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REVIEW

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Application of machine learning in migraine classification: a call for study design standardization and global collaboration

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Abstract

Migraine is a complex neurological disorder with diverse clinical phenotypes and a multifaceted pathophysiology, which poses substantial challenges for accurate diagnosis, subtype differentiation, and biomarker discovery. Machine learning (ML) techniques have emerged as promising tools for classifying migraine patients and uncovering the underlying neurobiological mechanisms that differentiate migraine types and subtypes. This systematic review identifies current ML classification models for migraine types and subtypes, evaluating the quality, reproducibility, and clinical utility of published studies. The findings demonstrate that current ML models, particularly support vector machines and linear discriminant analysis, can accurately classify migraine patients based on structural and functional neuroimaging features with accuracies ranging from 75 to 98%. However, quality assessment revealed significant methodological heterogeneity across studies, including inconsistent reporting of model performance, insufficient patient phenotyping, small and imbalanced datasets, and limited external validation. These limitations hinder the global generalizability and reproducibility of these studies. We propose a roadmap for future research emphasizing well-characterized clinical subgrouping, standardized data acquisition and feature engineering protocols, transparency in model development and reporting, and collaborative multicentric designs to enable large-scale validation. Furthermore, this review stresses the importance of incorporating real-world phenotypic data, such as treatment response, comorbidities, and digital phenotyping metrics, to enrich ML models and support the transition toward precision medicine in migraine care. Ultimately, this review highlights the urgent need for methodological rigor in migraine ML classification studies to bridge the gap between experimental success and clinical applicability.

Keywords Classification algorithms, Artificial intelligence, Support vector machine, Migraine types, Deep learning, Neuroimaging

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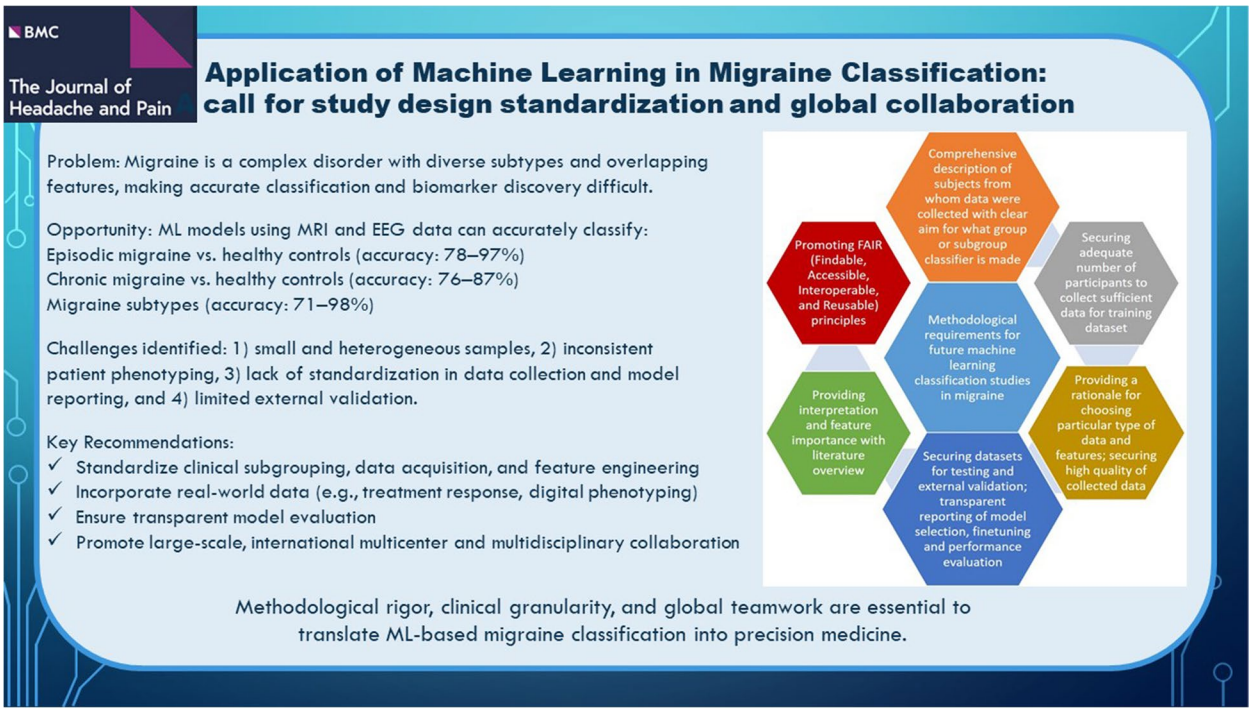
Graphical Abstract



Introduction

Migraine is a highly heterogeneous and disabling disorder [1, 2], with varying symptomatology, genetic basis, molecular pathways involved in the pathophysiology, attack triggers, and course of disease [1]. Although the varying symptomatology is well characterized by the International Classification of Headache Disorders (ICHD-3) [3], heterogeneous phenotypes are poorly characterized in neuroimaging, neurophysiological, and other multidisciplinary biomedical studies. Furthermore, the drawback of the current classification is that it does not fully include and recognize the heterogeneity of migraine in important domains such as neurobiological and psychosocial factors [4–6]. Even though the pursuit of migraine biomarkers is still undergoing progress, machine learning (ML) techniques are emerging as valuable tools to capture patterns of disease [7] and discover the most influential factors in differentiating migraine patients from healthy controls (HCs) [8]. Moreover, discovering differences between homogenous migraine subtypes, such as migraine with aura (MwA) characterized by only visual symptoms and MwA accompanied by additional somatosensory and/or dysphasic symptoms [9], using ML models could point to new biomarkers and allow innovative therapeutic strategies and precision medicine. In addition, the homogenization of investigated migraine subgroups according to clinical and neurobiological phenotypes can improve the chances of discovering new pathophysiological mechanisms [10, 11]. Collaborative efforts between global headache experts and data scientists are essential to overcoming current barriers and unlocking the full potential of artificial intelligence (AI) in transforming migraine research and management [12]. Furthermore, evaluating the quality of research in articles dealing with ML classification in the migraine field is necessary to move from hype to real impact [10].

This systematic review aims to report the current ML models for classifying migraine types and subtypes and assess the quality of identified studies. Furthermore, our goal is to determine the best models, types of data, and features for classifying migraine types and subtypes. Ultimately, we envision that findings from this review will serve as a practical guide for researchers aiming to leverage ML in migraine studies, ensuring international reproducibility and clinically meaningful findings.

Methodology

Search strategy

This systematic review followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines [13]. Search strategy combined information of two main terms, i.e. migraine and AI classification (with possible variations). PubMed and SCOPUS were searched for the terms, using database-specific variations, in the period between their inception and

February 19, 2025. The search string for PubMed was: ((migraine[Title/Abstract]) AND (classification[Title/Abstract] OR classifier*[Title/Abstract] OR "Machine Learning" [Title/Abstract] OR ML[Title/Abstract] OR "Support Vector Machine" [Title/Abstract] OR SVM[Title/Abstract] OR "deep learning" [Title/Abstract] OR "neural network*"[Title/Abstract] OR "artificial intelligence" [Title/Abstract] OR AI[Title/Abstract])). The SCOPUS string was: ((TITLE (migraine) AND TITLE ((classification OR classifier* OR "Machine Learning" OR ML OR "Support Vector Machine" OR SVM OR "deep learning" OR "neural network*" OR "artificial intelligence" OR AI))) OR ((ABS (migraine) AND ABS ((classification OR classifier* OR "Machine Learning" OR ML OR "Support Vector Machine" OR SVM OR "deep learning" OR "neural network*" OR "artificial intelligence" OR AI))). Retrieved references were exported as.csv files and imported into Rayyan QRCI [14] for duplicate checking. The set of records was then exported to MS Excel for study selection and data extraction.

Study selection

Retrieved references were equally and randomly assigned to the authors who screened titles and abstracts for eligibility. A double check on titles and abstracts eligibility was randomly performed on 30% of selected references: IP, WW, RM and LP performed the double check on abstracts. The inter-rater reliability was calculated using Krippendorff's alpha coefficient (α), which ranges between 0 (total disagreement) and 1 (total agreement). In case of disagreement, the record was considered as selected and retained for full-text evaluation. If α was below 0.70, a second 30% set of abstracts was submitted to double check.

To be eligible and be evaluated in full texts, abstracts of retrieved records had to refer to original research papers, written in English and dealing with the use of AI to classify migraine disorders, i.e. distinguishing migraine from healthy controls and/or different migraine subtypes (e.g., episodic migraine (EM) from chronic migraine (CM), MwA from migraine without aura (MwoA)). Therefore, records were excluded if: (a) had no abstract, (b) were not in English, (c) were letters, editorials, case reports, reviews or meta-analyses; (d) were not focusing on migraine; (e) did not employ an AI approach to classify migraine. In case of doubts, especially on the last criterion, we decided to keep the record and further re-assess it at the full-text evaluation stage.

The records maintained after the abstract check were equally and randomly assigned to the authors who screened full texts for inclusion. At this stage, we used a "shuffle" procedure, i.e. authors did not receive the file of the abstract they previously selected, and we applied for a 100% double check over PDFs: authors worked in couples, blind to the results of each other. Two authors (IP and AR) evaluated the presence of disagreement and resolved conflicts.

For full texts evaluation, studies were excluded if: (a) could not be retrieved; (b) description of migraine cohort did not include information about whether patients have EM or CM and MwA or MwoA, according to the ICHD-3 criteria; (c) it was unclear whether the data were collected during an ictal or interictal phase; (d) did not deal with binary migraine classification (ML task that involves distinguishing between two categories, e.g., EM vs. HCs); (e) the type of data and features used for classification were not clearly stated, i.e. if it was unclear what kind of neuroimaging or neurophysiological data was used; (f) data for classification were based only on symptoms from ICHD-3 criteria; (g) there was no report on the evaluation of the ML models (at least one of the following: accuracy, confusion matrix, sensitivity, specificity, AUC, and F1 score).

At this stage, authors also had to identify whether the paper was on ML approach. ML included: Support Vector Machines, K-Nearest Neighbors, Decision Trees, Naive Bayes, Linear Discriminant Analysis, Linear Regression and Random Forest. Deep learning, a subfield of ML, included: neural networks, such as a convolutional neural network, recurrent neural network and generative adversarial network. In case of disagreement or uncertainty on the approach, the main author (IP) resolved the conflict.

Data extraction

Data extraction was performed through ad hoc electronic spreadsheets of Microsoft Excel. Included studies were equally and randomly assigned to the authors who had to extract the following information: (a) author; (b) year of publication; (c) type of data (e.g. clinical, neuroimaging, neurophysiological, questionnaires); (d) migraine condition (i.e., episodic, chronic, episodic with/without aura, vestibular and/or other migraine types to be specified): the number of subjects; (e) if HCs: the number of subjects; (f) best ML model and its metrics (expressed in percentages); and (g) most important features for classification.

Finally, a comprehensive set of information for data quality was filled in. This information included: (1) Clinically homogenized group (MwoA and MwA differentiated into separate groups); (2) Clinically homogenized subgroup (differentiation into subgroups according to their deep profiled clinical phenotypes like migraine with only visual aura, migraine with somatosensory and dysphasic aura (with or without visual symptoms), hemiplegic migraine, vestibular migraine, etc.); (3) Frequency homogenized group (EM and CM differentiated into separate groups); (4) Frequency homogenized subgroup (EM with low frequency (up to 7 days with headache/month),

EM with high frequency (from 8 to 14 days with headache/month), and CM, differentiated into separate subgroups); (5) Comorbidity; (6) Preventive drugs groups; (7) Triptans groups; (8) Previous failed preventive treatment; (9) Age subgroups separately investigated; (10) Sex subgroups separately investigated; 11) Sufficient dataset; 12) Collected data reliable; 13) Missing data; 14) Outliers; 15) Data preprocessing and transformation; 16) Feature selection; 17) Data splitting into training and validation datasets; 18) Model selection; 19) Model finetuning; 20) Overfitting; 21) Model performance evaluation – reporting accuracy and confusion matrices or sensitivity and specificity; 22) Model performance evaluation - reporting accuracy and confusion matrix or sensitivity and specificity, plus area under the curve (AUC) or F1 score; 23) External validation; 24) Feature importance; 25) Interpretation; 26) Future perspective; 27) Limitations; 28) Data availability upon request; 29) Anonymized data shared on the platform; and 30) Code availability.

Results

Out of 2,583 records retrieved in PubMed and SCOPUS, we found 187 papers relevant to the topic based on the title and abstract screening. After the full-text assessment, eleven manuscripts fulfilled our inclusion criteria. Figure 1 shows the review processes and reasons for paper exclusion. The agreement rate at abstract check was 94.7%, and at Full-text selection was 91.4%.

Figure 2 reports the publication period coverage of selected studies. It shows that the first study focused on ML classification of a well-characterized migraine cohort was published in 2016. In the last three years, more studies have used ML classification for distinguishing migraine patients from HCs and between migraine subtypes, and for searching migraine biomarkers.

Table 1 summarizes the methodology and findings of studies employing an ML approach to classify patients with EM versus HCs. We identified seven studies, of which three pooled episodic migraine patients with aura (EMwA) and episodic migraine patients without aura (EMwoA) into one group [15–17], two studies exploring the classification of EMwA patients [9, 18], one study exploring the classification of EMwoA patients [19], and one study exploring the classification of EM with vestibular migraine [20]. The sample size was quite heterogeneous, ranging from 20 EM (10 EMwA and 10 EMwoA) versus 15 HCs up to 123 EM (including 18 EMwA and 105 EMwoA) versus 113 HCs. Almost all studies used MRI-derived data for ML models, showing promising ML model metrics. Support vector machines (SVM) were the most common best model classifier, achieving accuracies between 80% and 89% (AUC: 84–88%), while linear

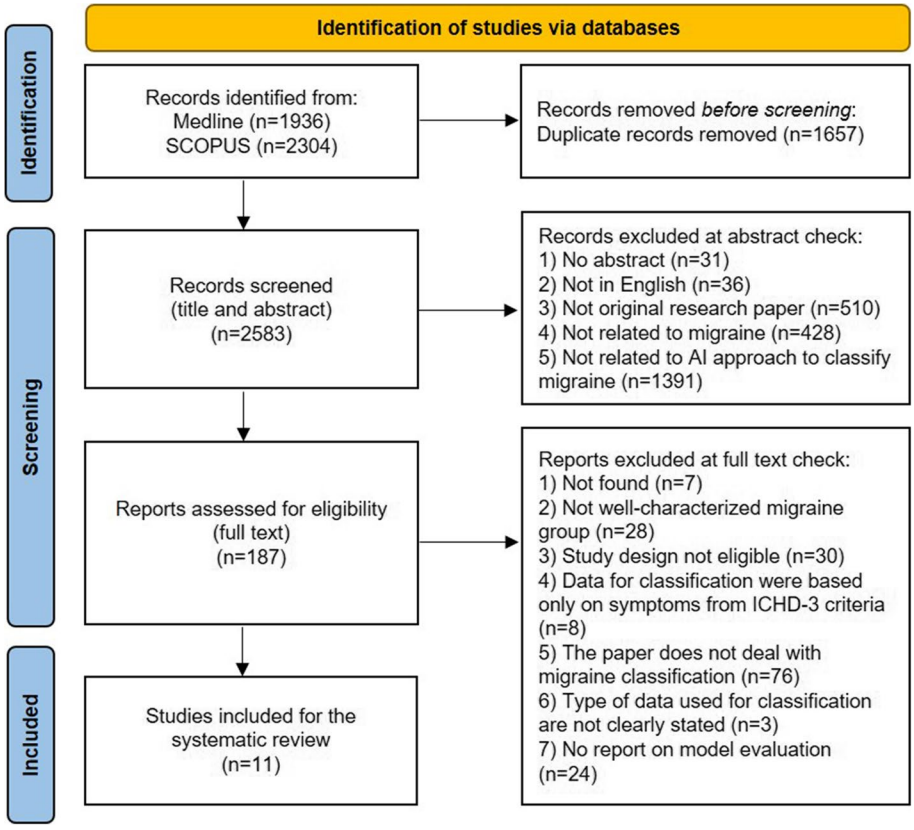


Fig. 1 Flowchart of selected studies

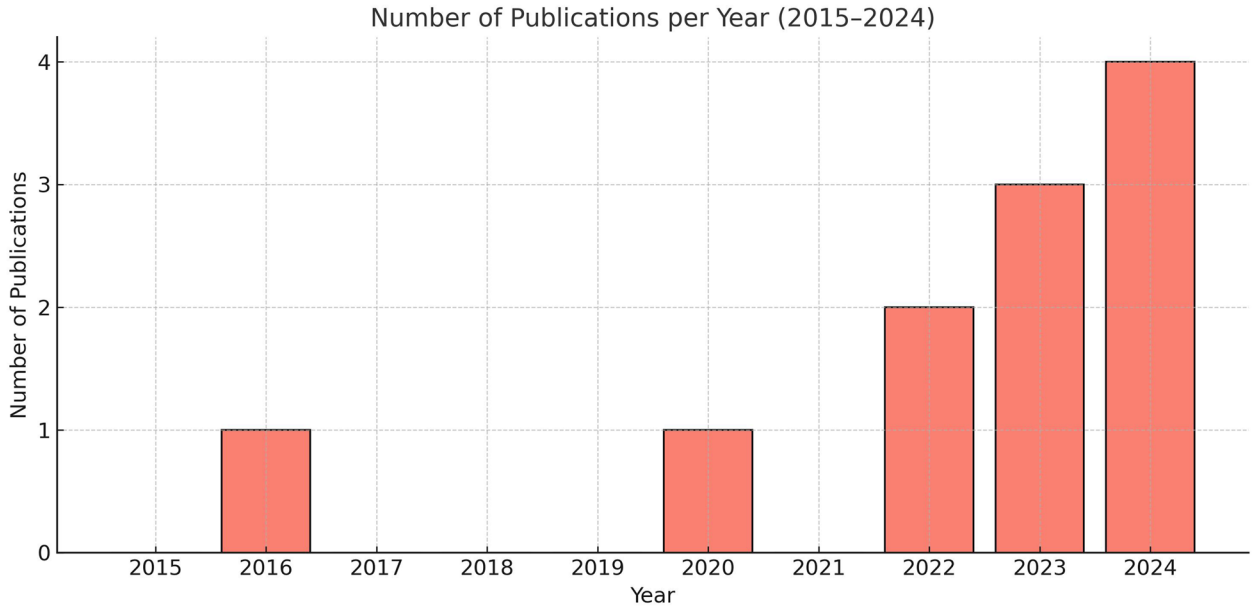


Fig. 2 Publishing trends of ML classification studies performed on well-characterized migraine patients

discriminant analysis reached 97% accuracy in one study. The most important features for distinguishing between EMwA and HCs were: left temporal pole thickness, right lingual gyrus thickness, left pars opercularis thickness, and volume of the medial occipital cortex. Key discriminative features for distinguishing between EM and HCs included decreased amplitude responses from somatosensory evoked potentials in the left insula and left primary motor cortex, and altered functional connectivity between the right periaqueductal gray region and frontal cortical areas and insula, as well as between the cerebellum and inferior occipital and orbitofrontal gyrus.

Quality scores for assessment of ML classification studies in migraine (out of 30) varied from 13 to 24, achieving from 5 to 13 (out of 13) obligatory requirements to ensure high-quality results and possible reproducibility of the study (Supplementary Table 1).

Table 2 details three ML studies [16, 17, 21] aiming to classify CM patients versus HCs. Sample sizes ranged from 40 CM (17 CM with aura) versus 40 HCs to 106 CM (22 CM with aura) versus 113 HCs. Decision trees and SVMs achieved accuracies of 76–87% (AUC: 84–89%). Feature sets included evoked potential oscillatory and somatosensory metrics and structural magnetic resonance imaging (MRI) measures of cortical volume, surface area, and thickness, pointing to decreased amplitude responses in the left insula as the most important feature for distinguishing CM from HCs. Quality scores for assessment ML classification studies in migraine were modest (13–21/30), achieving from 5 to 10 (out of 13) obligatory requirements to ensure high-quality results and possible reproducibility of the study, reflecting limited group homogenization, feature importance reporting, and transparency (Supplementary Table 1).

Table 3 presents five ML studies [9;17,18,22,23] classifying migraine types and subtypes (e.g., EMwA vs. EMwoA), using multimodal data such as electroencephalographic (EEG) connectivity, cerebral blood flow from arterial spin labeling, structural MRI, and somatosensory evoked potentials. Sample sizes ranged from 30 EMwA versus 22 EMwoA to 123 EM (18 EMwA) versus 106 CM (22 CMwA). Linear discriminant analysis and SVMs yielded accuracies of 71–98% (AUC: 73–88%). Key discriminative features for distinguishing EMwA patients with different aura subtypes included pericalcarine and pars opercularis thickness. Quality scores for assessment ML classification studies in migraine ranged from 15 to 21 (out of 30), achieving from 9 to 10 (out of 13) obligatory requirements to ensure high-quality results and possible reproducibility of the study, reflecting limited group homogenization, model performance evaluation, feature importance reporting, and transparency (Supplementary Table 1).

Table 4 describes a deep learning study employing a 3D ResNet-18 neural network on selected structural MRI regions (95 migraine patients with different types versus 532 HCs). The network achieved 75% accuracy and yielded several important gray and white matter features [24].

Discussion

Our systematic review highlights that ML applications in migraine classification have demonstrated promising accuracy and novel insights into disease mechanisms, yet several critical challenges remain to be addressed.

Table 1 Studies employing a machine learning approach to classify episodic migraine versus healthy controls

Study	Data	Best ML model and metrics	Most important features	Quality score (obligatory items)
Zhang et al., 2016 [19]	Amplitude of low-frequency fluctuations, regional homogeneity, regional functional correlation strength, and voxels of gray matter. 21 EMwoA vs. 28 HCs	Support vector machine classifier; Accuracy 80%, Sensitivity 89%, Specificity 67%, and AUC 84%.	ALFF (left anterior cingulate gyrus, left posterior cingulate gyrus), ReHo (right inferior parietal lobule, right superior temporal gyrus), RFCS (left superior frontal gyrus, orbital part, left and right amygdala), gray matter (left supplementary motor area, left hippocampus)	20/30 (10/13)
Messina et al., 2023 [15]	Brain volumetric, white matter fractional anisotropy, white matter mean diffusivity, cerebral blood flow maps, and resting state functional connectivity maps. 20 EM (10 EMwA and 10 EMwoA) vs. 15 HCs	Support vector machine classifier; Accuracy 89%, Sensitivity 95%, and Specificity 80%.	In migraine patients, the right periaqueductal gray region had increased resting-state functional connectivity with frontal cortical areas and the insula and decreased functional connectivity with the cerebellum and inferior occipital and orbitofrontal gyrus.	17/30 (9/13)
Mitrović et al., 2023 [9]	Cortical thickness, surface area, volume, mean Gaussian curvature, and folding index for cortical regions derived from the Desikan-Killiany Atlas. 46 EMwA (22 EMwA-S and 24 EMwA-C) vs. 32 HCs	Linear discriminant analysis; Accuracy 97%.	Left temporal pole thickness, right lingual gyrus thickness, and left pars opercularis thickness.	21/30 (10/13)
Yoon et al., 2024 [16]	Volume, surface area, and thickness for cortical regions derived from the Desikan-Killiany Atlas. 51 EM (22 EMwA and 29 EMwoA) vs. 54 HCs	Random Forest; AUC 74%.	N/A	13/30 (5/13)
Niddam et al., 2024 [18]	Voxels from structural neuroimaging derived from the masks yielded from functional magnetic resonance imaging of visual cerebral regions. 50 EMwA vs. 50 HCs	Binary Gaussian process classification; Accuracy 78% and AUC 84%.	Increased grey matter volume in the medial occipital cortex.	17/30 (9/13)
Hsiao et al., 2024 [17]	Multimodal data (amplitude derived from somatosensory evoked potentials, effective connectivity from spectral Granger causality analysis, and scores of psychometric assessments). 123 EM (18 EMwA and 105 EMwoA) vs. 113 HCs	Support vector machine; Accuracy 87%, Sensitivity 83%, Specificity 91%, and AUC 88%.	Decreased amplitude responses in the left insula and left primary motor cortex.	19/30 (9/13)
Chen et al., 2024 [20]	Graph-theoretical metrics and interregional morphological connectivity derived from structural and functional magnetic resonance imaging. 55 Episodic vestibular migraine vs. 57 HCs	Support vector machine; Accuracy 78%, Sensitivity 64%, Specificity 91%, and AUC 83%.	Kullback–Leibler divergence-based similarity between the left fusiform gyrus and right superior frontal gyrus, as well as left crus I of cerebellar hemisphere and right superior frontal gyrus.	24/30 (13/13)

EM episodic migraine, *HCs* healthy controls, *EMwA* episodic migraine with aura, *EMwoA* episodic migraine without aura, *EMwA-S* episodic migraine with only visual aura, *EMwA-C* episodic migraine with visual, somatosensory and dysphasic aura, *ML* machine learning, *AUC* area under the curve, *ALFF* amplitude of low-frequency fluctuations, *ReHo* regional homogeneity, *RFCS* regional functional correlation strength

Table 2 Studies employing a machine learning approach to classify chronic migraine versus healthy controls

Study	Data	Best ML model and metrics	Most important features	Quality score (obligatory items)
Hsiao et al., 2023 [21]	All three tasks measure evoked oscillatory latency, frequency, power, and power ratios, including non-painful, painful, and repetitive painful tasks. 40 CM (17 CMwA and 23 CMwoA) vs. 40 HCs	Decision tree; Accuracy 87%, Sensitivity 81%, Specificity 94%, and AUC 84%.	N/A	21/30 (10/13)
Yoon et al., 2024 [16]	Volume, surface area, and thickness for cortical regions derived from the Desikan-Killiany Atlas. 26 CM (15 CMwA and 11 CMwoA) vs. 42 HCs	XGBoost; AUC 70%.	N/A	13/30 (5/13)
Hsiao et al., 2024 [17]	Multimodal data (amplitude derived from somatosensory evoked potentials, effective connectivity from spectral Granger causality analysis, and scores of psychometric assessments). 106 CM (22 CMwA and 84 CMwoA) vs. 113 HCs	Support vector machine; Accuracy 76%, Sensitivity 60%, Specificity 91%, and AUC 89%.	Decreased amplitude responses in the left insula.	19/30 (9/13)

CM chronic migraine, *HCs* healthy controls, *CMwA* chronic migraine with aura, *CMwoA* chronic migraine without aura, *ML* machine learning, *AUC* area under the curve

Table 3 Studies employing a machine learning approach to classify migraine types and subtypes

Study	Data	Best ML model and metrics	Most important features	Quality score (obligatory items)
Frid et al., 2020 [22]	Functional connectivity metrics of resting-state EEG data. 30 EMwA vs. 22 EMwoA	Linear discriminant analysis; Accuracy 85%, Sensitivity 87%, Specificity 82%, and AUC 88%	N/A	15/30 (10/13)
Fu et al., 2022 [23]	Cerebral blood flow maps from arterial spin labeling magnetic resonance imaging. 32 EMwA vs. 56 EMwoA	Support vector machine classifier; Accuracy 81%, Sensitivity 88%, Specificity 74%, and AUC 84%.	N/A	15/30 (9/13)
Mitrović et al., 2023 [9]	Cortical thickness, surface area, volume, mean Gaussian curvature, and folding index for cortical regions derived from the Desikan-Killiany Atlas. 22 EMwA-S vs. 24 EMwA-C	Linear discriminant analysis; Accuracy 98%.	The thickness of the left pericalcarine gyrus and left pars opercularis.	21/30 (10/13)
Niddam et al., 2024 [18]	Voxels from structural neuroimaging derived from the masks yielded from functional MRI of visual cerebral regions. 50 EMwA vs. 50 EMwoA	Binary Gaussian process classification; Accuracy 71% and AUC 73%.	N/A	17/30 (9/13)
Hsiao et al., 2024 [17]	Multimodal data (amplitude derived from somatosensory evoked potentials, effective connectivity from spectral Granger causality analysis, and scores of psychometric assessments). 123 EM (18 EMwA and 105 EMwoA) vs. 106 CM (22 CMwA and 84 CMwoA)	Support vector machine; Accuracy 73%, Sensitivity 60%, Specificity 83%, and AUC 74%.	N/A	19/30 (9/13)

EM episodic migraine, *EMwA* episodic migraine with aura, *EMwoA* episodic migraine without aura, *EMwA-S* episodic migraine with only visual aura, *EMwA-C* episodic migraine with visual, somatosensory and dysphasic aura, *CM* chronic migraine, *CMwA* chronic migraine with aura, *CMwoA* chronic migraine without aura, *ML* machine learning, *AUC* area under the curve

Table 4 Study employing a deep learning approach to classify migraine versus healthy controls

Study	Data	Best deep learning model and metrics	Most important features
Siddiquee et al., 2022 [24]	Cortical and white matter parcellation derived from structural magnetic resonance imaging, as well as masks of subcortical structures. 95 migraine (37 EM and 58 CM; 49 MwA and 46 MwoA) vs. 532 HCs	3D ResNet-18; Accuracy 75%, Sensitivity 67%, and Specificity 83%.	Caudate, caudal anterior cingulate white matter, superior frontal, thalamus, ventral diencephalon, posterior cingulate, medial orbitofrontal white matter, pallidum, accumbens area, putamen, rostral anterior cingulate white matter, lateral orbitofrontal white matter, brain stem, rostral middle frontal white matter, insula white matter, hippocampus, caudal middle frontal white matter and precentral white matter.

EM episodic migraine, *CM* chronic migraine, *MwA* migraine with aura, *MwoA* migraine without aura, *HCs* healthy controls

The studies herein included show that migraine patients could be differentiated from HCs and even subdivided into subtypes using ML models: accuracy in distinguishing EM from HCs was 78–97%, CM from HCs was 76–87%, and the accuracy to differentiate patient subtypes was 71–98%. These results point out a considerable number of potential biomarkers derived from neuroimaging data, either structural or functional, that should be explored in the future. We are, in fact, only at the beginning of the AI era, striving to enhance our study designs with advanced data analysis. Before proceeding, we must first establish clear guidelines on patient selection and define essential elements that should be included in the design of migraine classification studies. Therefore, we used the recently proposed method for quality assessment of ML classification in migraine [10] to identify limitations of current studies and propose actions for standardizing future studies. The final goal is to achieve more generalizable ML models that can be implemented globally in migraine research and clinical practice.

The first important barrier for developing a generalizable ML classification model in migraine is not recognizing the importance of well-characterized patients included in model training and testing. It should be obligatory to record and mention in the study whether patients have EM or CM and MwA or MwoA, as well as whether the data were collected during an ictal or interictal phase. Not knowing this information imposes bias on the model. Therefore, in a real-world scenario, the performance of the model trained on such poorly described datasets may considerably vary from reported metrics. For example, cortical thickness alterations or functional connectivity changes may differ systematically between EM and CM or MwA and MwoA [1]; thus, aggregating these groups can obscure subtype-specific patterns and mislead feature selection. Furthermore, overlooking important cohort descriptors related to migraine, such as demographic factors, presence of allodynia [25], acute and preventive treatment response [26], comorbidities [27], active (at least 1 migraine attack in the last year before collecting data for the study) or inactive disease states [28], and level of disability [2] might impose additional biases and lead to limited and/or false interpretability of the importance of certain features for the model, and divert our attention from the right path in the search for biomarkers. Although homogenizing migraine patients into subgroups according to the above mentioned factors leads to the loss of the generalization capability of the model, it provides a better understanding of complex pathophysiological mechanisms in various migraine subtypes and allows progress toward precision medicine [10]. However, ML model trained on large migraine cohorts consisting of several clinical phenotypes and demographic backgrounds, that is adjusted to an adequate ratio for the general migraine population, would provide a powerful tool for decision-making in case of probable migraine in clinical practice. Another consideration would be to utilize unsupervised ML to explore the natural subgroups of patients with migraine using the imaging and clinical features that exist in the databases. Given the debate on whether the 15-day cutoff would be the most suitable way to characterize patients with migraine [29], such ML approach could help us explore subgroups of patients with migraine beyond the traditional classification based on aura status, and between episodic and chronic migraine.

Another important barrier in studies about ML classification of migraine types and subtypes is the number of patients included in the training of ML models, which prevents researchers from achieving the best model metrics for the used features, selecting the best feature candidates for biomarkers, and generalizability for the aimed migraine population. Our review found that most ML classification studies have relied on relatively small, clinically mixed datasets, which limits both the generalizability and translational potential of their findings. There are two ways in which this barrier could be overcome: the first is to increase the sample size by making multicentric international collaborations between institutions specialized in migraine research [16], while the second is to use repeated data collection from patients where the sample corresponds to the number of patients that provides a 95% confidence interval for a given migraine subpopulation. In the first case, this would lead to better rigor of selected features for the ML model and a harmonized dataset from diverse geographic and socio-demographic populations. Such efforts would enable external validation with a reduction of site-specific biases [30]. In addition, it would allow an adequate number of patients to reach the plateau of ML model metrics in the training dataset, which will, at the same time, indicate the number of patients needed to train the model for a particular data modality, such as structural MRI, functional MRI, and electrophysiological metrics. In the second case, where the sample size is limited, multiple data collections would allow training of an ML model until it reaches a plateau in the ML model metrics. This scenario would be most preferable in studies designed to collect data via digital phenotyping technologies, implementing the real-time collection and analysis of behavioral and physiological data using digital devices, including smartphones, wearable technology and biosensors [31–35]. Moreover, in migraine research, digital phenotyping offers an unprecedented opportunity to objectively quantify symptom patterns, physiological and behavioral changes associated with attacks, and disease cumulative burden during the interictal stage, which could significantly help in the characterization of migraine subtypes in individuals

contributing to well-characterized homogenous subgroups [36].

Beyond clinical subgrouping, our findings underscore that action should be initiated for the standardization of protocols for neuroimaging [37], neurophysiological, and other biomedical activities aiming to develop ML model for the classification of migraine and its subtypes. Standardization efforts should address MRI acquisition protocols (such as field strength, sequence parameters, harmonization across sites), EEG recording conditions (such as resting state vs. evoked potentials, electrode montage), and preprocessing pipelines (such as artifact removal, co-registration, parcellation schemes). Feature engineering must follow reproducible frameworks to allow consistent and transparent reporting, which will facilitate external validation and meta-analyses. In addition, when developing an ML model to distinguish CM patients from HCs or those with EM, it is crucial to exclude features inherently indicative of specific migraine types or subtypes according to ICHD-3 criteria. For instance, incorporating neurophysiological data alongside clinical variables and patient-reported outcome measures related to symptoms and disability, such as the frequency of attacks, presence of photophobia, or disability score, can enhance model accuracy by leveraging features that are a priori suggestive of a particular migraine phenotype [10]. In addition, future ML studies should aim to use high-quality data that already show potential to reveal pathophysiological mechanisms in migraine types and subtypes [9, 23, 38–53]. Although our systematic analysis revealed that most of the selected studies used advanced methodologies to acquire neuroimaging and electrophysiological data with standard programs for data processing and obtaining features, there were substantial differences in the design of these studies, which prevented us from performing a meta-analysis.

Another significant barrier in studies about ML classification of migraine types and subtypes is a lack of comprehensive reporting regarding the model metrics during training and testing the model. Researchers often report only accuracy or sensitivity and specificity, avoiding to provide a complete confusion matrix to both the training and testing phases of developing a model. The lack of this information prevents readers from analyzing and interpreting the study findings more in-depth. This should be obligatory in future studies if we want to achieve transparency and evaluate the significance of the study findings. For example, reporting only high sensitivity or specificity and avoiding the reporting of AUC and F1 can mask overfitting and class imbalance issues. Furthermore, if there are no reports regarding the metrics of the training and testing phases, the overfitting issue cannot be evaluated properly, indicating a problem with generalization.

Our findings suggest that SVM and linear discriminant analysis were the best techniques for classifying EM versus HCs, CM versus HCs, and between migraine subtypes. SVM is a supervised learning algorithm that finds the optimal hyperplane that best separates data points of different classes (e.g., EM vs. HCs) in a high-dimensional feature space. The advantages of this model are: (1) works well with small sample sizes (migraine neuroimaging and EEG datasets are often modest in size due to cost and complexity of data collection); (2) effective in high-dimensional spaces (migraine research often involves high-dimensional data such as voxel-based morphometry, functional connectivity matrices and EEG frequency bands); (3) the margin-maximizing property of SVM helps avoid overfitting, which is crucial when the dataset has more features than subjects; and (4) handles nonlinear patterns with kernels (migraine-related brain changes may be nonlinear and subtle). In addition to these advantages, linear discriminant analysis models each class as a Gaussian distribution with a shared covariance matrix and finds a linear combination of features that best separates the means of the classes while minimizing within-class variance. This offers better dimensionality reduction and high interpretability, providing coefficients for each feature and thus showing how much each coefficient contributes to the classification decision. However, linear discriminant analysis is sensitive to outliers and assumes a normal distribution of data.

Inconsistencies in study design and different types of datasets prevented us from performing a meta-analysis and led to various important features for classifying migraine types and subtypes, which were not replicated or validated in subsequent studies. These inconsistencies should motivate researchers to implement all the above proposed solutions (Fig. 3) for the identified barriers to improve ML classification models and identify potential migraine subtype biomarkers. However, it is also possible that migraine and its subtypes represent functional diseases of the neural network with multiple structural and functional changes in the brain, rather than diseases of a single brain area [54]. This hypothesis is further supported by previous neuroimaging non-ML studies showing structural and functional changes in the visual cortex, sensory processing regions, insula, hypothalamus, and brainstem across all migraine subgroups [55–58].

Datasets and codes for developed model should be made available upon request respecting general data protection regulations and FAIR principles (a set of guidelines for data management designed to make scientific data more Findable, Accessible, Interoperable, and Reusable), allowing researchers to access valuable datasets and study protocols to replicate, improve and/or validate findings [59–61]. Finally, translating ML discoveries into clinical practice requires multidisciplinary and global

Fig. 3 Methodological requirements for future machine learning classification studies in migraine

collaboration. Neurologists, neuroscientists, and data scientists must jointly develop clinically actionable pipelines that integrate ML outputs with clinical decision-making workflows.

Conclusion

Our findings highlight the potential value of ML techniques in understanding the neurobiological basis of migraine by discovering neuroimaging patterns in migraine types and subtypes. Furthermore, MRI and EEG classifiers can accurately classify individuals who suffer from migraine and those representing HCs, as well as distinguish migraine types and subtypes, supporting the view of migraine as a complex brain disorder characterized by multifaceted neurobiological pathophysiology. In the future, combining AI with multimodal biomarkers for stratifying migraine patients (such as genomics and modifiable risk factors) to develop personalized treatment and prevention strategies remains a potential research hotspot [62].

In conclusion, achieving the promise of ML in migraine classification hinges on three pillars: (1) rigorous clinical subgroup definitions that capture phenotypic, therapeutic, and demographic heterogeneity, (2) standardized, transparent high-quality data acquisition and feature-processing frameworks, and (3) large-scale international, multicentric and multidisciplinary collaborations that foster external validation and knowledge sharing. Embracing these strategies will not only accelerate the identification of migraine subtype biomarkers, deepen our understanding of multifaceted pathophysiological mechanisms, ensure ML migraine classification applicability in a real-world setting, but will ultimately pave the way for precision medicine approaches tailored to each patient's unique migraine profile.

Abbreviations

AI	Artificial intelligence
ALFF	amplitude of low–frequency fluctuations
AUC	Area under the curve
CM	Chronic migraine
CMwA	chronic migraine with aura
CMwoA	chronic migraine without aura

EEG	Electroencephalography
EM	Episodic migraine
EMwA	Episodic migraine with aura
EMwA	C–episodic migraine with visual, somatosensory and dysphasic aura
EMwA	S–episodic migraine with only visual aura
EMwoA	Episodic migraine without aura
HCs	Healthy controls
ICHD	3–International Classification of Headache Disorders – 3rd edition
ML	Machine learning
MRI	Magnetic resonance imaging
MwA	Migraine with aura
MwoA	Migraine without aura
ReHo	regional homogeneity
RFCS	regional functional correlation strength
SVM	Support vector machines

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

IP and AR led the manuscript preparation, selected studies, extracted data and drafted part of the manuscript; PM supervised the entire process and revised the manuscript; all the other authors selected studies, extracted data and revised the manuscript. All authors approved the final version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

IP serves as member of the Editorial Board of The Journal of Headache and Pain, Head of Imaging Section of the SN Comprehensive Clinical Medicine journal and as the Guest Editor in The Journal of Headache and Pain. Outside of this work, RM reports personal fees from Abbvie, Biomedia, Eli-Lilly, Lundbeck, Organon, Pfizer and Teva for participating in advisory boards and speaker activities. She is member of the Editorial Board of The Journal of Headache and Pain and Confinia Cephalalgica. She has received research support from the Italian Ministry of Health. LP serves as member of the Editorial Board of The Journal of Headache and Pain, BMC Neurology, Pain Research and Management and European Journal of Medical Research. In addition, LP is Editor-in-Training for Clinical and Translational Science. C-CC has received personal compensation for consulting or being on advisory boards for Pfizer, AbbVie, Ssatsuma and eNeura. She has received research grants from the American Heart Association, with funds paid to her institution. W-SH serves as member of the Junior Editorial Board of The Journal of Headache and Pain. ALR is an Editorial Board Member of The Journal of Headache and Pain. DO is member of the Editorial Board of The Journal of Headache and Pain and section editor of SN Comprehensive Clinical Medicine. RO declares personal fees from AbbVie, Bayer, Eli Lilly, Lundbeck. Novartis, Organon, Pfizer, and Teva; he is member of the Editorial Board of The Journal of Headache and Pain, Confinia Cephalalgica, Frontiers in Neurology, and Arquivos de Neuropsiquiatria. BR reports research grants from Lundbeck, Novartis, German Research Foundation, German Migraine and Headache Society, Else Kröne-Fresenius-Stiftung and personal fees from Abbvie, Lundbeck, Novartis, Organon, Perfood and Teva. BR is an Editorial Board Member of The Journal of Headache and Pain and Cephalalgia. ERB is member of the Editorial Board of The Journal of Headache and Pain, and the Headache Medicine and Facial Pain Section of Frontiers in Neurology. RR has received travel grants and/or honoraria for lectures or advisory boards, or has consulted for AbbVie, Betapharm, Lundbeck, Novartis, Pfizer and Teva. CT is Editor of the Primary Care section of Annals of Medicine and Editorial Board Member of The Journal of Headache and Pain. MW-P is member of the Editorial Board for The Journal of Headache and Pain and reports personal fees from AbbVie, Pfizer, Orion Pharma, Polpharma and Teva for speaker activities. WW serves as member of the Editorial Board of The Journal of Headache and Pain, Pain and Therapy, SN Comprehensive Clinical Medicine. He is also the Guest Editor of Frontiers in Neuroscience. PM declare no personal Conflict of Interest related to the content of this manuscript, intellectual position as Editor in Chief of The Journal of Headache and Pain and of SN Comprehensive Clinical Medicine, Member of Editorial Board of Internal and Emergency Medicine, Pain and Therapy, Neurology and Therapy, Clinical Drug Investigation, and EU Expert at European Medicines Agency. AR is Associate Editor of the Journal of Headache and Pain.

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