



# Factors Associated with Incidental Neuroimaging Abnormalities in New Primary Headache Patients

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**Background and Purpose** Deciding whether or not to perform neuroimaging in primary headache is a dilemma for headache physicians. The aim of this study was to identify clinical predictors of incidental neuroimaging abnormalities in new patients with primary headache disorders.

**Methods** This cross-sectional study was based on a prospective multicenter headache registry, and it classified 1,627 consecutive first-visit headache patients according to the third edition (beta version) of the International Classification of Headache Disorders (ICHD-3 $\beta$ ). Primary headache patients who underwent neuroimaging were finally enrolled in the analysis. Serious intracranial pathology was defined as serious neuroimaging abnormalities with a high degree of medical urgency. Univariable and multivariable logistic regression analyses were conducted to identify factors associated with incidental neuroimaging abnormalities.

**Results** Neuroimaging abnormalities were present in 170 (18.3%) of 927 eligible patients. In multivariable analysis, age  $\geq 40$  years [multivariable-adjusted odds ratio (aOR)=3.37, 95% CI=2.07–6.83], male sex (aOR=1.61, 95% CI=1.12–2.32), and age  $\geq 50$  years at headache onset (aOR=1.86, 95% CI=1.24–2.78) were associated with neuroimaging abnormalities. In univariable analyses, age  $\geq 40$  years was the only independent variable associated with serious neuroimaging abnormalities (OR=3.37, 95% CI=1.17–9.66), which were found in 34 patients (3.6%). These associations did not change after further adjustment for neuroimaging modality.

**Conclusions** Incidental neuroimaging abnormalities were common and varied in a primary headache diagnosis. A small proportion of the patients incidentally had serious neuroimaging abnormalities, and they were predicted by age  $\geq 40$  years. These findings can be used to guide the performing of neuroimaging in primary headache disorders.

**Key Words** primary headache disorders, headache, neuroimaging, magnetic resonance imaging, logistic models.

## INTRODUCTION

Headache disorders are very common, with a global prevalence of 47% and a lifetime prevalence  $\geq 66\%$ .<sup>1-3</sup> Although detailed history-taking and a neurological examination form the basis for an accurate diagnosis of headache disorders, neuroimaging is a critical tool in headache clinical practice when brain imaging facilities are available.<sup>4</sup> However, financial restrictions and exposure to radiation prevent routine neuroimaging being performed in every patient who presents with headache.<sup>5</sup> Several guidelines discourage routine neuroimaging in patients with migraine or chronic headache due to a low yield found in previous studies.<sup>6-9</sup> Nonetheless, the number of neuroimaging orders for evaluating headache has increased in the US and other advanced countries since the publication of these guidelines.<sup>5,10-14</sup>

In real-world practice, the probability of a serious intracranial abnormality in patients

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with headache differs widely according to the care setting (outpatient clinic vs. emergency department), patient characteristics (e.g., age, past medical illness, and cancer history), and headache features (typical primary headache vs. sinister features suggesting secondary headache).<sup>11,15-21</sup> Moreover, the development of clinical manifestations in a serious secondary headache are occasionally similar to that in a typical primary headache.<sup>11,19,22-25</sup> These issues can make it difficult to decide whether or not to perform neuroimaging for a headache disorder based only on clinical findings or simple criteria in daily clinical practice.

Given the discrepancy between the guidelines and real-world practice, identifying the predictors of intracranial abnormalities in specific situations might facilitate the development of a good practical guide for decision-making regarding neuroimaging. Outpatient clinics are typically the most-common setting in which primary headaches are encountered.<sup>26,27</sup> Most neuroimaging tests can be ordered on the first visit, but little is presently known about the predictors of incidental intracranial abnormalities in new primary headache patients. The aim of this study was therefore to identify the factors associated with incidental neuroimaging abnormalities in new patients diagnosed with primary headache disorders using data in a multicenter headache registry.

## METHODS

### Study design and patients

This cross-sectional study performed a post-hoc analysis of data from the HEREIN multicenter headache registry study [Headache Registry using the third edition (beta version) of the International Classification of Headache Disorders (ICHD-3 $\beta$ ) for First-Visit Patients].<sup>28</sup> This registry prospectively enrolled consecutive first-visit outpatients with headache at the headache clinics of 11 educational referral hospitals (9 university and 2 general hospitals) across Korea (4 in Seoul, 1 in Daejeon, 4 in Gyeonggi-do, 1 in Kangwon-do, and 1 in Gyeongsangnam-do) between August 2014 and February 2015. The details of the HEREIN study have been reported previously.<sup>29,30</sup>

The protocol of the HEREIN study including obtaining informed consent and information-use agreement forms were reviewed and approved by the Institutional Review Board (IRB) at each hospital. Each patient gave written informed consent before participating in the study if the need for informed consent had not been waived by the IRB board at a particular hospital. The study protocol for this post-hoc analysis was approved by the IRB (Bundang Jesaeng General Hospital IRB no: 2018-12-003). The need for obtaining written consents in this post-hoc analysis was waived by the IRB

based on the anonymity of the data.

The eligibility criteria in the HEREIN study were as follows: 1) headache being the chief reason for visiting the headache clinic, 2) being Korean and aged  $\geq 19$  years, and 3) having no disability in communication that would affect appropriate history-taking. The exclusion criteria were as follows: 1) having significant communication disabilities because of impaired hearing, speech, or cognition, and 2) having any other serious medical or psychiatric problem identified by the attending physician. The headache disorders were classified by each investigator into the current headache phenotypes using the ICHD-3 $\beta$  based on an evaluation that included a structured questionnaire, clinical evaluation, and laboratory or neuroimaging studies as needed. The reliability of the ICHD-3 $\beta$  was 0.61, indicating substantial agreement with the HEREIN study.<sup>30</sup>

In the analysis, the investigator selected the most-important headache for each patient. This study enrolled patients who were diagnosed with a primary headache disorder and underwent clinical neuroimaging. The details of secondary headache disorders and cranial neuropathy and other facial pains have been reported previously.<sup>30</sup>

### Assessment of neuroimaging

CT or MRI neuroimaging was performed selectively in each patient according to the initial clinical impressions obtained during history-taking and a neurological examination. Some patients were evaluated by CT angiography or magnetic resonance angiography according to the decision of the individual investigator. During the study period, patients in eight of the hospitals underwent 3-T MRI (Avanto, Ingenia, or Achieva, Philips Medical Systems, Best, the Netherlands; Verio or Skyra, Siemens, Erlangen, Germany) and those in the remaining three hospitals underwent 1.5-T MRI (Achieva or Intera, Philips Medical Systems; Magnetom Avanto, Siemens; Signa Excite, GE Healthcare, Chicago, IL, USA). The neuroimaging results were interpreted based on the consensus of two neuroradiologists in six hospitals, while one neuroradiologist interpreted the neuroimaging results in the other five hospitals. The neuroimaging results were then validated by the researchers and used to make the final headache classification based on the ICHD-3 $\beta$ .

The present analysis included patients who were diagnosed as having primary headaches based on the results of history-taking and physical and neurological examinations, including those who were found to have abnormal neuroimaging results that were not judged to be a cause of their headaches by the researchers. Nevertheless, if a patient had a serious intracranial finding with headache potentiality and medical urgency, such as a primary brain tumor, clinical isch-

emic infarct or hemorrhage, cerebral aneurysm, or cerebral vascular malformation, we classified them further into groups with and without serious neuroimaging abnormalities.

### Statistical analysis

The data are present as mean±standard deviation or number (percentage) values. The study patients were first dichotomized into a normal group and a neuroimaging abnormalities group. To evaluate factors associated with serious neuroimaging abnormalities, the subjects were further classified according to whether or not they had serious neuroimaging abnormalities. The following clinical variables were available in the prospective registry: age, sex, route of referral (self-referral vs. referral by a doctor), age at headache onset, duration of headache, intensity of headache (severe vs. mild to moderate), medication overuse, primary headache classification, and neuroimaging modality (MRI vs. CT).

To define a practical age cutoff for the included patients, we considered the prevalence of serious and overall neuroimaging abnormalities according to age decades. Given recently updated data on the prevalence of incidental abnormalities in the general population,<sup>31</sup> we determined the cutoff age as that at which the prevalence of neuroimaging was  $\geq 10\%$ . Fifty years was taken as the cutoff value for the age at headache onset. We assumed that a stable history of headache can be inversely associated with the risk of serious neuroimaging abnormalities, so we defined the cutoff value as  $\geq 1$  year. We measured the headache intensity using a visual analog scale with scores ranging from 1 to 10, and defined severe headache as a score of  $\geq 7$ .

Univariable logistic regression analyses were conducted to

calculate the odds ratio (OR) and 95% confidence interval (CI) values for the clinical variables related to neuroimaging abnormalities. Multivariable-adjusted logistic regression analysis was conducted for variables that showed a significant association in univariable analyses ( $p < 0.05$ ) in order to identify independent predictors for overall and serious neuroimaging abnormalities. To compensate for variations according to the selected neuroimaging modality (MRI vs. CT), we verified the results of multivariable-adjusted logistic regression analysis by further adjusting for neuroimaging modality. All statistical analyses were carried out using SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA). All reported probability values are two-tailed, and  $p < 0.05$  was considered statistically significant.

## RESULTS

### Study patients and neuroimaging abnormalities

During the study period, 1,627 patients were prospectively included in the multicenter headache registry (Fig. 1). Of these 1,627 patients, 1,429 were diagnosed with primary headache disorder, and 927 eligible patients (62.6% females) aged  $47.7 \pm 14.1$  years (range, 19–85 years) were finally enrolled in the study for analysis. The eligible patients were older than the 502 patients excluded from the analysis due to no neuroimaging ( $47.7 \pm 14.1$  years vs.  $46.0 \pm 15.0$  years,  $p = 0.026$ ). The proportions of male sex and medication overuse were higher for the study patients than for the excluded patients (37.4% vs. 31.9%,  $p = 0.036$ ; and 6.4% years vs. 2.6%,  $p = 0.002$ ; respectively), whereas the proportion with a headache duration  $\geq 1$  year was lower (33.9% vs. 41.4%,  $p = 0.005$ ). MRI and CT were ap-

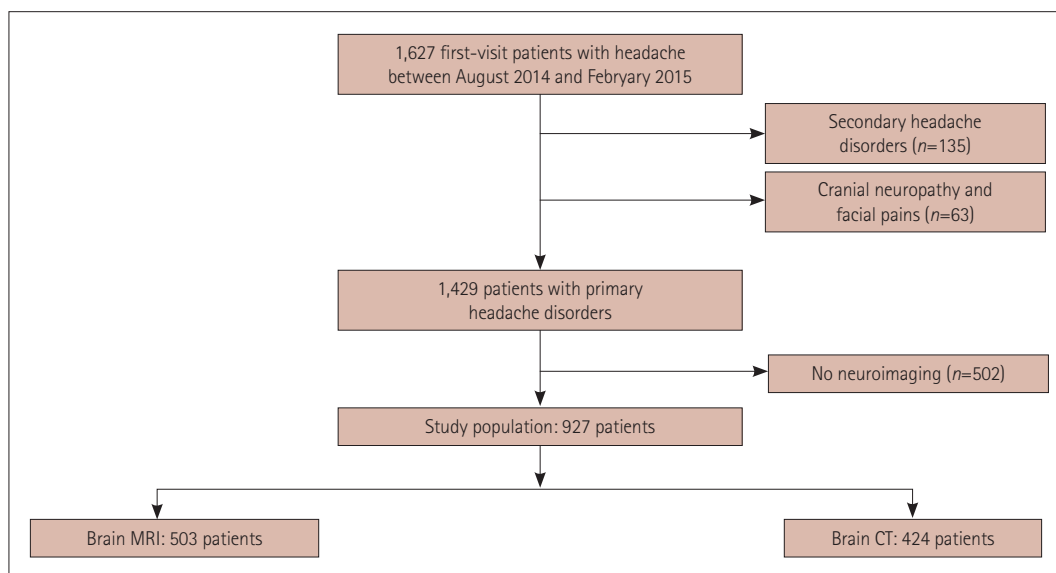


Fig. 1. Flowchart showing patient enrollment in the study.

plied to 503 (54.2%) and 424 (45.8%) patients, respectively, which revealed neuroimaging abnormalities in 170 patients (18.3%); these abnormalities were serious in 34 patients (3.6%). The proportions of patients with overall and serious neuroimaging abnormalities were 29.6% and 5.7%, respectively, in MRI, and 4.9% and 1.1% in CT. The most-common serious abnormalities were cerebral aneurysm ( $n=13$ ), clinical ischemic infarct ( $n=7$ ), and primary brain tumor ( $n=5$ ) (Table 1). The proportions of overall and serious neuroimaging abnormalities increased with increasing age decade (Fig. 2). The cutoff value for age was predefined as  $\geq 40$  years.

**Factors associated with neuroimaging abnormalities**

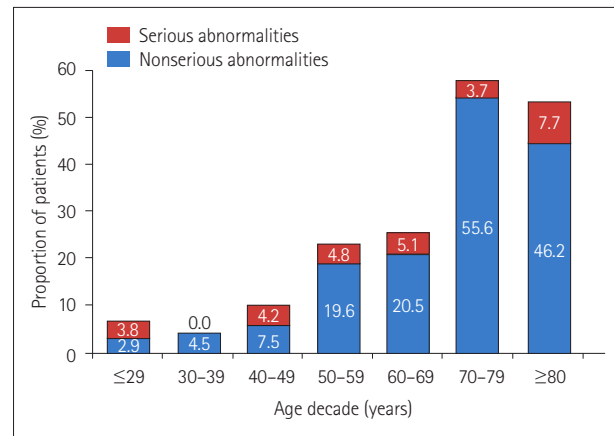
In univariable analyses, age  $\geq 40$  years, male sex, and age  $\geq 50$  years at headache onset were significantly associated with neuroimaging abnormalities (Table 2). Compared with mi-

**Table 1.** Neuroimaging abnormalities in first-visit patients with primary headache disorders

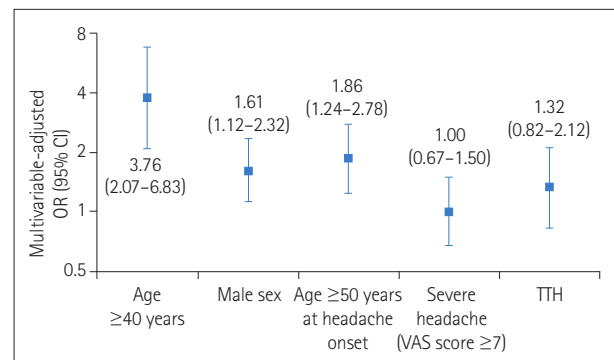
Neuroimaging abnormality	Number	Prevalence (%)
<b>Serious neuroimaging abnormalities</b>		
Primary brain tumor	5	0.54
Cerebrovascular disease		
Aneurysm	13	1.40
Dissection	1	0.11
Clinical ischemic infarct	7	0.76
Intracerebral hemorrhage	3	0.32
Vasculitis	1	0.11
Moyamoya disease	2	0.22
Vascular malformation	3	0.32
Arnold-Chiari malformation	1	0.11
<b>Nonserious neuroimaging abnormalities</b>		
Chronic cerebral ischemia (white-matter hyperintensity or leukoaraiosis)	80	8.63
Cerebrovascular disease		
Cerebral arterial stenosis	20	2.16
Subclinical ischemic infarct	7	0.76
Arachnoid cyst	3	0.32
Pineal cyst	1	0.11
Choroid fissure cyst	1	0.11
Hydrocephalus	1	0.11
Other ventricle abnormalities	1	0.11
Cerebral calcification	1	0.11
Brain atrophy	4	0.43
Encephalomalacia	2	0.22
Craniotomy not related to headache	1	0.11
Sinusitis not related to headache	24	2.59
Sinus/nasopharyngeal cyst	4	0.43
Sinus polyp	1	0.11
Mastoiditis not related to headache	2	0.22

graine as the reference, tension-type headache (TTH) was associated with neuroimaging abnormalities (OR=2.59, 95% CI=1.78–3.77). Severe headache intensity was inversely associated with neuroimaging abnormalities (OR=0.63, 95% CI=0.45–0.88). A headache duration  $\geq 1$  year and the presence of another primary headache disorder were marginally associated with neuroimaging abnormalities (OR=1.34, 95% CI=0.95–1.89; and OR=1.51, 95% CI=0.92–2.46; respectively); these associations did not reach statistical significance.

Based on the results of the univariable analyses, a multivariable-adjusted model was created by entering the following potential covariates for which  $p < 0.05$  in the univariable analyses: age  $\geq 40$  years, male sex, age  $\geq 50$  years at headache onset, severe headache intensity, and TTH (Fig. 3). In contrast to the results of univariable analyses, severe headache intensity and TTH were not significantly associated with neuroimaging abnormalities in the multivariable-adjusted



**Fig. 2.** Proportions of neuroimaging abnormalities according to age decades.



**Fig. 3.** Multivariable-adjusted ORs for neuroimaging abnormalities. Potential variables for which  $p < 0.05$  in univariable analyses were entered in multivariable-adjusted logistic regression models: age  $\geq 40$  years, male sex, age  $\geq 50$  years at headache onset, severe headache intensity (VAS score  $\geq 7$ ), and TTH (vs. migraine). CI: confidence interval, OR: odd ratio, TTH: tension-type headache, VAS: visual analog scale.

model. Age  $\geq 40$  years [multivariable-adjusted odds ratio (aOR)=3.76, 95% CI=2.07–6.83], male sex (aOR=1.61, 95% CI=1.12–2.32), and age  $\geq 50$  years at headache onset (aOR=1.86, 95% CI=1.24–2.78) were significant predictors of neuroimaging abnormalities. In a multivariable analysis with further adjustment for neuroimaging modality, age  $\geq 40$  years (aOR=3.37, 95% CI=1.82–6.23), male sex (aOR=1.55, 95% CI=1.04–2.30), and age  $\geq 50$  years at headache onset (aOR=2.14, 95% CI=1.38–3.32) remained as significant predictors of neuroimaging abnormalities.

**Factors associated with serious neuroimaging abnormalities**

In univariable analyses, age  $\geq 40$  years was the only independent variable associated with serious neuroimaging abnormalities (OR=3.37, 95% CI=1.17–9.66) (Table 2), with headache characteristics of the age at headache onset, duration of headache, severe headache intensity, and headache classification not being associated with serious neuroimaging abnormalities. After adjusting for the neuroimaging modality, the association between age  $\geq 40$  years and serious neuroimaging abnormalities persisted (aOR=3.00, 95% CI=1.04–8.64).

**DISCUSSION**

This study investigated incidental neuroimaging abnormalities and their predictors in new patients with primary headache disorders. It was found that 18.3% of first-visit patients with a primary headache disorder had neuroimaging abnormalities, while 3.6% of these patients had serious intracranial pathology despite only exhibiting the typical characteristics of primary headache. Among the clinical variables, except for the neuroimaging modality, age  $\geq 40$  years, male sex, and age  $\geq 50$  years at headache onset were independently associated with neuroimaging abnormalities, while age  $\geq 40$  years was identified as the only predictor of serious neuroimaging abnormalities.

The US guideline did not draw any conclusions regarding the relative sensitivity of MRI and CT in migraine or non-acute headache, which was due to a lack of available data.<sup>6</sup> Previous studies have produced conflicting results regarding the superiority of MRI over CT in detecting serious intracranial pathology.<sup>32-34</sup> Nevertheless, the recent so-called Choosing Wisely campaign recommends MRI as being the generally preferred neuroimaging modality over CT in patients with headache disorders, except in emergency settings, considering the better diagnostic sensitivity in most circumstanc-

**Table 2.** Clinical characteristics and univariable ORs for neuroimaging abnormalities and serious neuroimaging abnormalities

	Neuroimaging abnormalities				Serious neuroimaging abnormalities			
	Normal (n=757)	Neuroimaging abnormalities (n=170)	OR (95% CI)	p	Normal and nonserious neuroimaging abnormalities (n=893)	Serious neuroimaging abnormalities (n=34)	OR (95% CI)	p
Age $\geq 40$ years	491 (64.9)	155 (91.2)	5.59 (3.22–9.70)	<0.001	616 (69.0)	30 (88.2)	3.37 (1.17–9.66)	0.024
Male sex	267 (35.3)	80 (47.1)	1.63 (1.16–2.28)	0.004	333 (37.3)	14 (41.2)	1.17 (0.58–2.36)	0.646
Visit route								
Self-referral	465 (61.4)	112 (65.9)	Reference		558 (62.5)	19 (55.9)	Reference	
Referred by doctor	293 (38.6)	58 (34.1)	0.82 (0.58–1.16)	0.279	335 (37.5)	15 (44.1)	1.31 (0.65–2.62)	0.437
Age $\geq 50$ years at headache onset	224 (29.6)	97 (57.1)	3.16 (2.24–4.44)	<0.001	306 (34.3)	15 (44.1)	1.51 (0.75–3.02)	0.239
Headache duration $\geq 1$ year	247 (32.6)	67 (39.4)	1.34 (0.95–1.89)	0.092	300 (33.6)	14 (41.2)	1.38 (0.68–2.77)	0.361
Severe headache intensity, VAS score $\geq 7$	398 (52.6)	70 (41.2)	0.63 (0.45–0.88)	0.008	453 (50.7)	15 (44.1)	0.76 (0.38–1.52)	0.450
Medication overuse	46 (6.1)	13 (7.6)	1.28 (0.67–2.42)	0.449	59 (6.6)	0 (0.0)	NA	
Headache classification								
Migraine	396 (52.3)	58 (34.1)	Reference		439 (49.2)	15 (44.1)	Reference	
Tension-type headache	216 (28.5)	82 (48.2)	2.59 (1.78–3.77)	<0.001	284 (31.8)	14 (41.2)	1.44 (0.68–3.03)	0.334
Trigeminal autonomic cephalalgias	14 (1.8)	1 (0.6)	0.48 (0.06–3.77)	0.492	15 (1.7)	0 (0.0)	0.86 (0.30–2.40)*	0.775
Other primary headache disorders	131 (17.3)	29 (17.1)	1.51 (0.92–2.46)	0.097	155 (17.4)	15 (14.7)		

Data are n (%) values except where indicated otherwise.

\*OR of trigeminal autonomic cephalalgias plus other primary headache disorders for significant neuroimaging abnormalities.

CI: confidence interval, NA: not applicable, OR: odds ratios, VAS: visual analog scale.



es and the lack of radiation exposure.<sup>35,36</sup> Our study showed a disparity in capturing intracranial abnormalities between MRI and CT: 29.6% vs. 4.9% for overall neuroimaging abnormalities, and 4.9% vs. 1.1% for serious intracranial abnormalities. These findings suggest that using MRI rather than CT will increase the probability of capturing both overall and serious neuroimaging abnormalities in patients with primary headache disorder, which is consistent with the neuroimaging recommendation made in the Choosing Wisely campaign.

Several similar studies have been performed since the guidelines were published, but they did not strictly apply the ICHD-3 $\beta$  criteria and included patients with recurrent, chronic, and nonacute headaches.<sup>16,32-34</sup> Hence, to the best of our knowledge, the present neuroimaging study is the first to have focused on a strictly defined primary headache population. The prevalence of serious abnormalities has ranged from 1.2% to 3.7% in previous studies, which is consistent with the present results.<sup>16,32-34</sup> These findings clearly do not support performing routine neuroimaging in patients with primary or nonacute headaches. However, it seems certain that indiscriminately omitting neuroimaging in all patients with primary headache simply because they have primary headache may also be impetuous and dangerous.<sup>11,19,24,34</sup> In such a situation, clinicians need a more-sophisticated strategy to increase the probability of identifying neuroimaging abnormalities while reducing the routine utilization of neuroimaging in patients with primary headache disorders.<sup>11,21,27</sup>

This study found that patients aged  $\geq 40$  years were at risk of serious neuroimaging abnormalities, whereas the characteristics of the headache had no association. This finding is somewhat consistent with a Spanish report on neuroimaging in patients with nonacute headaches.<sup>34</sup> That study evaluated in minute detail the factors that warrant referral for neuroimaging according to the guidelines (i.e., the results of neurological examinations and sinister headache characteristics such as worsening and new-onset headaches), and found that sinister headache characteristics were not associated with significant neuroimaging abnormalities. While abnormal results in a neurological examination were identified as a strong predictor in that study, it was a predictor in only 29.4% of cases. The results of that study indicated that normal findings in a neurological examination and an unremarkable history of headache are not sufficient conditions for not order neuroimaging in patients with nonacute headaches.<sup>19,22-24,34</sup> It is therefore preferable for clinicians to decide on neuroimaging based on their integrative judgement covering not only the headache characteristics and neurological examination results but also demographic characteristics and the past medical history.

The US guideline has withheld a decisive judgement on neuroimaging in TTH.<sup>6</sup> It is particularly interesting that, compared to migraine, TTH was a predictor of neuroimaging abnormalities in the present univariable analysis; however, this association was attenuated in the multivariable models. Furthermore, TTH was not associated with serious neuroimaging abnormalities. It therefore remains unclear whether or not neuroimaging should be ordered in TTH patients. As a primary headache disorder, TTH may receive less attention and interest from both clinicians and patients because it is less likely to produce headache-related disability.<sup>37</sup> However, a manifestation of TTH can be risky: a previous study focusing on headache in 111 patients with brain tumors revealed that 77% of these patients had headaches similar to TTH.<sup>38</sup> Therefore, further studies should investigate neuroimaging abnormalities and their associated factors in patients with this featureless type of headache.<sup>25,38</sup>

This study was subject to several limitations that should be considered when interpreting its findings. First, it had a retrospective analytic design, which meant that certain important variables such as the results of neurological and physical examinations could not be included in the analysis. Furthermore, detailed information on some serious intracranial abnormalities such as the size and location of aneurysms, cerebral infarcts, and brain tumors, and the degree of cerebral arterial stenosis could not be collected. Second, with regard to enrollment of study patients, the judgement of each individual investigator contributed to decisions about performing neuroimaging based on clinical practice guidelines and patient preferences, rather than a standard protocol. This approach could have resulted in selection bias. Third, the generalizability of this study is reduced by it only including study patients who were enrolled at secondary or tertiary referral hospitals. Finally, we did not classify subclinical cerebrovascular disease into serious abnormalities, considering their low potential to induce headache and the low degree of medical urgency. However, advanced small-vessel disease, significant intracranial atherosclerotic stenosis, or subclinical embolic infarct might not be benign findings, because these lesions can be risk factors for future stroke, mortality, and dementia.<sup>39-42</sup> Thus, these patients might need further appropriate medical management in addition to caring for their primary headache. In this context, we need to keep in mind that although such neuroimaging abnormalities are harmless in terms of headache, they should not be ignored in order to ensure optimal medical care.

In conclusion, this study found that incidental neuroimaging abnormalities were common in new patients with primary headache disorders, whereas serious neuroimaging abnormalities were only found in a small proportion of them.

Age  $\geq 40$  years was the only independent predictor of serious neuroimaging abnormalities. These results indicate that neuroimaging should be selectively performed in patients with primary headache disorders.

### Author Contributions

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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