7%)	N=4536	N=694 (91.7%)	N=63 (8.3%)	N=757
Age									
Median (IQR), years	40 (29–54)	53 (35–69)	40 (29–55)	40 (29–54)	54 (36–71)	41 (29–55)	38 (28–50)	46 (31–62)	39 (28–51)
Female, n (%)	3309 (66.6)	179 (55.4)	3488 (65.9)	2767 (64.7)	140 (53.9)	2907 (64.1)	542 (78.1)	39 (61.9)	581 (76.8)
Referred by, n (%)									
Self	4162 (83.7)	238 (73.7)	4400 (83.1)	3554 (83.1)	194 (74.6)	3748 (82.6)	608 (87.6)	44 (69.8)	652 (86.1)
Doctor	808 (16.3)	85 (26.3)	893 (16.9)	722 (16.9)	66 (25.4)	788 (17.4)	86 (12.4)	19 (30.2)	105 (13.9)
Mode of arrival, n (%)									
Non-ambulance	4209 (84.7)	226 (70.0)	4435 (83.8)	3570 (83.5)	175 (67.3)	3745 (82.6)	639 (92.1)	51 (81.0)	690 (91.2)
Ambulance	761 (15.3)	97 (30.0)	858 (16.2)	706 (16.5)	85 (32.7)	791 (16.2)	55 (7.9)	12 (19.1)	67 (8.9)
Triage category, n (%)									
Immediate	53 (1.1)	35 (10.8)	88 (1.7)	45 (1.1)	32 (12.3)	77 (1.7)	8 (1.2)	3 (4.8)	11 (1.5)
Urgent	2793 (56.2)	241 (74.6)	3034 (57.3)	2112 (49.4)	182 (70.0)	2294 (50.6)	681 (98.1)	59 (93.7)	740 (99.2)
Non-urgent	2124 (42.7)	47 (14.6)	2171 (41.0)	2119 (49.6)	46 (17.7)	2165 (47.7)	5 (0.7)	1 (1.6)	6 (0.8)

Table 2 Serious headache causes

	HEAD and HEAD-Colombia studies	HEAD study	HEAD-Colombia study
	n (%)	n (%)	n (%)
Neoplasm	58 (18.0)	44 (19.2)	14 (22.2)
Non-subarachnoid haemorrhage intracranial haemorrhage	57 (17.6)	50 (19.2)	7 (11.1)
Meningitis	50 (15.5)	46 (16.9)	6 (9.5)
Subarachnoid haemorrhage	44 (13.6)	34 (13.1)	10 (15.9)
Stroke	44 (13.6)	34 (13.1)	10 (15.9)
Idiopathic intracranial hypertensions	39 (12.1)	26 (10.0)	13 (20.6)
Temporal arteritis	12 (3.7)	12 (4.6)	0
Hydrocephalus	4 (1.2)	4 (1.5)	0
Encephalitis	3 (0.9)	3 (1.2)	0
Vascular dissection	3 (0.9)	2 (0.8)	1 (1.6)
Ventriculoperitoneal shunt complications	3 (0.9)	3 (1.2)	0
Cerebral abscess	2 (0.6)	0	2 (3.2)
Hypertensive crisis	2 (0.6)	2 (0.8)	0
Pregnancy hypertension	2 (0.6)	2 (0.8)	0
Total	323	260	63

of investigation and final ED and hospital diagnosis in adult patients presenting to ED with acute non-traumatic headache (absence of head trauma within 48 hours of ED presentation).

Outcome

The primary outcome was serious secondary headache defined as any of the following: subarachnoid haemorrhage (SAH), intracranial haemorrhage (ICH), meningitis, encephalitis, cerebral abscess, intracranial neoplasm, hydrocephalus, vascular dissection, stroke/transient ischaemic attack, hypertensive crisis, pregnancy-related hypertension/eclampsia, temporal arteritis, idiopathic intracranial hypertension (IIH) and ventriculoperitoneal (VP) shunt complications. Final ED diagnosis was used for patients discharged from ED and the final hospital diagnosis was used for patients admitted to hospital.

Overall cohort and subgroup analyses

The outcome was analysed in the overall cohort and in the subgroup without neurological findings. In the overall cohort, 10 commonly accepted SNNOOP10 red flag criteria were examined. The 10 criteria were fever (>38°C), history of neoplasm, neurological deficit (new focal neurological signs or GCS≤12), sudden-onset headache, age >50 years, headache precipitated by exertion including sexual activity, papilloedema, pregnancy or puerperium, recent trauma (between 3 and 7 days previously) and pathology of the immune system.[5] History of neoplasm included cerebral or non-cerebral malignant neoplasm. Sudden onset was described as peaking instantly or almost instantly. Pathology of immune system was defined as chemotherapy, immunosuppressant medication, HIV, intravenous drug user or systemic lupus erythematosus. It should be noted that the HEAD studies did not collect data on the other five SNNOOP10 criteria (positional nature, painful eye with autonomic features, headache pattern change or new onset, painkiller overuse and progressive headache with atypical features) because its design preceded publication of the SNNOOP10 list.

The association between serious secondary headaches and SNNOOP10 red flags was sought using a multivariate binary logistic regression analysis of patients with non-missing data for all red flags. Specifically, the outcome was serious secondary headaches. The predictor variables were fever, neoplasm, neurological deficit, sudden-onset headache, age >50 years, exertion or sexual activity, pregnancy or puerperium, head trauma and pathology of the immune system. The choice of predictor variables was based on their availability in the HEAD study datasets as noted above. Furthermore, as it became apparent that most (88.7%) patients did not undergo funduscopy, papilloedema was not included as a predictor in the logistic regression because this would have significantly reduced the sample size available for the regression analysis.

For the subgroup without neurological findings, patients with new focal neurological signs or GCS≤12 were excluded, as was papilloedema. A logistic regression was similarly performed. The regression analysis provided the ORs for serious secondary headache of each of the red flag criteria adjusted for other red flags or predictors. Statistical analysis was performed using Stata V.16.1 (College Station, Texas).

Additional statistical analysis

The proportions of patients with red flags in the serious and non-serious secondary headache groups were compared using the Pearson χ^2 or Fisher's exact test as appropriate. We also performed an evaluation of the diagnostic accuracy of the red flags using the same method as described by García-Azorín *et al*.[7] Notably, that method excluded patients with missing data as in our study. The sensitivity, specificity, predictive values and area under the receiver operating characteristic curve (AUC) of the SNNOOP10 criteria were reported. The AUC is a measure of how well the criteria discriminate between serious and non-serious secondary headaches.

A sensitivity analysis was performed and explored whether the patient had neurological findings and whether funduscopy was performed. Four groups were analysed: (1) overall cohort including papilloedema (present or absent) as a predictor, (2) overall cohort not including papilloedema, (3) subgroup without neurological findings including papilloedema as a predictor and (4) subgroup without neurological findings not including papilloedema. The analysis regarding neurological findings was planned while the analysis on papilloedema stemmed from the knowledge that most patients did not have a funduscopy.

Sample size

No sample size calculation was performed because this was a secondary analysis.

Clinical trial registration

The study was registered with the Australian New Zealand Clinical Trials Registry (trial number 376695).

Patient and public involvement

Patients and the public were not involved in the design or recruitment of this study. Results were not disseminated to patients.

RESULTS

A total of 5293 patients were included in the HEAD (n=4536) and HEAD-Colombia (n=757) studies. Demographic data of the sample overall are shown in table 1. The breakdown by country is shown in online supplemental table 1. A defined serious headache cause was found in 6.1% (323/5293, 95% CI 5.5% to 6.8%; table 2).

Predictors of serious secondary headaches

Sample derivation for each of the analyses is shown in figure 2. The presence of red flag criteria in the serious versus non-serious

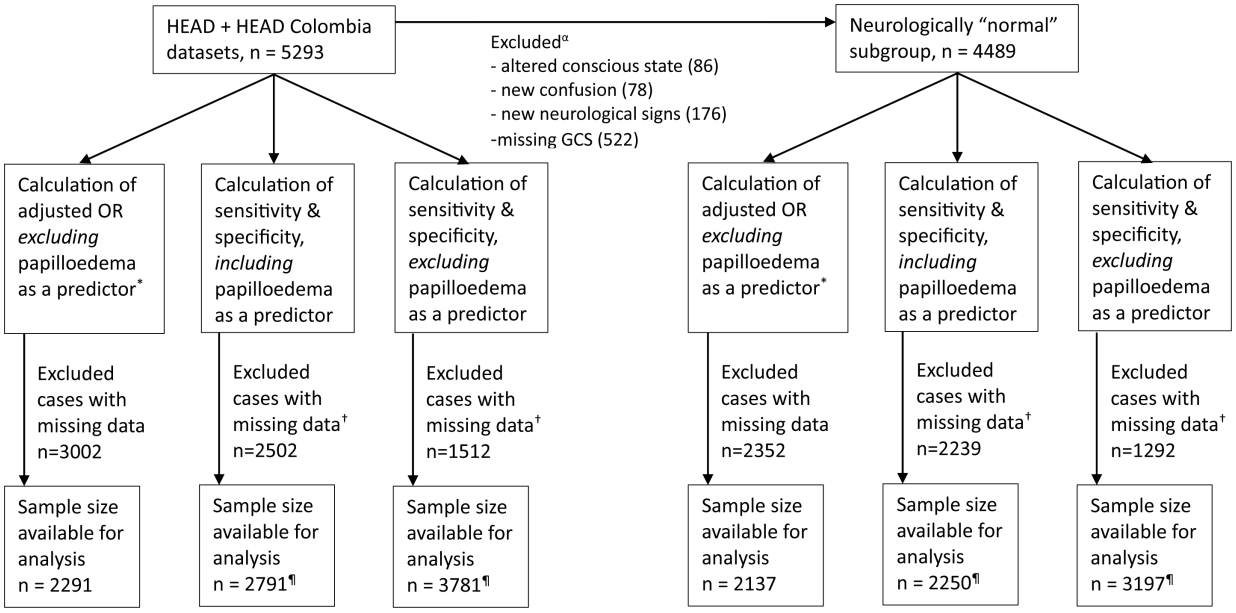

Figure 2 Diagram showing the population derivation for analyses. [α]May be more than one reason for exclusion. *The calculation of adjusted ORs from the logistic regression model requires all predictor variables (red flags) to have non-missing data. Papilloedema was excluded as a predictor because data on papilloedema were missing in most (88.7%) patients as funduscopy was not performed. †Cases with missing data to determine whether SNNOOP10 criteria were present (one or more red flags were present) or absent (all red flags were absent). ¶When papilloedema was excluded as a predictor in the analysis, there were less cases with missing data, and so the sample size analysed became larger.

secondary headache groups is shown in table 3. Key findings were that neurological deficit (new focal neurological signs or GCS≤12; adjusted OR (aOR) 6.63, 95% CI 4.00 to 10.99) and history of neoplasm (aOR 7.82, 95% CI 4.89 to 12.52) were strongly associated with serious secondary headache diagnosis, with older age (>50 years; aOR 2.00, 95% CI 1.39 to 2.86) and head trauma (between 3 and 7 days previously; aOR 2.67, 95% CI 1.08 to 6.55) also being significantly associated but less strongly. Notably, sudden onset of headache was not after adjusting for other predictors (aOR 1.43, 95% CI 0.91 to 2.24) and nor was fever (aOR 2.03, 95% CI 0.73 to 5.62). Onset during exertion or sexual activity, pregnancy or puerperium and

Table 3 Red flags by serious secondary headache diagnosis

	Non-serious secondary headaches n=4970		Serious secondary headaches n=323		Adjusted OR* (95% CI)
Fever (T>38°C)	115/4649	2.5%	17/295	5.8%	2.03 (0.73 to 5.62)
Neoplasm	119/2915	4.1%	43/206	20.9%	7.82 (4.89 to 12.52)
Neurological deficit					
New focal neurological signs	126/4970	2.5%	50/323	15.5%	–
GCS≤12	6/4451	0.13%	13/303	4.3%	–
Any of the above	129/4463	2.9%	58/305	19.0%	6.63 (4.00 to 10.99)
Sudden-onset headache	639/3972	16.1%	62/253	24.5%	1.43 (0.91 to 2.24)
Age >50 years	1480/4970	29.8%	170/323	52.6%	2.00 (1.39 to 2.86)
Precipitated by					
Exertion	283/4970	5.7%	18/323	5.6%	–
Sexual activity	61/4970	1.2%	4/323	1.2%	–
Any of the above	322/4970	6.5%	21/323	6.5%	1.31 (0.64 to 2.68)
Papilloedema	9/539	1.7%	12/61	19.7%	–†
Pregnancy or puerperium‡					
Pregnancy	114/3308	3.5%	5/179	2.8%	–
Puerperium	5/3309	0.15%	1/179	0.56%	–
Any of the above	119/3309	3.6%	6/179	3.4%	1.23 (0.29 to 5.24)
Head trauma§	128/4970	2.6%	10/323	3.1%	2.67 (1.08 to 6.55)
Pathology of immune system¶	16/4970	0.32%	1/323	0.31%	0.85 (0.10 to 7.17)

*From a multivariate logistic regression analysis, n=2291.
†Papilloedema was omitted in the logistic regression model because 88.7% of patients did not have a funduscopy performed.
‡Percentages in females without and with serious secondary headaches, respectively.
§Head trauma >2 days and <1 week.
¶Included immunosuppressive drugs (excluding steroids), chemotherapeutic agents, HIV, intravenous drug user and systemic lupus erythematosus.

Table 4 Subgroup analysis for patients without focal neurological signs, confusion or reduced level of consciousness (GCS<15)

	Non-serious secondary headaches n=4269		Serious secondary headachesn=220		Adjusted OR* (95% CI)
Fever (T>38°C)	99/4126	2.4%	13/211	6.2%	3.27 (1.20 to 8.92)
Neoplasm	111/2576	4.3%	30/143	21.0%	7.27 (4.34 to 12.19)
Sudden-onset headache	485/3477	14.0%	33/177	18.6%	1.07 (0.61 to 1.88)
Age >50 years	1227/4269	28.7%	100/220	45.5%	1.88 (1.25 to 2.82)
Precipitated by					
Exertion	256/4269	6.0%	17/220	7.7%	–
Sexual activity	53/4269	1.2%	3/220	1.4%	–
Any of the above	289/4269	6.8%	19/220	6%	1.32 (0.62 to 2.80)
Papilloedema	8/471	1.7%	12/46	26.1%	–†
Pregnancy or puerperium‡					
Pregnancy	98/2875	3.4%	4/134	3.0%	–
Puerperium	4/2876	0.14%	1/134	0.75%	–
Any of the above	102/2876	3.6%	5/134	3.7%	1.41 (0.33 to 6.01)
Head trauma§	113/4269	2.7%	8/220	3.6%	2.66 (1.01 to 6.97)
Pathology of immune system¶	16/4269	0.37%	0/220	0%	–**

*From a multivariate logistic regression analysis, n=2137.
†Papilloedema was omitted in the logistic regression model because 88.7% of patients did not have a funduscopy performed.
‡Percentages in females without and with serious secondary headaches, respectively.
§Head trauma >2 days and <1 week.
¶Included immunosuppressive drugs (excluding steroids), chemotherapeutic agents, HIV, intravenous drug user and systemic lupus erythematosus.
**Omitted because of no pathology of immune system in serious secondary headache group.

immune suppression were not associated with a serious headache diagnosis.

The subgroup analysis for patients who did not have neurological findings is shown in table 4. In this subgroup, fever (>38°C; aOR 3.27, 95% CI 1.20 to 8.92) was associated with a serious headache diagnosis while other predictors (history of neoplasm, older age and head trauma) also remained significantly associated after adjusting for other predictors.

Diagnostic accuracy in overall cohort including papilloedema as a predictor

In the overall cohort, data to determine whether red flag is present (one or more red flags are present) or absent (all red flags are absent) were only available in half the patients (52.7%, 2791/5293). Diagnostic accuracy was calculated with the available data including funduscopy data. The sensitivity of the 10 red flag criteria studied was 96.5% (95% CI 93.4% to 98.4%) but specificity was very low, 5.1% (95% CI 4.3% to 6.0%). AUC was 0.51 (0.50–0.52) . Positive predictive value (PPV) was 9.3% (95% CI 8.2% to 10.4%) and negative predictive value (NPV) was 93.5% (95% CI 88.0% to 97.0%) (table 5).

Diagnostic accuracy in the overall cohort excluding papilloedema as a predictor

Funduscopy was not performed in a large proportion of patients (88.7%) resulting in missing data on papilloedema (present or absent). When papilloedema was excluded as a predictor, data to determine whether red flag is present or absent were increased to 71.7% of patients (3781/5293). Diagnostic accuracy was calculated with the available data. The sensitivity of the remaining nine red flags was 87.5% (95% CI 82.9% to 91.2%) with improved specificity of 31.6% (95% CI 30.1% to 33.2%).

Table 5 Predictive performance of 10 red flag criteria and outcome

SNNOOP10 criteria	Overall cohort			Overall cohort—funduscopy excluded			No neurological features subgroup (funduscopy included)			No neurological features subgroup (funduscopy excluded)		
	Serious headache cause	Non-serious cause	Total	Serious headache cause	Non-serious cause	Total	Serious headache cause	Non-serious cause	Total	Serious headache cause	Non-serious cause	Total
Present*	246	2407	2653	237	2400	2637	153	1965	2118	144	1958	2102
Absent†	9	129	138	34	1110	1144	9	123	132	33	1062	1095
	255	2536	2791	271	3510	3781	162	2080	2250	177	3020	3197
Sensitivity	96.5% (93.4–98.4%)			87.5% (82.9–91.2%)			94.4% (89.7–97.4%)			81.4% (74.8–86.8%)		
Specificity	5.1% (4.3–6.0%)			31.6% (30.1–33.2%)			5.9% (4.9–7.0%)			35.2% (33.5–36.9%)		
PPV, % (95% CI)	9.3% (8.2% to 10.4%)			9.0% (7.9% to 10.1%)			7.2% (6.2% to 8.4%)			6.9% (5.8% to 8.0%)		
NPV, % (95% CI)	93.5% (88.0% to 97.0%)			97.0% (95.9% to 97.9%)			93.2% (87.5% to 96.8%)			97.0% (95.78% to 97.9%)		

*At least one red flag.
†All were recorded as absent, that is, not as missing.
NPV, negative predictive value; PPV, positive predictive value.

AUC was 0.60 (95% CI 0.57 to 0.62) (online supplemental figure 1). PPV was 9.0% (95% CI 7.9% to 10.1%) and NPV was 97.0% (95% CI 95.9% to 97.9%) (table 5).

Diagnoses that were missed by the red flags were IIH (15), neoplasm (6), viral meningitis (6), SAH (2), stroke (2), ICH (not SAH) (1), VP shunt complication (1) and hydrocephalus (1), constituting a total 34 (12.5%) of serious diagnosis cases.

Diagnostic accuracy in subgroup without neurological findings including papilloedema as a predictor

In this subgroup without neurological findings, data to determine whether red flag is present or absent were again only available in half the patients (50.1%, 2250/4489). Diagnostic accuracy was calculated with the available data including funduscopy data. The sensitivity of the 10 red flag criteria was 94.4% (95% CI 89.7% to 97.4%) and specificity was 5.9% (95% CI 4.9% to 7.0%). AUC was 0.52 (95% CI 0.48 to 0.52). PPV was 7.2% (95% CI 6.2% to 8.4%) and NPV was 93.2% (95% CI 87.5% to 96.8%) (table 5).

Diagnostic accuracy in subgroup without neurological findings excluding papilloedema as a predictor

When papilloedema was excluded, data to determine whether red flag is present or absent were available in 71.2% (3197/4489). Diagnostic accuracy was calculated with the available data. The sensitivity of the remaining nine red flags was 81.4% (95% CI 74.8% to 86.8%) and specificity was 35.2% (95% CI 33.5% to 36.9%). AUC was 0.58 (95% CI 0.55 to 0.61) (online supplemental figure 2). PPV was 6.9% (95% CI 5.8% to 8.0%) and NPV was 97.0% (95% CI 95.8% to 97.9%) (table 5).

Diagnoses that were missed by the red flags (excluding funduscopy) were similar to the group described above with the exception of a case of ICH.

DISCUSSION

Summary

This analysis of a large multinational study addressed the association between commonly accepted red flags for a serious headache diagnosis in the specific setting of ED. Its findings challenge the utility of some of the SNNOOP10 criteria in that setting.

For the overall cohort, new focal neurological signs and history of neoplasm were most strongly associated with serious secondary headache diagnosis, with older age and head trauma also being significantly associated but less strongly. Papilloedema was also associated with serious causes in the univariate analysis, but small numbers of patients with funduscopy precluded its inclusion in the multivariate analysis. Interestingly, headache of sudden onset was not associated with serious causes after adjusting for other predictors.

Perhaps of most relevance to clinical practice in the ED is the subgroup analysis of patients who presented with normal conscious state and without new neurological features (other than headache) or new confusion as these patients have higher diagnostic uncertainty. In that analysis, history of neoplasm, age >50 years and head trauma were again associated with a serious headache diagnosis along with fever. In particular, sudden (thunderclap) headache was not, with and without adjusting for other predictors.

Our findings highlight a key problem with the validation of the red flag approach to identification of serious headache in the ED setting. In particular, the broad range of headache causes and the association of some red flags with specific rare conditions are likely to result in poor predictive performance of some red flags in large and diverse headache populations. That said, the high sensitivity of the red flags as a group may support the use of red flags in conjunction with clinical gestalt. The relative diagnostic accuracy of clinical gestalt, a red flag approach or a combination of these has not yet been investigated.

The low rate of funduscopy is a challenge to the validity of our results. It, however, reflects the reality of contemporary emergency medicine practice.[1] With ready access to advanced imaging in most developed countries, the additional benefit of funduscopy can be questioned. Importantly, there is evidence that even when funduscopy is performed in ED, it has poor accuracy for detection of serious conditions—as low as 0% in one study.[8–10] This emphasises the importance of identifying objective, reliable and easily assessable criteria other than funduscopy that accurately predict a serious headache cause.

Comparison to previous literature

In this study, sensitivity of the combined red flag criteria was lower than previously reported and specificity of the criteria was also low. One previous study of the red flag criteria has shown associations between immunosuppression and older age with secondary headache aetiologies but did not confirm a similar association for sudden onset of headache or abnormal neurological examination.[6] Another study reported that all patients with study-defined high-risk headaches had at least one SNNOOP10 criterion.[7] In that study, the criteria significantly associated with high-risk headache were older age, post-traumatic onset, neurological deficit or dysfunction, and neoplasm in history.[7] That study also noted that most of the criteria had low specificity for high-risk headache.[7] As noted above, the number of patients in both of these studies was much smaller than our cohort.

Regarding sensitivity of the red flag criteria, a study of the SNOOP4 reported a sensitivity of 77.8% with specificity of 73%.[11] Only one small study (of 100 patients) found sensitivity of 100% but had significant selection bias due to inclusion of urgent triage categories only which may have overestimated the sensitivity.[7] In the experience of our research group, patients who are neurologically normal with normal vital signs are more likely to be assigned low triage categories so would have been excluded from that analysis. Unpublished data from this analysis found that approximately 14% of serious headache occurred in patients with lower triage categories.

Onset during exertion including sexual activity, pregnancy and immune suppression were not associated with a serious headache diagnosis. A subgroup analysis of the pregnant subgroup in the HEAD study has previously been published to support this finding.[12]

It should be noted that the previous research studies were both single-centre studies with much smaller sample sizes than this study.[6 7] They collected data on patient and headache features prospectively and using structured tools. All patients were then assessed by a neurologist with ready access to advanced neuroimaging. It is not clear if study neurologists were blinded to the study hypotheses. This is different from the real world of most EDs where assessments are mainly performed by ED doctors of varying seniority and experience and without ready access to all neuroimaging modalities.

Strengths and weaknesses

The strengths of this study are that it represents a real-world ED cohort of patients presenting with headache, has large numbers and was carried out in ED in several countries with different healthcare models.

Limitations include that classification of headache as the main symptom and ED diagnosis were based on clinician judgement. This has been shown to be difficult to classify accurately in ED.[13] Although patients were identified prospectively, some data were collected retrospectively with the inherent risks that impose, including of missing data.[13] With the exception of some Queensland sites and the UK where some form of consent was required, participating institutions were instructed to include all patients presenting with headache within the enrolment period, but some patients may have been missed. Resource did not allow verification of this. That said, given the high number of participating patients, it is unlikely that missed patients at individual EDs would have introduced systematic bias. The design of the study and resource limitations precluded assessment of inter-rater reliability of data collection. Diagnosis was as determined by the ED physician at the end of the ED phase of care. It is possible that some patients may have had further investigations after the ED phase of care which may have identified an alternative diagnosis. Similarly, the nature of ED practice precludes validation of diagnoses. The hospitals were mostly located in developed countries so findings may not be generalisable to the developing world.

Regarding the pooling of data, the parent study was a 1-month snapshot while that HEAD-Colombia study included data collected over a longer period. The HEAD-Colombia study site is a specialist neurological referral centre. This may have resulted in different ED attendance patterns for patients with headache. Not all patients had complete data. We chose to exclude patients with missing data. We chose not to use other approaches such as imputation. We considered the risk of bias from using complete data cases only was less than that of using other statistical approaches to missing data.

Implications for clinical practice and research

The high sensitivity of the SNNOOP10 criteria suggests that they are useful to identify patients at higher risk of a serious secondary headache cause. Sensitivity, however, was not high enough that their absence alone should not be used to determine whether further investigation is required. The low rate of funduscopy and its reported inaccuracy suggest that new and more accurate ways of examining the optic fundus may be needed. Further research is needed, especially focusing on patients with no new neurological features, to identify clinical features predictive of serious secondary headache diagnoses.

CONCLUSION

In this ED-based study, sensitivity of the red flag criteria was lower than previously reported and specificity of the criteria was also low, more so for patients with no new neurological features (other than headache) and in patients in whom funduscopy was not performed. Further research is needed, especially focusing on patients with no new neurological features, to identify clinical features predictive of serious secondary headache diagnoses.

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Acknowledgements HEAD Study Steering Group: Anne Maree Kelly; Kevin H Chu; Win Sen Kuan; Gerben Keijzers; Frances B Kinnear; Mehmet A Karamercan; Sharon Klim; Tissa Wijeratne; Sinan Kamona; Colin A Graham; Richard Body; Tom Roberts; Daniel Horner; Said Laribi. HEAD-Colombia: Alejandro Cardozo-Ocampo; Valentina Jaramillo; Paola Parra. HEAD Study Group: Catherine Lunter (Coffs Harbour Hospital, New South Wales, Australia); Rochelle Facer (Concord Repatriation Hospital, New South Wales, Australia); David Thomson (Port Macquarie Base and Kempsey District Hospitals, New South Wales, Australia); Robert Day (Royal North Shore Hospital, New South Wales, Australia); Greg McDonald (Sydney Adventist Hospital, New South Wales, Australia); Sarah Jones (Tamworth Regional Hospital, New South Wales, Australia); Julian Cochrane (Orange Base Hospital, New South Wales, Australia); Stephen Gourley (Alice Springs Hospital, Northern Territory, Australia); Mark Ross and Vinay Gangathimmaiah (Royal Darwin Hospital, Northern Territory, Australia); Kim Hansen (St Andrew's War Memorial Hospital, Queensland, Australia); Frances B Kinnear (The Prince Charles Hospital, Queensland, Australia); Gerben Keijzers (Gold Coast University Hospital, Queensland, Australia); Kevin Chu (Royal Brisbane and Women's Hospital, Queensland, Australia); Paul Bowe (Robina Hospital, Queensland, Australia); Raymund de la Cruz (Lyell McEwin and Modbury Hospitals, South Australia, Australia); Daniel Haustead (The Queen Elizabeth and Royal Adelaide Hospitals, South Australia, Australia); Jean Moller (University Hospital Geelong, Victoria, Australia); Katie Walker (Cabrini Malvern, Victoria, Australia); Richard D Smith (Bendigo Health, Victoria, Australia); Ron Sultana (Epworth Healthcare, Victoria, Australia); John Pasco (Werribee Mercy Hospital, Victoria, Australia); Neil Goldie and Andis Graudins (Monash Health, Victoria, Australia); Rosamond Dwyer (Peninsula Health, Victoria, Australia); George Plunkett (Melbourne Health, Victoria, Australia); Anne-Maree Kelly (Western Health, Victoria, Australia); Hugh Mitenko (WA Country Health Service, Western Australia); Michael Lovegrove (Joondalup Health Campus, Western Australia); Ben Smedley (Rockingham General Hospital, Western Australia); Colin A Graham and Ling Yan Leung (Prince of Wales Hospital, Hong Kong SAR), Win Sen Kuan and Ying Wei Yau (National University Hospital, Singapore); Wei Ming Ng (Ng Teng Fong General Hospital, Singapore); Ranjeev Kumar (Khoo Teck Puat Hospital, Singapore); Dennis Wen Jie Chia (Sengkang General Hospital, Singapore); Said Laribi (CHU Tours, Tours, France); Mounir Hilal and Rarthtana Mil (CH Vendôme, France); Audrey Gerineau (CHR Orléans, France); Matthew J Reed (Emergency Medicine Research Group Edinburgh (EMERGE), Royal Infirmary of Edinburgh, UK); Daniel Horner (Salford Royal NHS Foundation Trust, Salford, UK); Edward Carlton and Tom Roberts (North Bristol NHS Trust, UK); Girish Boggaram and Jayne Foot (Musgrove Park Hospital, Taunton, UK); Andy Appleboam, Rachel Goss and Hamza Malik (Royal Devon and Exeter NHS Foundation, UK); Richard Body (Manchester Royal Infirmary, Manchester, UK); John-Paul Williamson (Royal Oldham Hospital, Oldham, UK); Adela Golea and Sonia Luka (University County Hospital Cluj-Napoca, Romania); Huseyin Avni Demir (University of Health Sciences Mehmet Akif Inan Training and Research Hospital, Department of Emergency Medicine, Şanlıurfa, Turkey); Şafak Öner Gülpinar (Tokat Erbaa Government Hospital, Tokat, Turkey); Lale Tolu (Bursa Çekirge Government Hospital of Emergency Service, Bursa, Turkey); Muhammet Hacimustafaoğlu (Hakkari Yuksekova Government Hospital, Hakkari, Turkey); Mehmet A Karamercan (Gazi University Faculty of Medicine, Department of Emergency Medicine, Ankara, Turkey); Elif Çelikel (Numune Research and Training Hospital, Department of Emergency Medicine, Ankara, Turkey); Çilem Çaltili (University of Health Sciences Bağcılar Training and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey); Selahattin Gürü (Yıldırım Beyazıt University Faculty of Medicine, Department of Emergency Medicine, Ankara, Turkey); Gülşah Yavuz (Antalya Ataturk Government Hospital of Medicine, Department of Emergency Medicine, Antalya, Turkey); Franck Verschuren (Institute of Experimental and Clinical Research, Emergency Department, Saint-Luc University Hospital, Brussels, Belgium); Christopher Ramos (Emergency Department, Saint-Luc University Hospital, Brussels, Belgium); Paule Denoel and Nicolas Wilmet (Saint Michel, Clinique de l'Europe,

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Contributors KC and A-MK had the concept for the study. The authors codesigned the study and facilitated data collection. KC undertook the analysis and is the guarantor for this work. All authors had input into interpretation of the results. A-MK drafted the manuscript. All authors contributed to refinement of the manuscript.

Funding The Royal College of Emergency Medicine (UK) provided part funding (G/2018/1).

Competing interests RB is deputy editor of *EMJ*.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The lead ethics approvals were from Melbourne Health Human Research Ethics Committee (HREC/43148/MH-2018) and Instituto Neurologico de Colombia–Medellin (PR0107). Approval was obtained for other participating sites according to local requirements.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be available subject to HREC approval.

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Case Number and Demographics

Record ID	_____
Select your Country	◯ 1 Australia ◯ 2 New Zealand ◯ 3 Hong Kong ◯ 4 Singapore ◯ 5 France ◯ 6 United Kingdom ◯ 7 Israel ◯ 8 Belgium ◯ 9 Turkey ◯ 10 Romania ◯ 11 Ireland ◯ 12 Switzerland
Australian State	◯ 1 ACT ◯ 2 NSW ◯ 3 NT ◯ 4 QLD ◯ 5 SA ◯ 6 TAS ◯ 7 VIC ◯ 8 WA
NSW site	◯ 1 Blacktown ◯ 2 Calvary Mater Newcastle ◯ 3 Canterbury ◯ 4 Coffs Harbour ◯ 5 Concord Repatriation General ◯ 6 Kempsey District ◯ 7 Lismore Base ◯ 8 Mt Druitt ◯ 9 Orange Base ◯ 10 Port Macquarie ◯ 11 Royal North Shore ◯ 12 Shoalhaven ◯ 13 Sydney Adventist ◯ 14 Tamworth ◯ 15 The Maitland (Select from drop down list)
ACT site	◯ 1 Calvary Public Bruce
NT Site	◯ 1 Alice Springs ◯ 2 Royal Darwin
QLD site	◯ 1 Cairns ◯ 2 Gold Coast ◯ 3 Mater Adult Public ◯ 4 Mt Isa ◯ 5 Queen Elizabeth II Jubilee ◯ 6 Robina ◯ 7 St Andrew's War Memorial ◯ 8 Royal Brisbane and Women's ◯ 9 The Prince Charles

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SA Site	◯ 1 Calvary Wakefield ◯ 2 Flinders Medical Centre ◯ 3 Lyell McEwin ◯ 4 Modbury Public ◯ 5 Royal Adelaide ◯ 6 The Queen Elizabeth
TAS Site	◯ 1 North West Regional (Burnie) ◯ 2 Royal Hobart
VIC site	◯ 1 Austin Health ◯ 2 Bendigo ◯ 3 Cabrini (Malvern) ◯ 4 Casey (Monash Health) ◯ 5 Clayton (Monash Health) ◯ 6 Dandenong (Monash Health) ◯ 7 Epworth Richmond ◯ 8 Footscray (Western Health) ◯ 9 Frankston (Peninsula Health) ◯ 10 Royal Melbourne ◯ 11 St John of God (Geelong) ◯ 12 Sunshine (Western Health) ◯ 13 University Hospital Geelong (Barwon) ◯ 14 Mercy Health
WA site	◯ 1 Bunbury Regional ◯ 2 Joondalup Health ◯ 3 Sir Charles Gairdner ◯ 4 St John of God (Midland) Public ◯ 5 Rockingham General
Hong Kong Site	◯ 1 Prince of Wales
Singapore Site	◯ 1 Khoo Teck Puat ◯ 2 National University ◯ 3 Ng Teng Fong General ◯ 4 Sengkang General
France site	◯ 1 CHU Tours ◯ 2 CH Le Mans ◯ 3 CH Vendome ◯ 4 CH Chinon ◯ 5 CHR Orleans
Belgium Site	◯ 1 UC Louvain Brussels Belgium University ◯ 2 Cliniques Universitaires Saint-Luc ◯ 3 Cliniques de l'Europe- sainte-Elisabeth ◯ 4 Cliniques de l'Europe- St-Michel ◯ 5 CHU de Charleroi ◯ 6 CHU Liège ◯ 7 CHR Hal ◯ 8 Cliniques Saint-Jean
Ireland Site	◯ 1 St Vincents Dublin

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United Kingdom Site	◯ 1 Royal Infirmary of Edinburgh ◯ 2 Salford Royal NHS Foundation Trust ◯ 3 North Bristol NHS Trust ◯ 4 Taunton and Somerset NHS Foundation Trust (Musgrove Park site) ◯ 5 Royal Devon and Exeter NHS Foundation Trust ◯ 6 Manchester Royal Infirmary ◯ 7 Cardiff and Vale University Health Board (UHB) ◯ 8 Royal Oldham
Romania Site	◯ 1 County Hospital Cluj Cluj Napoca
Turkey Site	◯ 1 Gazi University School of Medicine ◯ 2 Ankara Numune Education and Research Hospital ◯ 3 Istanbul Bagcilar Education and Research Hospital ◯ 4 Ankara Yildirim Beyazit Faculty of Medicine (University) ◯ 5 Sanliurfa Mehmet Akif Inan Education and Research Hospital ◯ 6 Tokat Erbaa Government Hospital ◯ 7 Bursa Cekirge Government Hospital ◯ 8 Hakkari Yuksekova Government Hospital ◯ 9 Antalya Ataturk Government Hospital
Israel Site	◯ 1 Tel-aviv Sourasky Medical Center
New Zealand Site	◯ 1 Auckland City ◯ 2 North Shore ◯ 3 Waitakere ◯ 4 Tauranga ◯ 5 Wellington Regional ◯ 6 Christchurch ◯ 7 Dunedin ◯ 8 Hutt Valley ◯ 9 Middlemore ◯ 10 Nelson ◯ 11 Rotorua ◯ 12 Waikato ◯ 13 Taranaki Base

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Ethnicity (NZ only)	☐ 1 NZ European ☐ 2 Australian ☐ 3 European NFD ☐ 4 NZ Maori ☐ 5 Samoan ☐ 6 Tongan ☐ 7 Cook Island Maori ☐ 8 Pacific Islander NFD ☐ 9 African ☐ 10 American ☐ 11 Asian NFD ☐ 12 Chinese ☐ 13 Fijian ☐ 14 Fijian Indian ☐ 15 Indian ☐ 16 Latin American/Hispanic ☐ 17 Middle Eastern ☐ 18 Niuean ☐ 19 Southeast Asian ☐ 20 Tokelauan ☐ 21 Other ☐ 22 Unknown (Check all boxes that apply (for NZ sites only; required under NZ national ethics approval guidelines))
Age	_____
Gender	◯ 1 Male ◯ 2 Female ◯ 3 Transgender ◯ 4 Unknown
Known Current Pregnancy	◯ 1 No ◯ 2 Yes
Referred by	◯ 1 Self ◯ 2 GP/other doctor (if not documented assume self)
Mode of Arrival	◯ 1 Private Transport/Self ◯ 2 Ambulance ◯ 3 Other
Triage Category	◯ 1 Immediate ◯ 2 Urgent (2 and 3 on a five point scale) ◯ 3 Non Urgent (4 and 5 on a five point scale)

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Past Medical History and Regular Medication

Known Past Medical History
(if not documented assume No)

◯ 1 No
◯ 2 Yes
(If not documented select NO)

	No	Yes
History of recurrent headache (migraine excluded)	◯	◯
Previous migraine diagnosis	◯	◯
Previous cluster headache diagnosis	◯	◯
Previous tension headache diagnosis	◯	◯
Previous stroke/ TIA	◯	◯
Serious intracranial injury - EDH, SDH, traumatic SAH, cerebral contusion requiring hospital admission/ neurosurgery	◯	◯
Presence of a ventriculo-peritoneal shunt	◯	◯
Malignant Intracranial neoplasm - primary	◯	◯
Malignant Intracranial neoplasm - secondary	◯	◯
Intracranial neoplasm - unknown benign v malignant	◯	◯
Known benign intracerebral tumour e.g. Meningioma	◯	◯
Non-cerebral malignancy without known intracranial secondary neoplasm	◯	◯
Subarachnoid haemorrhage	◯	◯
Intracranial aneurysm without SAH	◯	◯
Intracranial hypertension	◯	◯
Known Intracranial vascular abnormality e.g.AVM	◯	◯
Other Past Medical History (not listed above and you consider relevant to the cause of headache)	◯	◯

Other Past Medical History

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Regular Medications Taken	◯ 1 No ◯ 2 Yes

Regular Medications (If information is NOT documented select NO)

	No	Yes
Triptan	◯	◯
Beta-blockers - propranolol, metoprolol, atenolol, bisoprolol, timolol, etc	◯	◯
Pizotifen (Sandomigran)	◯	◯
Topiramate (Topamax)	◯	◯
Tricyclic antidepressants - amitriptyline, nortriptyline, etc	◯	◯
Sodium valproate	◯	◯
Candesartan	◯	◯
Verapamil	◯	◯
Botulinum toxin	◯	◯
Anticoagulants - Novel Oral Anticoagulants (NOAC), warfarin, Vit K antagonist	◯	◯
Long term use of codeine preparations	◯	◯
Other opioids	◯	◯

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Clinical History and Clinical Examination

Duration of Symptoms	◯ 1= < 24 hours ◯ 2= 1-3 days ◯ 3= >3 days ◯ 4= Unknown
Onset of Symptoms	◯ 1 Gradual ◯ 2 Sudden/Thunderclap (peaking instantly or almost) ◯ 3 Peak within 1 hour but not instant ◯ 4 Unknown
Location of Headache	◯ 1 Generalized ◯ 2 Unilateral ◯ 3 Unclear
Severity	◯ 1 Mild (pain score up to 3/10) ◯ 2 Moderate (pain score 4-7/10) ◯ 3 Severe (pain score 8 or more/10) ◯ 4 Unclear
Worst headache ever?	◯ 1 No ◯ 2 Yes (If not documented select NO)
Head Trauma within the last week	◯ 1 No ◯ 2 Yes
Relationship to exertion	◯ 1 No ◯ 2 Yes (If not documented select NO)
Relationship to sexual activity	◯ 1 No ◯ 2 Yes (If not documented select NO)
Reported neck pain or stiffness	◯ 1 No ◯ 2 Yes (If not documented select NO)
Nausea or vomiting	◯ 1 No ◯ 2 Yes (If not documented select NO)
Syncope/ loss of consciousness	◯ 1 No ◯ 2 Yes (If not documented select NO)
Photophobia. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)
New limb weakness transient or current. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)

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New limb paraesthesia transient or current. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)
New speech difficulty - including slurred speech, inability to speak, etc. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)
New reported visual disturbance - transient or ongoing. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)
Subjective fever or rigors. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)
Rash. Reported by patient.	◯ 1 No ◯ 2 Yes (If not documented select NO)
Current or recent Intravenous drug use	◯ 1 No ◯ 2 Yes (If not documented select NO)
Medication Taken Pre- ED (this episode) - must specify to have been self administered by patient	◯ 1 No ◯ 2 Yes

	No	Yes
Paracetamol (pre-ED self administered)	◯	◯
Aspirin (pre-ED self administered)	◯	◯
NSAID, excluding Aspirin (pre-ED self administered)	◯	◯
Codeine containing preparation (pre-ED self administered)	◯	◯
Triptan (pre-ED self administered)	◯	◯
Oxycodone (e.g. endone, oxycontin, oxynorm, targin) (pre-ED self administered)	◯	◯
Tramadol (pre-ED self administered)	◯	◯
Other Opiate (pre-ED self administered)	◯	◯
Antiemetic-metoclopramide, prochlorperazine, ondansetron (pre-ED self administered)	◯	◯

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Other medication to treat headache (pre-ED self administered)	◯	◯

Pre ED medications to treat headache or cause of headache- Specify other type not previously listed

_____
(specify other medication if applicable)

Ambulance Pre Hospital Medication Administered

◯ 1 No
◯ 2 Yes
◯ 3 Not documented
(This refers to medications administered to treat headache or presumed cause of headache. Must specify medication administered by Ambulance Team)

	No	Yes
Paracetamol (in ambulance)	◯	◯
Aspirin (in ambulance)	◯	◯
NSAID, excluding Aspirin (in ambulance)	◯	◯
Codeine containing preparation (in ambulance)	◯	◯
Triptan (in ambulance)	◯	◯
Oxycodone (e.g. endone, oxycontin, oxynorm, targin) (in ambulance)	◯	◯
Tramadol (in ambulance)	◯	◯
Fentanyl (in ambulance)	◯	◯
Oramorph (in ambulance)	◯	◯
Morphine Sulphate IV (in ambulance)	◯	◯
Other Opiate (in ambulance)	◯	◯
Antiemetic-metoclopramide, prochlorperazine, ondansetron (in ambulance)	◯	◯
Methoxyflurane (in ambulance)	◯	◯
Antibiotics (in ambulance)	◯	◯
Other medication to treat headache or presumed cause of headache (in ambulance)	◯	◯

Other Medications given by Ambulance to treat headache or presumed cause of headache. Please specify type

_____
(specify other medication if applicable)

Clinical Examination in ED
Pulse Rate

_____
(FIRST RECORDED IN EMERGENCY DEPARTMENT)

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Clinical Examination in ED Systolic BP	_____ (FIRST RECORDED IN EMERGENCY DEPARTMENT)
Clinical Examination in ED TEMPERATURE TAKEN (recorded numerically Celcius)	◯ 1 No ◯ 2 Yes
Clinical Examination in ED Temperature recorded AFEBRILE / NO FEVER FEBRILE / FEVER	◯ 1 AFEBRILE / NO FEVER ◯ 2 FEBRILE / FEVER ◯ 3 UNKNOWN (No numerical temperature recorded, but history does specify temperature in words)
Clinical Examination in ED Temperature (Celsius)	_____ (FIRST RECORDED IN EMERGENCY DEPARTMENT)
Clinical Examination in ED Is GCS score known	◯ 1 Known ◯ 2 Unknown
GCS- Eye	_____
GCS Verbal	_____
GCS Motor	_____
GCS Overall	_____
Clinical Examination in ED Rash (observed by Clinician)	◯ 1 No ◯ 2 Yes (If not documented select NO)
Clinical Examination in ED Confusion (observed by Clinician)	◯ 1 No ◯ 2 Yes (If not documented select NO)
Clinical Examination in ED Meningism	◯ 1 No ◯ 2 Yes (If not documented select NO)
Clinical Examination in ED Limited Neck Flexion (on examination)	◯ 1 No ◯ 2 Yes (If not documented select NO)
Clinical Examination in ED New Focal Neurological Signs	◯ 1 No ◯ 2 Yes (If not documented select NO)

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New Focal Neurological Sign	◯ 1 Isolated speech deficit ◯ 2 Isolated unilateral limb weakness ◯ 3 Speech deficit and limb weakness ◯ 4 Incoordination/cerebellar signs ◯ 5 Other
Describe Other New Focal Neurological Sign	_____
Clinical Examination in ED New Vision Defect	◯ 1 No ◯ 2 Yes (If not documented select NO)
Clinical Examination in ED Ophthalmoscopy Findings	◯ 1 Not done ◯ 2 Normal ◯ 3 Papilloedema ◯ 4 Other (specify) (If not documented select NO)
Ophthalmoscopy Findings (specification of other findings)	_____

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Investigations

White Cell Count Done	◯ 1 No ◯ 2 Yes
White Cell Count x10-9/L	_____
Neutrophil Count Done	◯ 1 No ◯ 2 Yes
Neutrophil Count (x10-9/L)	_____
C-Reactive Protein Done	◯ 1 No ◯ 2 Yes
C-Reactive Protein unit of measure	◯ mg/L ◯ micromol/L (Select the unit of measure for the C- Reactive Protein Value to be inserted below)
C-Reactive Protein	_____
Lumbar Puncture Performed	◯ 1 No ◯ 2 Yes
Lumbar Puncture Results	◯ 1 Normal ◯ 2 Indicative of infection on microscopy ◯ 3 Indicative of SAH (red cell count or xanthochromia) ◯ 4 Indicative of raised intracranial pressure ◯ 5 Inconclusive
CT Scan Performed	◯ 1 No ◯ 2 Yes
CT Scan Result	◯ 1 Normal ◯ 2 Abnormal
CT Abnormality	◯ 1 SAH ◯ 2 Other bleed ◯ 3 Abscess ◯ 4 Neoplasm ◯ 5 Other (free text describe)
CT Abnormality (OTHER) description	_____
MRI Performed	◯ 1 No ◯ 2 Yes
MRI Result	◯ 1 Normal ◯ 2 Abnormal

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MRI Abnormality	◯ 1 Bleed ◯ 2 Abscess ◯ 3 Neoplasm ◯ 4 Other (describe below)
MRI Abnormality (OTHER) description	_____
CT Angiography Performed	◯ 1 No ◯ 2 Yes
CT Angiography Result	◯ 1 Normal ◯ 2 Abnormal
CT Angiography Abnormality	◯ 1 Aneurysm with bleed ◯ 2 Aneurysm without bleed ◯ 3 No aneurysm ◯ 4 Other (free text describe)
CT Angiography (Other) description	_____
Other Imaging Performed	◯ 1 No ◯ 2 Yes
Other Imaging (specify what type of imaging and provide results description)	_____

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ED Treatment and Intervention

Medication to treat headache or cause of headache given in ED	◯ 1 No ◯ 2 Yes
Medications given after the initial clinical assessment (including nurse-initiated medications)	◯ 1 No ◯ 2 Yes

	No	Oral	Parenteral
Paracetamol administered in ED	◯	◯	◯
Aspirin administered in ED	◯	◯	◯
NSAID (other than Aspirin) administered in ED	◯	◯	◯
Codeine containing compounds administered in ED	◯	◯	◯
Triptan administered in ED	◯	◯	◯
Oxycodone administered in ED	◯	◯	◯
Pethidine/Meperidine administered in ED	◯	◯	◯
Other Opioid administered in ED	◯	◯	◯
Chlorpromazine Infusion administered in ED	◯	◯	◯
Metoclopramide administered in ED	◯	◯	◯
Ondansetron administered in ED	◯	◯	◯
Prochlorperazine administered in ED	◯	◯	◯
Droperidol/ Haloperidol administered in ED	◯	◯	◯
Ergot Alkaloids administered in ED	◯	◯	◯
Corticosteroid administered in ED	◯	◯	◯
Antibiotic/ Antiviral agent administered in ED	◯	◯	◯
Other Medication administered in ED to treat headache or cause of headache	◯	◯	◯

OTHER ED Medication. Please specify	_____
Treatment in ED after initial clinical assessment	◯ 1 No ◯ 2 Yes
Treatment in ED Oxygen Therapy	◯ 1 No ◯ 2 Yes (after initial clinical assessment)

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Treatment in ED Acupuncture	◯ 1 No ◯ 2 Yes (after initial clinical assessment)
Treatment in ED Intravenous fluids (not part of a drug infusion)	◯ 1 No ◯ 2 Yes (after initial clinical assessment)
Follow-up Medications given > 30 minutes after initial medications	◯ 1 No ◯ 2 Yes

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	No	Oral	Parenteral
Paracetamol administered in ED - more than 30 mins after primary treatment	○	○	○
Aspirin administered in ED - more than 30 mins after primary treatment	○	○	○
NSAID (other than Aspirin) administered in ED - more than 30 mins after primary treatment	○	○	○
Codeine containing compounds administered in ED - more than 30 mins after primary treatment	○	○	○
Triptan administered in ED - more than 30 mins after primary treatment	○	○	○
Pethidine/Meperidine administered in ED - more than 30 mins after primary treatment	○	○	○
Other Opioid administered in ED - more than 30 mins after primary treatment	○	○	○
Oxycodone administered in ED - more than 30 mins after primary treatment	○	○	○
Chlorpromazine Infusion administered in ED - more than 30 mins after primary treatment	○	○	○
Metoclopramide administered in ED - more than 30 mins after primary treatment	○	○	○
Ondansetron administered in ED - more than 30 mins after primary treatment	○	○	○
Prochlorperazine administered in ED - more than 30 mins after primary treatment	○	○	○
Droperidol/ Haloperidol administered in ED - more than 30 mins after primary treatment	○	○	○
Ergot Alkaloids administered in ED - more than 30 mins after primary treatment	○	○	○

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Antibiotic/ Antiviral Agent administered in ED - more than 30 mins after primary treatment	◯	◯	◯
Corticosteroid administered in ED - more than 30 mins after primary treatment	◯	◯	◯
Other Medication (oral or parenteral) administered in ED - more than 30 mins after primary treatment	◯	◯	◯

Other medication given > 30 minutes after initial treatment. Provide description	_____
Treatment in ED > 30 minutes after initial treatment	◯ 1 No ◯ 2 Yes
Treatment in ED Oxygen Therapy	◯ 1 No ◯ 2 Yes (> 30 minutes after initial treatment)
Treatment in ED Acupuncture	◯ 1 No ◯ 2 Yes (> 30 minutes after initial treatment)
Treatment in ED Intravenous fluids (not part of a drug infusion)	◯ 1 No ◯ 2 Yes (> 30 minutes after initial treatment)
ED Intubation and mechanical ventilation	◯ No ◯ Within 30 minutes of arrival at ED ◯ After 30 minutes of arrival at ED
Neurosurgical Intervention performed	◯ 1 No ◯ 2 Yes
Neurosurgical Intervention Time	◯ 1 Within 24 hours ◯ 2 = >24 hours
Interventional Radiology Performed	◯ 1 No ◯ 2 Yes
Interventional Radiology Time	◯ 1= Within 24 hours ◯ 2 = >24 hours

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Final ED Diagnosis and Disposition

Final ED Diagnosis	◯ 1 Primary headache (benign headache not otherwise specified) ◯ 2 Migraine ◯ 3 Cluster headache ◯ 4 Musculoskeletal ◯ 5 Tension headache ◯ 6 Subarachnoid haemorrhage ◯ 7 Other intracranial haemorrhage ◯ 8 Post coital headache ◯ 9 Neoplasm ◯ 10 Viral illness without meningitis ◯ 11 Sinusitis ◯ 12 Meningitis (viral) ◯ 13 Meningitis (bacterial) ◯ 14 Meningitis (Fungal) ◯ 15 Meningitis(unknown) ◯ 16 Encephalitis ◯ 17 Stroke ◯ 18 Post-traumatic headache ◯ 19 Cerebral abscess ◯ 20 Toxicity e.g. CO (specify) ◯ 21 Trigeminal neuralgia/ cranial neuralgias ◯ 22 Glaucoma ◯ 23 Alcohol-related hangover ◯ 24 Analgesia overuse ◯ 25 Temporal arteritis ◯ 26 Intracranial hypertension ◯ 27 Vascular dissection ◯ 28 Shingles (herpes zoster) of head/ neck ◯ 29 Other (specify) ◯ 30 Unclear
ED Diagnosis (OTHER or TOXICITY) please describe	_____
Disposition	◯ 1 Home from ED Observation Unit (EOU) ◯ 2 Home from ED ◯ 3 Admit ward ◯ 4 Admit critical care ◯ 5 Transfer ◯ 6 Unknown ◯ 7 Died in ED ◯ 8 Theatre ◯ 9 Interventional Radiology

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Final Hospital Diagnosis (for admitted patients only)	◯ 1 Primary headache (benign headache not otherwise specified) ◯ 2 Migraine ◯ 3 Cluster headache ◯ 4 Musculoskeletal ◯ 5 Tension headache ◯ 6 Subarachnoid haemorrhage ◯ 7 Other intracranial haemorrhage ◯ 8 Post coital headache ◯ 9 Neoplasm ◯ 10 Viral illness without meningitis ◯ 11 Sinusitis ◯ 12 Meningitis (viral) ◯ 13 Meningitis (bacterial) ◯ 14 Meningitis (fungal) ◯ 15 Meningitis(unknown) ◯ 16 Encephalitis ◯ 17 Stroke ◯ 18 Post-traumatic headache ◯ 19 Cerebral abscess ◯ 20 Toxicity e.g. CO (specify) ◯ 21 Trigeminal neuralgia/ cranial neuralgias ◯ 22 Glaucoma ◯ 23 Alcohol-related hangover ◯ 24 Analgesia overuse ◯ 25 Temporal arteritis ◯ 26 Intracranial hypertension ◯ 27 Vascular dissection ◯ 28 Shingles (herpes zoster) of head/ neck ◯ 29 Other (specify) ◯ 30 Unclear (Select from drop down list)
Final Hospital Diagnosis (OTHER or TOXICITY) please describe	_____
In-Patient Outcome (for admitted patients only)	◯ 1= discharged alive ◯ 2= died ◯ 3= unknown (Select from drop down list)
Length of Stay (total days - including day of admission and day of discharge)	_____ (Any partial days =1 day. If admitted and discharged within 24 hours = 1 day.)
Medication prescribed at discharge from ED/ ED Observation Unit	◯ No ◯ Yes

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	No	Yes
Paracetamol (on discharge from ED or EOU)	◯	◯
Aspirin (on discharge from ED or EOU)	◯	◯
Codeine containing compounds (on discharge from ED or EOU)	◯	◯
NSAID (other than aspirin) (on discharge from ED or EOU)	◯	◯
Triptan (on discharge from ED or EOU)	◯	◯
Oxycodone (on discharge from ED or EOU)	◯	◯
Tramadol (on discharge from ED or EOU)	◯	◯
Other Opioid (on discharge from ED or EOU)	◯	◯
Metoclopramide (on discharge from ED or EOU)	◯	◯
Prochlorperazine (on discharge from ED or EOU)	◯	◯
Ondansetron (on discharge from ED or EOU)	◯	◯
Ergot Alkaloids (on discharge from ED or EOU)	◯	◯
Antibiotic/antiviral agent (on discharge from ED or EOU)	◯	◯
Corticosteroid (on discharge from ED or EOU)	◯	◯
Other medication to treat headache or cause of headache prescibed (on discharge from ED or EOU)	◯	◯

Other ED discharge medications. This refers to medications to treat headache or cause of headache _____

Representation within 72 hours (patients discharged from ED only)
◯ 1 No
◯ 2 Yes

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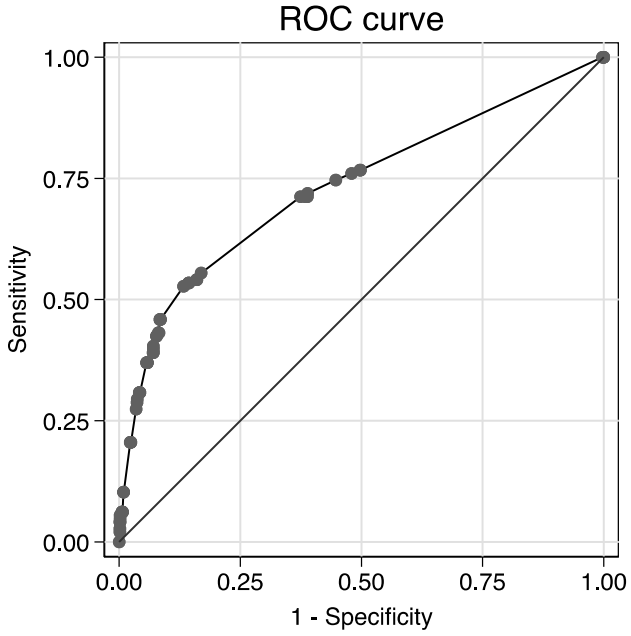
Representation Final ED Diagnosis	◯ 1 Primary headache (benign headache not otherwise specified) ◯ 2 Migraine ◯ 3 Cluster headache ◯ 4 Musculoskeletal ◯ 5 Tension headache ◯ 6 Subarachnoid haemorrhage ◯ 7 Other intracranial haemorrhage ◯ 8 Post coital headache ◯ 9 Neoplasm ◯ 10 Viral illness without meningitis ◯ 11 Sinusitis ◯ 12 Meningitis (viral) ◯ 13 Meningitis (bacterial) ◯ 14 Meningitis (Fungal) ◯ 15 Meningitis(unknown) ◯ 16 Encephalitis ◯ 17 Stroke ◯ 18 Post-traumatic headache ◯ 19 Cerebral abscess ◯ 20 Toxicity e.g. CO (specify) ◯ 21 Trigeminal neuralgia/ cranial neuralgias ◯ 22 Glaucoma ◯ 23 Alcohol-related hangover ◯ 24 Analgesia overuse ◯ 25 Temporal arteritis ◯ 26 Intracranial hypertension ◯ 27 Vascular dissection ◯ 28 Shingles (herpes zoster) of head/ neck ◯ 29 Other (specify) ◯ 30 Unclear
Representation ED Diagnosis (OTHER or TOXICITY) please describe	_____
If represented, was patient admitted/ transferred for admission	◯ 1 No ◯ 2 Yes
Neurosurgery at Representation Visit	◯ 1 No ◯ 2 Within 24 hours ◯ 3 Within 1 week
Interventional Radiology at Representation	◯ 1 No ◯ 2 Within 24 hours ◯ 3 Within 1 week

Supplementary table 1. Sample size by country

Country	n	(%)
Australia	1,777	(33.6)
Turkey	982	(18.6)
Colombia	757	(14.3)
New Zealand	593	(11.2)
Singapore	579	(10.9)
United Kingdom	276	(5.2)
France	114	(2.2)
Belgium	70	(1.3)
Romania	69	(1.3)
Hong Kong	64	(1.2)
Israel	12	(0.2)
Total	5,293	

Supplementary figure 1. Area under ROC curve (AUC) calculated from a multivariate logistic model of 2137 patients with no missing data for any red flags (papilloedema was not included as a predictor) – Overall cohort



Supplementary figure 2. Area under ROC curve (AUC) calculated from a multivariate logistic model of 2137 patients with no missing data for any red flags (papilloedema was not included as a predictor) – No neurological features cohort