

PERSPECTIVE

Red flags in headache care

Headaches are a prevalent, but highly non-specific, complaint. Although most patients seek symptom relief, reducing the pain is never the sole aim of a consultation.¹ Understanding whether the pain is the first manifestation of dangerous disease is equally essential; headaches offer the opportunity to detect early potentially life-threatening disorders.²

Secondary headaches divide into two categories.³ Diagnosing those in the first group requires no additional examinations (e.g., “headaches attributed to a substance or its withdrawal”). Conversely, additional examinations are indispensable to diagnose those in the second group (e.g., “headaches attributed to intracranial neoplasia”).

Diagnostic tests investigating the presence of underlying diseases are available, but their use warrants consideration given their price and the sheer number of headache patients. Therefore, diagnosing a headache comprises pondering the available evidence and the need for more evidence. Red Flags may simplify the latter.

Red Flags can be interpreted like *screening tests* identifying patients whose *headache diagnosis is not known yet* as having an elevated risk of a secondary headache. The primary strategy is to use readily available information to infer the unknown.

Different publications share a similar understanding of Red Flags but offer only conceptualized definitions.^{4,5} A possible operationalized definition that accommodates all published Red Flags, therefore, would consist of the following.

Definition: In patients with an undetermined headache, a sign or symptom is a Red Flag if a secondary headache is more likely in its *presence* than in individuals who do not screen positive for the Red Flag.

The disadvantage of this definition is that the probability of a secondary headache in the presence of the Red Flag might be tiny and marginally bigger than the prior probability (see Example 1 in the Supporting Information). Moreover, there is a risk of this definition being applicable only under certain circumstances (e.g., in primary but not tertiary care).

Above, we defined Red Flags as a symptom or sign. However, using them to predict the probability of a secondary headache implies a second meaning of the term. It is also a diagnostic test that reports the probability of a secondary headache, given the presence of one defined symptom or sign. Thus, it is a measure of *conditional probability*.

Let $SH+$ be the event of the presence of a secondary headache, and $RF+$ the event of the presence of a Red Flag. Then, Bayes' theorem describes the relationships of the probabilities of the investigated events as follows.

$$P(SH+|RF+) = \frac{P(RF+|SH+) \cdot P(SH+)}{P(RF+)}$$

According to Bayes' theorem, three factors determine the conditional probability of a secondary headache in the presence of a Red Flag.

- The higher the number of patients with a secondary headache *exhibiting a Red Flag*, the higher the probability of a secondary headache in the presence of the Red Flag. Consequently, a Red Flag is better at diagnosing a secondary headache if the Red Flag *regularly* accompanies the headache (Example 2).
- The probability of a secondary headache in the presence of a Red Flag, is higher if the secondary headache is prevalent. Put differently, *frequently occurring* headaches occur *frequently*—even in the absence of a Red Flag.
- As the probability of a Red Flag occurrence stands in the denominator, the conditional probability of a headache being secondary given a Red Flag is higher if the Red Flag occurs *infrequently*. Conversely, a *frequent* Red Flag increases the probability of a *rare* secondary headache only slightly (Example 3).

The following recommendations may help design Red Flags.

1. Red Flags must be unequivocal and easy to assess, as collecting inaccurate information will flaw the conclusions (Examples 4 and 5).
2. Unless otherwise specified, Red Flags assess *single headache attacks*—not recurring headache disorders—but their application is not necessarily limited to *present* headaches (Example 6).
3. “Catch all” Red Flags that nonspecifically suggest the presence of any secondary headache are not helpful because they do not indicate which diagnostic test to order and which underlying disease to suspect (Example 7).
4. A Red Flag should meet the definition (see above) in all non-trivial subsets of patients with headache; otherwise, their application would be limited to specific populations (Example 8). Consequently, if this condition is met, Red Flags must be seen as indicative of a secondary headache irrespective of the context in which they occur (Example 9).
5. Red Flags should regularly accompany the secondary headache they are to detect, but infrequently occur in patients without the secondary headache (Examples 2 and 3).

6. It is acceptable to assume a secondary headache erroneously and order additional tests; however, mistakenly diagnosing a primary headache is not. Thus, Red Flags must have a sensitivity close to 100% (Example 10). The term sensitivity refers to the true positive rate (i.e., the probability of exhibiting a Red Flag of patients in whom the headache actually is a secondary headache).⁶
7. Whereas single Red Flags screen for a subset of secondary headaches, all Red Flags *must screen for all* of those that require Red Flags (see above). Otherwise, one might miss a secondary headache (Example 11).
8. The total number of Red Flags should be as low and their specificity as high as possible.
Although having more information is better than having less, it must be borne in mind that the information collected through Red Flags is, generally, imprecise. The specificity of a Red Flag that indicates the probability of the absence of a Red Flag in patients who do not have a secondary headache (i.e., the true negative rate),⁶ is unlikely to be 100% in any Red Flag. However, as this parameter influences the likelihood of unnecessarily ordered examinations, a higher number of Red Flags might increase the number of unnecessarily ordered examinations (Example 12).
9. A Red Flag should appear together with the secondary headache because, otherwise, it is more difficult to relate them. Red Flags that appear independently from the secondary headache convey no temporal information (Example 13).
10. Red Flags and the secondary headache should, ideally, have a *causal* link.

The association of Red Flags with the underlying disorder is either probabilistic or probabilistic *and* mechanistic. It is a *risk factor* in the former case, and, in the latter, a *symptom* or a *cause*. The difference is that a symptom implies that the patient is already diseased, whereas a risk factor provides less temporal information (Example 13). Note that diagnostic criteria are not Red Flags despite a causal connection (Example 14).

[Correction added on 4th February 2022, after first online publication: Part of the text for recommendation 10 had been mistakenly listed in a separate point 11 and this has been corrected.]

Accuracy, measured by sensitivity and specificity, and reliability determine the quality of screening tests and their value in clinical practice.⁷ They need to be assessed for all Red Flags.

However, although reliability and accuracy are crucial, further information is necessary to appreciate Red Flags' quality fully. Given that the prevalence of secondary headaches differs between populations (primary, secondary, and tertiary care and emergency department) and influences the positive predictive value⁷ (i.e., the probability of suffering from a secondary headache in patients exhibiting a Red Flag⁶) and likely sensitivity and specificity,⁸ it is important to report how data were collected. In addition, it would be prudent to report the evidence level for each Red Flag.

Currently, recommended Red Flags are a heterogeneous group of screening tests that assess risk factors or symptoms of secondary

headaches. They are an indispensable tool to identify patients at risk of a secondary headache and decide the need for further testing. However, their quality requires meticulous attention as they do not all perform equally well.

KEYWORDS

diagnosis, secondary headache, sensitivity, specificity

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CONFLICT OF INTEREST

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REFERENCES

1. Packard RC. What does the headache patient want? *Headache*. 1979;19(7):370-374.
2. Filler L, Akhter M, Nimlos P. Evaluation and management of the emergency department headache. *Semin Neurol*. 2019;39(1):20-26.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
4. Do TP, Remmers A, Schytz HW, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. *Neurology*. 2019;92(3):134-144.
5. Randall Clinch C. Evaluation of acute headaches in adults. *Am Fam Physician*. 2001;63(4):685-693.
6. Held L, Rufibach K, Seifert B. *Medizinische Statistik*, 1st edition. Pearson Studium; 2013:448.
7. Mahe C, Gaffikin L. Screening test accuracy studies: how valid are our conclusions? Application to visual inspection methods for cervical screening. *Cancer Causes Control*. 2005;16(6):657-666.
8. Leeflang MMG, Rutjes AWS, Reitsma JB, et al. Variation of a test's sensitivity and specificity with disease prevalence. *CMAJ*. 2013;185(11):E537-E544.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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