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Artificial Intelligence in the Diagnosis of Migraine (with or without Aura) in Adults: A Systematic Review

Avnika Jain, Ojasvini Bali*, Nupur Ritchie*, Sumeet Singla***

Abstract

***Objective:** To assess the performance of artificial intelligence (AI) systems in the diagnosis of migraine with aura and migraine without aura in adults.*

***Background:** Migraine is a chronic neurovascular disorder that affects over 1 billion people across the world. Currently diagnosed based on clinical criteria given by the International Headache Society, its accurate diagnosis is challenging because of the existence of numerous mimics.*

***Methods:** Literature search of PubMed, Scopus, and Embase was conducted on July 6, 2021. Original peer-reviewed articles in which AI was applied for diagnosis of migraine with or without aura in adults (>18 years) were included. The risk of bias was evaluated using Quality Assessment of Diagnostic Accuracy Studies-2.*

***Results:** Thirty-four papers were included, spanning close to a hundred AI models being used for neurophysiological, clinical or radiological diagnosis of migraine. The most common were Support Vector Machine and Artificial Neural Network. The median accuracy in the studies included was highest for those employing radiological data (88.85%) and lowest for clinical attributes (81%). Risk of bias assessment yielded four studies (11.8%) with an overall low-risk of bias. Twenty-three out of 34 studies had 'high'-risk of bias in the patient selection domain, the most frequent cause being a case-control study design.*

***Conclusion:** Evidence suggests that AI is potentially valuable in the diagnosis of migraine. Concerted efforts are necessary to ensure uniformity in reporting of data, ethical handling of datasets, and for progress from experimental status to deployment in actual clinical settings.*

***Key words:** Migraine, artificial intelligence, migraine with Aura, migraine without Aura.*

***Key message:** Artificial intelligence (AI) models are being developed for application in various fields of medicine. This is the first systematic review to highlight the use of AI in the diagnosis of migraine and thirty-four papers were included. This review has found that AI has the potential to classify migraine with a high degree of accuracy with objective use of clinical, EEG or radiological data. Future studies in this field should aim to include larger and more diverse datasets, report outcomes in a standard manner, and integrate AI into actual clinical settings.*

Introduction

Migraine is a chronic neurovascular disorder that affects over 1 billion people across the world[1]. It is the third most frequent disorder worldwide with a 1-year prevalence of 15%[2,3] and is the second most disabling disease globally contributing to 45·1 million years lived with disability (YLDs)[4,5]. It accounts for nearly 5·6% of the global disease burden[6]. This burden is largely avoidable with effective and affordable treatments. However, a major challenge is its accurate and timely diagnosis.

Headache is the most common presenting neurological symptom in primary care[7]. Currently, the diagnosis of headache disorders is based on clinical history and is therefore susceptible to a high degree of information bias. To standardise the process, a classification system was developed by the International Headache Society (IHS), the most recent of which is the third edition of the International Classification of Headache Disorders (ICHD-3), launched in 2018[8]. The ICHD classifies headache disorders into primary headaches, secondary headaches, and neuropathies and facial pains. Migraine is a primary headache disorder which has two major types-migraine with aura and migraine without aura. In migraine with aura, transient focal neurological symptoms may precede or accompany the headache. Migraine without aura is more than twice as frequent as migraine with aura[9].

Due to the existence of numerous migraine 'mimics', migraine is frequently underreported and misdiagnosed (in ~50% of headache cases) as sinusitis, other headache

**MBBS Student, **Professor, Department of Medicine, Maulana Azad Medical College and Lok Nayak Hospital, Bahadur Shah Zafar Marg, Delhi - 110 002.*
Corresponding Author: Dr Sumeet Singla, Professor, Department of Medicine, Maulana Azad Medical College and Lok Nayak Hospital, Bahadur Shah Zafar Marg, Delhi - 110 002. Phone: 9810104431, E-mail: sumeetsingla555@gmail.com.

disorders like tension headache and cervical pain syndrome, stroke, transient ischaemic attack, multiple sclerosis, among others[5,10,11]. In another study, 88% patients who met the ICHD criteria for migraine were wrongly diagnosed with sinusitis[12,13]. Kernick *et al* reported that a formal diagnosis was not made in nearly 70% of patients presenting with new onset headache[14].

Data-driven approaches using machine learning (ML) or deep learning (DL) are being tested in the medical field to avoid biases attributed to human factors. Artificial intelligence (AI) models accelerate the identification and interpretation of relevant medical data from multiple sources and areas of interest[15]. ML methods analyse a large number of 'training' cases to produce the correct output for the given input on test cases. According to the types of tasks that they intend to solve, basic ML algorithms fall roughly into two categories: supervised and unsupervised. 'Supervised' algorithms learn from pre-labelled datasets to classify a specific outcome (e.g., presence or absence of migraine in the context of the current study). Newer 'unsupervised' AI systems such as DL analyse unlabelled data finding complex co-relations in previously unrecognised patterns (e.g., use of principal component analysis for feature selection). Supervised models may achieve high accuracies since the data used for training has already been labelled. Performance of ML models can be evaluated using different outcome measures such as accuracy, area under the receiver operating characteristic curve (AUC), recall (sensitivity), precision (positive predictive value) and calibration (goodness of fit). While accuracy and AUC are the most frequently reported performance metrics, if considered in isolation they may not always reflect the true performance of the model[16].

As per our knowledge, this is the first systematic review aiming to assess the potential role of different AI-based approaches in the diagnosis of migraine with and without aura in adults.

Methodology

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) guidelines[17]. The study protocol was registered and published on the international Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42021267186).

Search Strategy

A search syntax was created using relevant keywords for migraine and artificial intelligence. The search was conducted on July 6, 2021 on three databases, i.e., PubMed, Scopus, and Embase. Filters were applied to include English language search results published in or after 2000. The search results were compiled using EndNote software. The titles and abstracts were then independently screened by three reviewers (AJ, OB, NR). Disagreements were resolved either through discussion or by consulting the fourth reviewer (SS). Full texts of the selected results were retrieved and matched against the inclusion criteria in the same manner.

Selection Process

We included studies in which an AI algorithm was applied for diagnosis/ classification of migraine with and/or without aura in adult patients (>18 years) in any hospital setting. We excluded case reports, case series, reviews and meta-analyses as well as studies mentioning neither the accuracy nor AUC of the chosen model. Rare subtypes of migraine (e.g., familial, vestibular, hemiplegic) were not included in this review.

The studies were assessed for eligibility by AJ, OB and NR independently with a final consensus reached through discussion or by consulting SS.

The references of the full texts chosen for the study were screened for articles matching the eligibility criteria.

Data Collection

The data was extracted independently by the three reviewers, on (1) study characteristics; and (2) performance metrics of the index test and was then tabulated and cross-checked by all the reviewers (Tables I, II, III).

Since 31 out of 34 papers reported accuracy of their ML models, this was chosen as the primary performance metric. Median accuracy was subsequently calculated using the highest accuracy reported in each paper.

Risk of Bias Assessment

The risk of bias was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria[18]. Bias was assessed by AJ, OB and NR independently using various signalling questions tailored for the review. Each of the four domains could be of low, unclear or high-risk of bias. If the answer to any one signalling question was 'no' or 'unclear', the risk of bias of that domain was considered high or unclear respectively. A high or unclear risk of bias of any one domain resulted in the risk of bias of that study being high or unclear respectively.

Table I: Summary of the studies included in this systematic review using neurophysiological data as input.

S. No.	Authors	Year	Reference for diagnosis	Model(s)	Total number of participants	Input	Training/ Validation/ Test set/ Validation Method	Accuracy/ AUC	Sensitivity/ Specificity
					Input data: Neurophysiological Investigations				
1.	Akben *et al*[19]	2012	IHS	MLPNN (and RBF, LVQ, SOM for comparison)	30 (15 migraineurs + 15 HC)	EEG	80%/–/20%	93.3% (4 Hz)	93.3% / 93.3%
2.	Akben *et al*[20]	2016	IHS	SVM	60 (30 MwoA + 30 HC)	EEG	–/–/–	88.4% (T3)	90% /86.7%
3.	Alkan *et al*[21]	2011	IHS	K-means clustering	30 (15 migraineurs + 15 HC)	EEG	90%/–/10%	86.6%	–/–
4.	Bellotti *et al*[22]	2007	–	ANN	31 (16 MwoA + 15 HC)	Spontaneous EEG	–/–/–	AUC > 0.95 (tau-TDG)	–/–
5.	Cao *et al*[25]	2018	ICHD-2	LDA kNN MLPNN NB SVM, linear kernel SVM, RBF kernel	80 (40 MwoA + 40 HC)	Inter-ictal and pre-ictal phase EEGs	27/13/-K-fold CV (k = 3)	63.0 ± 6% (LDA) 71.0 ± 5% (kNN) 67.0 ± 6% (MLPNN) 65.0 ± 5% (NB) 71.0 ± 4% (SVM, linear kernel) 76.0 ± 4% (SVM, RBF kernel)	–/–
6.	de Tommaso *et al*[23]	2003	IHS	ANN SVM	30 (15 MwoA + 15 HC)	SVEP-EEG	–/–/–	AUC 0.78 (ANN; F1) AUC 0.88 (ANN; α wav) AUC 0.92 (SVM; F1) AUC 0.86 (SVM; α wav)	–/–
7.	Frid *et al*[24]	2020	ICHD-3 beta	SVM with RBF	53 females with episodic migraine	EEG	–/–/–	84.62%/AUC 0.88	–/–
8.	Subasi *et al*[26]	2019	–	SVM kNN ANN RF DT (CART) DT (C4.5) Rotation forest DT (REPTree) DT (Random Tree) DT (ADTree) DT (LADTree) DT (NBTree)	30 (15 MwoA + 15 HC)	EEG	–/–/– 10-fold CV, LOOCV	(Window period = 3s Without flash/with flash 80.74%/84.07% (SVM) 77.78%/83.33% (kNN) 75.93%/82.22% (ANN) 75.19%/85.19% (RF) 67.04%/77.78% (CART) 64.81%/77.04% (C4.5) 77.41%/83.70% (Rotation Forest) 65.93%/74.81% (REPTree) 68.15%/76.30% (Random tree) 66.67%/73.33% (ADTree) 70.74%/77.41% (LADTree) 65.93%/75.93% (NBTree)	–/–
9.	Taufique *et al*[27]	2021	–	ANN	57 (Patient data taken from Zhu *et al*)	SSEP-EEG	–/–/– 5-fold CV	76% (ANN)	–/–
10.	Zhu *et al*[28]	2019	–	DT (XGB trees) RF SVM kNN MLPNN LDA LR	57 (29 MII, 13 MI, 15 HCs)	SSEP-EEG	–/–/– 10-fold CV	HC-MI - 88.0% (XGBTree) HC-MI - 84.4% (RF) HC-MII - 84.6% (SVM) HC-MI - 78.5% (kNN) HC-MII - 83.3% (MLPNN) MI-MII - 69.5% (LDA) HC-MI - 69.7% (LR)	89.3%/90.3% (XGBTree) 84.1%/84%(RF) 85.7%/85.8% (SVM) 78%/78.2%(kNN) 82.6%/85.2% (MLPNN) 69.3%/67.1% (LDA) 68.9%/70.6%(LR)

ANN: Artificial neural network; CART: Classification and regression tree; DT: Decision tree; HC: Healthy controls; IHS: International Headache Society; ICHD: International Classification of Headache Disorders; KNN: k-nearest neighbors; LDA: Linear discriminant analysis; LOOCV: Leave one out cross validation; LVQ: Learning vector quantisation; LR: Logistic regression; MI: Migraine ictal; MII: Migraine inter-ictal; MLPNN: Multi-layer perceptron neural network; MwA: Migraine with aura; MwoA: Migraine without aura; NB: Naïve bayes; RBF: Radial basis function; RF: Random forest; SOM: Self-organising map; SSEP: Somatosensory evoked potential; SVEP: Steady state visual evoked potential; SVM: Support vector machine; XGB: Extreme gradient boosting.

Table 2: Summary of the studies included in this systematic review using clinical attributes as input data.

S. No.	Authors	Year	Reference for diagnosis	Model(s)	Total number of participants	Input	Training/ Validation/ Test set/ Validation Method	Accuracy/ AUC	Sensitivity/ Specificity
					Input data: Clinical Attributes				
11.	Çelik *et al*[30]	2015	ICHD-2	Immunos-1 Immunos-2 Immunos-99 AIRS1 AIRS2 AIRS2-Parallel CLONALG CSCA	850 people with "headache problems" Questionnaire, 40 attributes	–/–/–	94.4706% (Immunos-1)	0.947/1 (Immunos-1) 71.6471% (Immunos-2) 95.6471% (Immunos-99) 99.2941% (AIRS1) 98.8235% (AIRS2) 99.6471% (AIRS2-Parallel) 98.7059% (CLONALG) 99.1765% (CSCA)	1/0 (Immunos-2) 0.949/1 (Immunos-99) 0.995/1 (AIRS1) 0.995/0.992 (AIRS2) 0.998/1 (AIRS2-Parallel) 0.998/0.967 (CLONALG) 0.995/0.992 (CSCA)
12.	Çelik *et al*[29]	2017	ICHD-2	ACO	850 people with "headache problems" Questionnaire, 40 attributes	–/–/–	10-fold CV	98.2%	0.982/0.967
13.	Holsteen *et al*[31]	2020	ICHD-3	Multivariable LR LR	178 patients with episodic migraine	Diary entry	178/–/– 10-Fold CV	0.56 (95% CI, 0.54 - 0.58)	–/–
14.	Katsuki *et al*[32]	2020	ICHD-3 beta	NLP using ANN	848 patients with primary headache	Questionnaire	–/–/–	77.59%	–/–
15.	Khayamnia *et al*33	2019	–	Fuzzy C MLPNN SVM	190 patients with headache (133 with migraine)	Clinical attributes	90% /–/10% 10-Fold CV	92% (Fuzzy C) 92% (MLPNN) 100% (SVM)	0.94/0.81 (Fuzzy C) 0.96/0.81 (MLPNN) 1/0.99 (SVM)
16.	Kwon *et al*[35]	2020	ICHD-3, ICHD-3 beta	XGBoost	2,162 patients	Clinical attributes	864 /–/ 600 10-Fold CV	81%	88%/95%
17.	Krawczyk *et al*[34]	2012	ICHD-2	NB DT (C4.5) SVM Bagging Boosting RF	579 with headache (169 with migraine)	Clinical attributes	–/–/–10-Fold CV	72.02 ± 4.21% (NB) 76.51 ± 3.04% (C4.5) 76.34 ± 1.76% (SVM) 78.24 ± 2.98% (Bagging) 76.68 ± 2.43% (Boosting) 79.97 ± 3.13% (RF)	–/–
18.	Sarsam *et al*[36]	2020	–	SVM (SMO) DT (J48) 1-rule classifier (OneR) kNN (IBk)	237,098,462 English tweets	Tweets	90%/–/– 10-fold CV	95.53% (SMO) 61.49% (J48) 55.27% (OneR) 50.93% (IBk)	–/–
19.	Sedghi *et al*[37]	2016	Neurologist	NB SVM LR	6,912 records (392 migraine)	Clinical attributes	66%/–/33% 10-fold CV	79.3% (NB) 78.4% (SVM) 77.4% (LR)	–/–
20.	Simiae et al[40]	2020	ICHD-3	LR	579 instances (103 MwoA, 66 MwA)	Selected attributes from the IHS criteria	–/–/–	77.4%	–/–
21.	Simiae *et al*[38]	2021	ICHD-2	Weighted Fuzzy C-means Clustering Algorithm	579 with primary headache	Clinical features	–/–/–	75%	86%/–
22	Wu *et al*[39]	2015	ICHD-3	Multiple Fuzzy C-means Clustering Fuzzy C Fuzzy C with genetic algorithm ACO	379 total (213 for migraine)	20 weighted clinical features	–/–/–	97.2% (multiple Fuzzy C) 63.6% (Fuzzy C) 59.8% (Fuzzy C with genetic algorithm) 89.2% (ACO)	–/–

ACO: Ant colony optimisation-based classification algorithm; AIRS: Artificial immune-recognition system; ANN: Artificial neural network; CLONALG: Clonal algorithm; CSCA: Clonal selection classification algorithm; DT: Decision tree; HC: Healthy controls; IBk: Instance-based learning with parameter k; IHS: International Headache Society; ICHD: International Classification of Headache Disorders; KNN: k-nearest neighbours; LR: Logistic regression; MLPNN: Multi-layer perceptron neural network; MwA: Migraine with aura; MwoA: Migraine without aura; NB: Naïve bayes; NLP: Natural language processing; RF: Random forest; SMO: Sequential Minimal Optimisation; SVEP: Steady state visual evoked potential; SVM: Support vector machine; XGB: Extreme gradient boosting.

Table 3: Summary of the studies included in this systematic review using radiological imaging as input data.

S. No.	Authors	Year	Reference for diagnosis	Model(s)	Total number of participants	Input	Training/Validation/ Test set/ Validation Method	Accuracy/AUC	Sensitivity/ Specificity
					Input data: Radiological Imaging				
23.	Chen *et al*[42]	2021	IHS	SVM	42 (21 MwoA + 21 HC)	fMRI	–/–/–LOOCV	83.33%	90.48%/76.19%
24.	Chong *et al*[41]	2017	–	DQDA	108 (58 with migraine + 50 HC)	fMRI	–/–/–10-fold CV	86.1%	–/–
25.	Chong *et al*[52]	2021	ICHD-3	LR	34 with migraine (18 MwA, 16 MwoA) and 48 with PPTH	MRI (T1 weighted and DTI) + Clinical data	–/–/–LOOCV	97.06%	–/–
26.	Garcia-Chimeno *et al*[51]	2017	–	SVM Boosting (Adaboost) NB	52 (15 HC, 19 sporadic migraine, 18 chronic migraine and medication overuse)	MRI (diffusion tensor) and multiple questionnaire	–/–/– Stratified K fold method for SVM	All Feature selection method 90% / 78-98% (SVM; best with gradient tree boosting) 93% / 87-95% (AdaBoost; best with random forest) 67% / 60-98% (NB; best with gradient tree boosting)	–/–
27.	Jorge-Hernandez *et al*[49]	2014	–	ANN LDA SVM k means Cluster kNN AdaBoost	53 (15 HC, 20 sporadic migraine, 19 with migration due to medication overuse)	fMRI	20/15/19	92.86% (ANN) 50% (LDA) 79.92% (SVM) 57.14% (k means cluster) 57.14% (kNN) 64.29% (AdaBoost)	1/0.9(ANN) 0.45/0.38 (LDA) 0.36/0.38 (SVM) 0.47/0 (k means) 0.49/0.47 (kNN) 0.74/0.64(AdaBoost)
28.	Li *et al*[48]	2020	–	SVM kNN DT NB RF ANN	26 (14 migraineurs + 12 HC)	fMRI	58% /–/42%	92% (SVM) 100% (kNN) 88% (DT) 92% (NB) 83% (RF) 93% (ANN)	–/–
29.	Meng *et al*[50]	2018	–	CNN	40 (20 migraineurs + 20 HC)	MEG	30/–/104-Fold CV	81.25%	–/–
30.	Rocca *et al*[43]	2021	ICHD-2	CNN	268 imaging scans (56 for migraine)	MRI	56%/14%/30%	92.90%	–/97.10%
31	'Schwedt *et al*[47]	2015	ICHD - 2	DQDA DT	120 (66 migraineurs + 54 HCs)	sMRI	90%/–/10% 10-fold CV	Migraine vs HC – 68% (DQDA) EM vs HC - 67.2% (DQDA) CM vs HC - 86.3% (DQDA) CM vs EM - 84.2% (DQDA) Migraine vs HC - 64.7% (DT) EM vs HC - 66.5% (DT) CM vs HC - 74.6% (DT) CM vs EM - 83% (DT)	–/–
32.	Tu *et al*[44]	2020	ICHD-2	Linear SVM	Study 1: 116 (70 MwoA, 46 HC) Study 2: 38 (19 MwoA, 19 HC) Study 3: 76 (18 MwoA, 58 non-migraine pain and HC)	MRI	–/–/–LOOCV	91.4% (SVM; Study 1) 84.2% (SVM; Study 2) 73.1% (SVM; Study 3)	93%/89% (SVM; Study 1) 84.2%/84.2% (SVM; Study 2 77.8%/71.4% (SVM; Study 3)
33.	Yang *et al*[45]	2018	ICHD - 2	AlexNet CNN Inception module - based GoogleNet CNN SVM(for comparison)	64 (21 MwoA, 15 MwA, 28 HC)	fMRI	80% /–/20%4 -fold CV	98.63% (AlexNet CNN ; HC vs migraine using RFCS) 99.25% (GoogleNet CNN; HC vs migraine using RFCS) 83.67% (SVM)	–/–
34	Zhang *et al*[46]	2016	ICHD - 2	Multi-kernel SVM	49 (21 MwoA, 28 HC)	fMRI and sMRI	–/–/–LOOCV	83.67%	92.86%/71.43%

ANN: Artificial neural network; CM: Chronic Migraine; CNN: Convolutional neural network; DT: decision tree; DQDA: Diagonal quadratic discriminate analysis; EM: Episodic migraine; HC: Healthy controls; IHS: International Headache Society; ICHD: International Classification of Headache Disorders; KNNP: k-nearest neighbours; LDA: Linear discriminant analysis; LOOCV: Leave one out cross validation; LR: Logistic regression; MEG: Magnetoencephalogram; MwA: Migraine with aura; MwoA: Migraine without aura; NB: Naïve bayes; PPTH: Persistent post-traumatic headache; RF: Random forest; RFCS: Regional functional correlation strength; SVM: Support vector machine.

Results

Study selection

After removal of duplicates and manual reference checking, 884 citations from PubMed, Scopus and Embase were screened based on title/abstract. 75 studies were sought for retrieval. Finally, 34 articles remained after full-text screening (as shown in the PRISMA diagram).

Study characteristics

AI models gather data from a multitude of sources and emulate logical decision making to achieve the desired output. In the current review, these models aid neurophysiological, clinical and radiological diagnosis of migraine. The most popular models used were Support Vector Machine (SVM), Artificial Neural Network (ANN) and Decision Tree (DT). Other algorithms used include K-Nearest Neighbour (KNN), Logistic Regression (LR), Fuzzy-C, Naive Bayes (NB) (Fig. 1). A general trend showing an increasing number of studies on the use of AI algorithms in the diagnosis of migraine over the past 2 decades was noted (Fig. 2).

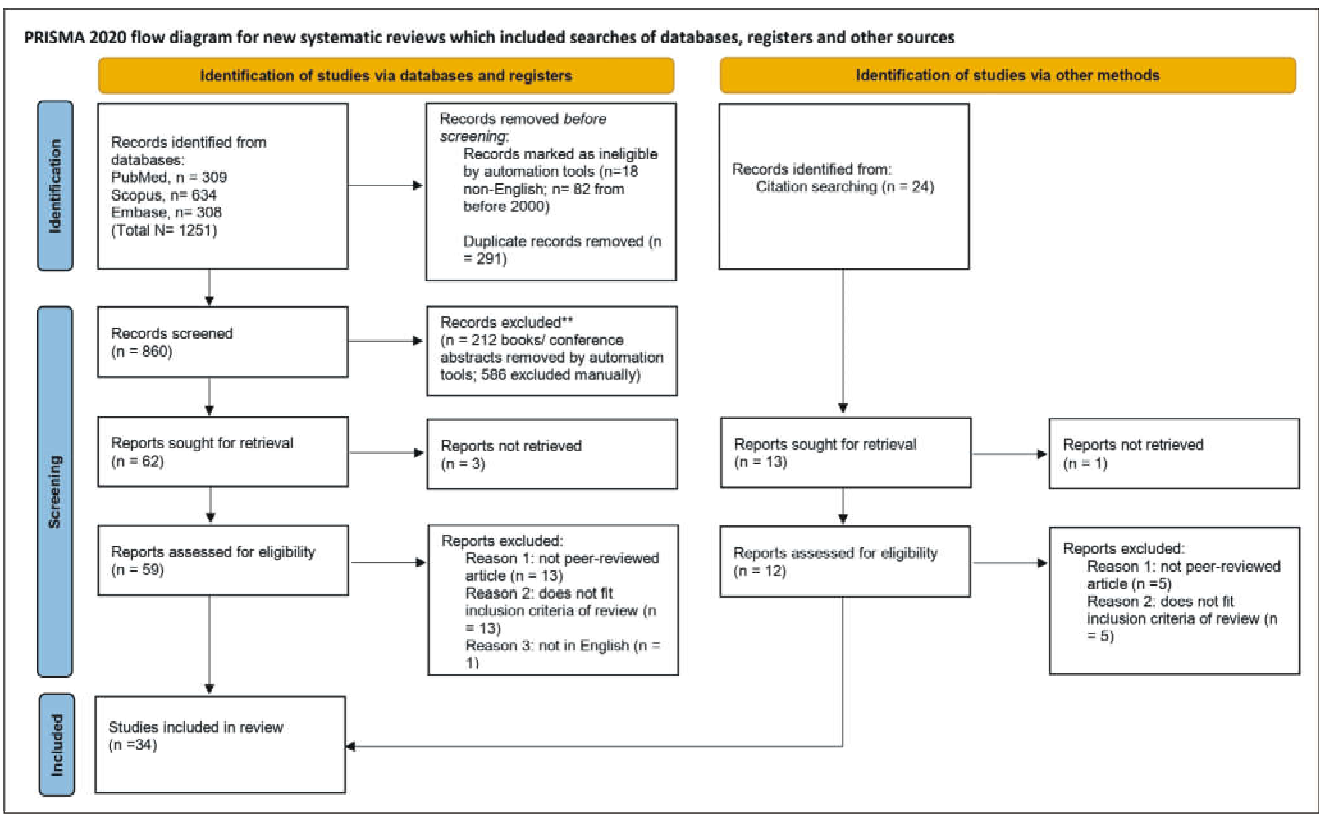
AI in Neurophysiological Diagnosis of Migraine

10 studies used AI models to diagnose migraine based on neurophysiological modalities. The median accuracy was found to be 85.9% (range 76.0 to 93.3%).

In their 2010 study, Akben *et al*[19] aimed to determine the most effective flash stimulation frequency and time duration to detect migraine using an Artificial (Multi-layer perceptron) Neural Network (MLPNN) classifier and radial basis function networks (RBF), learning vector quantisation and self-organizing map networks for comparison. Best accuracy obtained was 93.3% for MLPNN, at 4 Hz. Their 2016 study[20] assessed which EEG channels and brain lobes were the most decisive for diagnosis, using an SVM model. Power spectral densities (PSDs) obtained from flash stimulated and non-stimulated EEG signals were fed to the classifier. Best accuracy was 88.4% for T3 channel.

Alkan *et al* (2011)[21] used histogram differences of flash and non-stimulation EEGs to detect migraine using a K-means cluster algorithm, achieving an accuracy of 86.6%.

Bellotti *et al* (2007)[22] recorded spontaneous EEGs to classify migraineurs (without aura) and healthy controls. Using a supervised feed-forward two-layered neural network, they recorded an AUC of >0.95 (tau-TDG).



Flowchart 1: *PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.*

From: Page MJ, McKenzie JE, Bossuyt PM et al. *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi: 10.1136/bmj.n71.*

de Tomasso *et al* (2003)[23] elicited steady-state visual evoked potentials (SVEPs) in the low frequency range (3-9 Hz) and studied the temporal variations in the F1 component obtaining a maximum AUC of 0.92 using SVM.

Frid *et al* (2020)[24] recorded 3-minute-long resting state EEGs in the interictal period to compare patients of migraine with and without aura. Using SVM with RBF kernel, they were able to obtain an average classification rate of 84.62%. The same model was found to achieve the highest accuracy (76 ± 0.04%) in a study by Cao *et al* (2018)[25] where they tested six AI models to compare the interictal and preictal phase brain electric activity using resting-state EEGs.

Subasi *et al* (2019)[26] assessed accuracy of 12 models in the diagnosis of migraine without aura using a 10 - 20 EEG system with 256 Hz sampling frequency. The highest accuracy obtained was 84.07% for SVM for a window period of 3 seconds with photic stimulation.

Taufique *et al* (2021)[27] used a hardware chip-based ANN classifier, with its utility in wearable settings, to facilitate early diagnosis of migraine. The somatosensory evoked potential (SSEP) data was pre-processed with features extracted – N20 latency, root-mean-square of late high frequency oscillations (HFO) and power spectral bands – and fed into the classifier. An accuracy of 76% was achieved.

Zhu *et al* (2019)[28] conducted a study to differentiate between migraineurs in the ictal and inter-ictal phases and healthy controls using various features of SSEP signals. A total of 8 ML algorithms were assessed, with the highest accuracy obtained for extreme gradient boosting (XGB) trees at 89.3% in the ictal phase.

AI in Clinical Diagnosis of Migraine

12 studies used AI models to diagnose migraine based on clinical attributes. The median accuracy was 81% (range 75 to 100%).

Celik *et al* diagnosed different types of primary headaches using an ant colony optimisation-based algorithm (2017 paper)[29] and multiple artificial immune system (AIS) algorithms (2015 paper)[30]; achieving best accuracy of 98.2% and 99.65% (AIRS2-Parallel) respectively (Table II).

Holsteen *et al* (2020)[31] developed an LR model to classify subjects with episodic headache into migraine day and

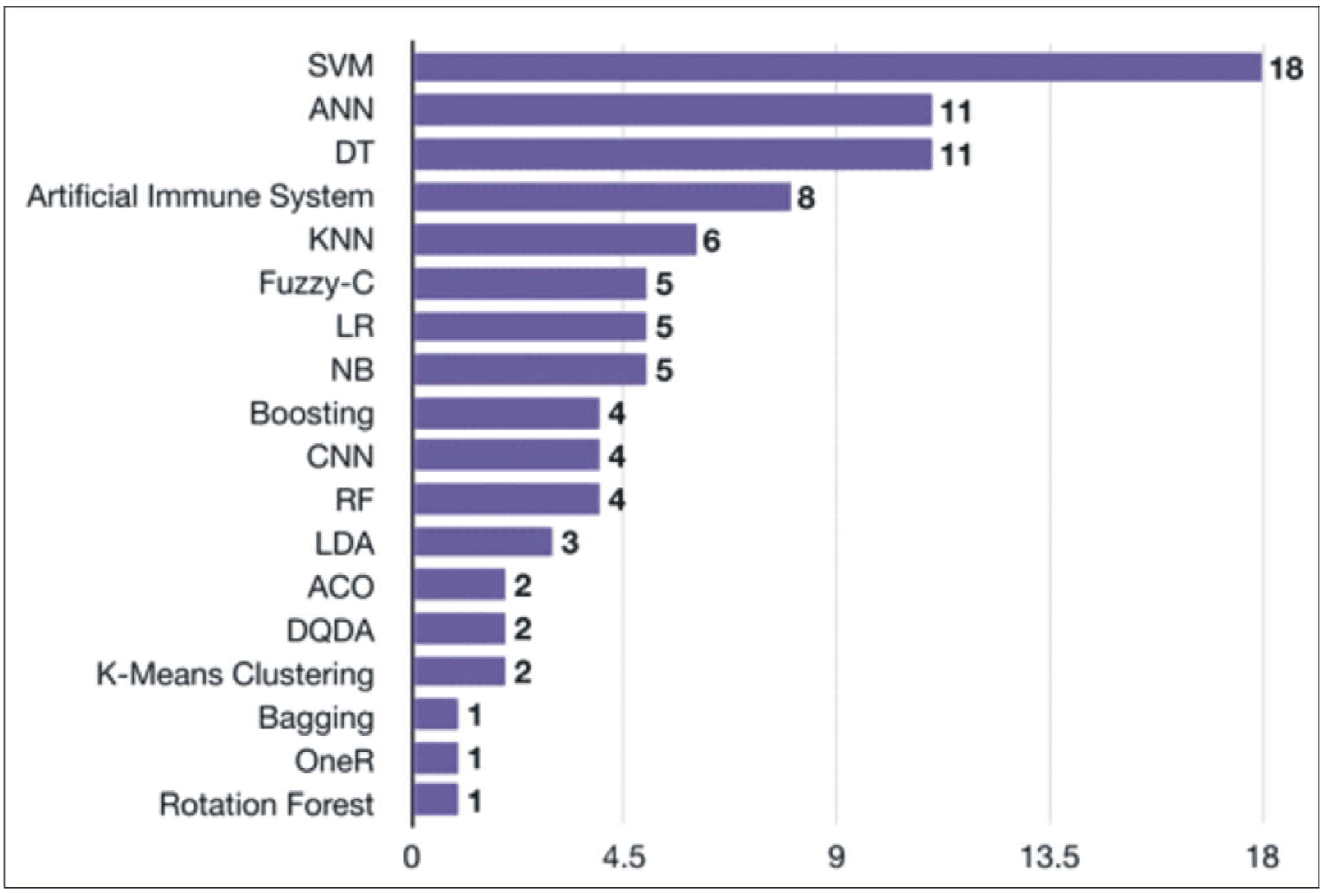


Fig. 1: *The various AI algorithms used in the diagnosis of migraine.*

healthy day categories based on prospective daily diary entries (including self-prediction and self-reported exposure to common trigger factors), using a custom mobile phone application. The model could predict migraine risk only slightly better than chance with an AUC of 0.56 (95% CI: 0.54, 0.58) (Table II).

Katsuki *et al* (2020)[32] developed an ANN model for automated diagnosis of primary headache using demographic characteristics and unstructured sentences (in Japanese) in the questionnaire which were analysed using natural language processing (NLP). The overall AUC, mean precision, mean recall, and mean F value of the model were 0.7759, 0.8537, 0.6086, and 0.6353, respectively (Table II).

Khayamnia *et al* (2019)[33] developed a fuzzy expert-based system using the Learning-From-Examples algorithm and Mamdani model for the diagnosis of common headache types including migraine. Diagnostic parameters like presence or absence of symptoms like aura, vomiting, diplopia, etc., were used as input variables. They also evaluated the performance of MLPNN and multiclass SVM. For classification of migraine, SVM was the most accurate (accuracy = 100%). Overall accuracy of SVM was 90% (vs 88% for MLPNN) (Table II).

In studies by Krawczyk *et al* (2012)[34] and Kwon *et al* (2020)[35], automated diagnosis of headache disorders was done based on clinico-demographic data collected using questionnaires. Krawczyk *et al* tested six machine learning algorithms (Table II). Highest accuracy of 79.97 ± 3.13% was achieved by the random forest model. Kwon developed a four layered binary XGBoost13 based stacked model. This model was compared with other classifiers (Table II). XGBoost13 using the least absolute shrinkage and selection operator (LASSO) method for feature selection was the most accurate (80.71%; sensitivity 52.73%, specificity 45.61%).

Sarsam *et al* (2020)[36] collected and labelled a total of 238,506,796 English tweets according to their geo-spatial location information. The data was clustered into 'sad' and 'neutral' using K-means clustering. The association rules mining approach (using Apriori algorithm) was applied to extract the features of migraine associated with certain climatic factors in each of the two emotions. Finally, four classification algorithms (Table II) were applied to detect migraine, with Sequential Minimal Optimisation (SMO) attaining the highest accuracy of 95.53%.

Sedghi *et al* (2016)[37] distinguished migraine patients from stroke or other mimics using structured and unstructured clinical data-sources. A sampling method was utilised to create two balanced datasets from the original imbalanced data and the data then analysed by NLP, text-mining and data mining methods. The performance of different classifiers was assessed (Table II) – with the highest average accuracy obtained for NB (79.3%).

Simiae *et al* (2021)[38], using the clinico-demographic data collected in an earlier study[34], estimated the optimal number of clusters using the Calinski-Harabasz index, assigned weights to the chosen attributes using the Analytical

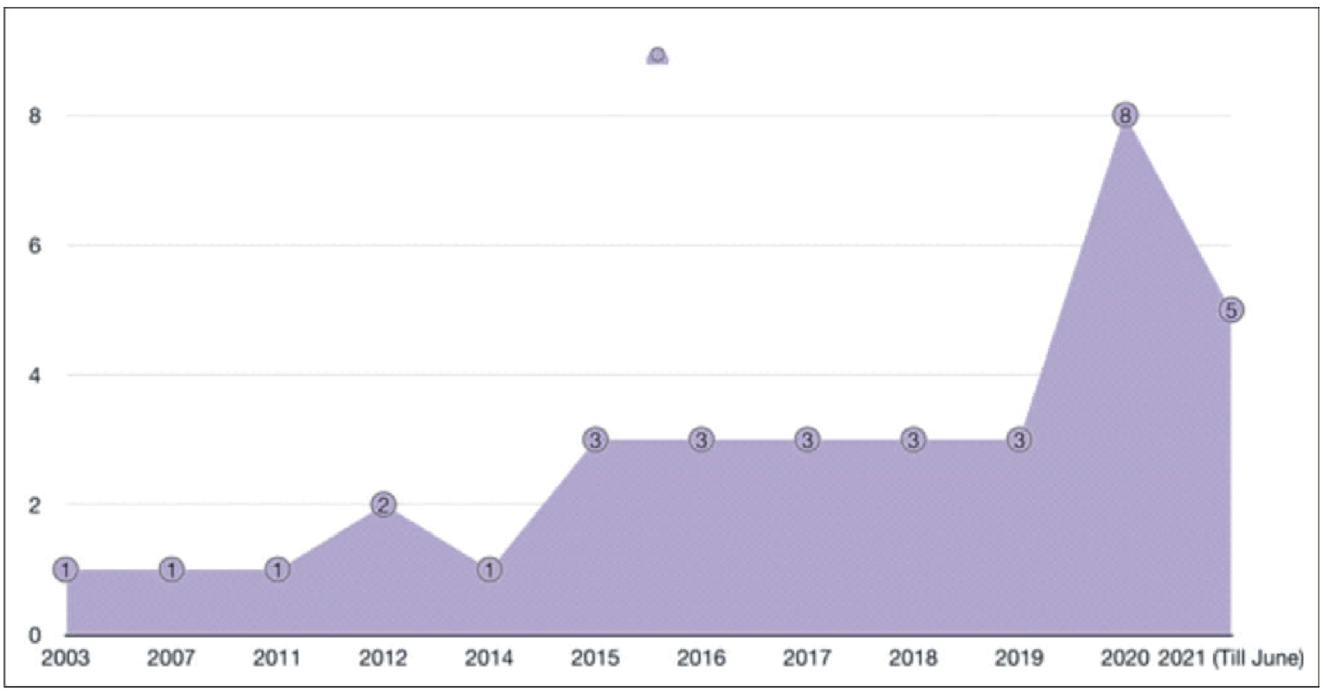


Fig. 2: *Number of studies conducted in the last two decades.*

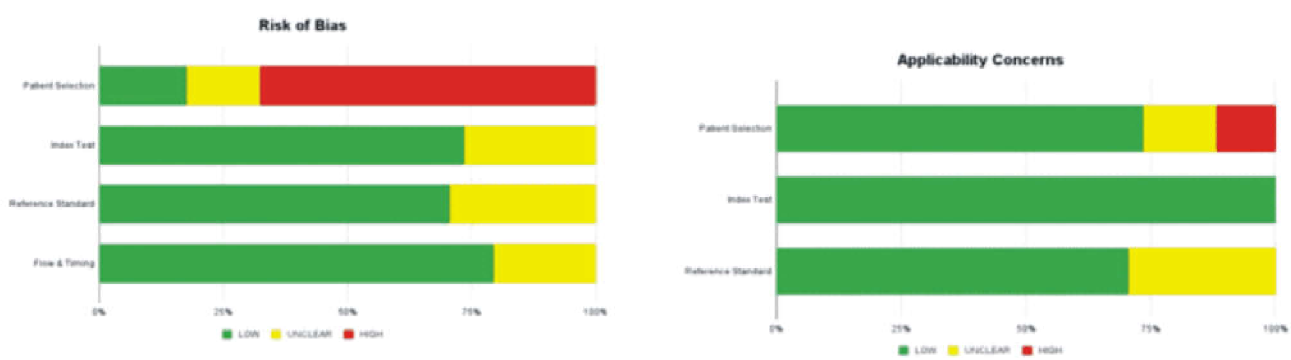
Hierarchical Process and classified the various primary headache disorders using the Fuzzy C-Means Clustering algorithm; obtaining an overall accuracy of 75% (Table II).

Wu *et al* (2015)[39] also used weighted clinical features to

First Author	Year	Patient Selecti	Index Test	Reference Standard	Flow & Timin
Akben	2016	HIGH	UNCLEAR	LOW	LOW
Akben	2012	HIGH	UNCLEAR	LOW	LOW
Alkan	2011	HIGH	UNCLEAR	LOW	LOW
Bellotti	2007	HIGH	UNCLEAR	UNCLEAR	UNCLEAR
Cao	2018	HIGH	LOW	LOW	LOW
Celik	2017	LOW	LOW	LOW	LOW
Celik	2015	LOW	LOW	LOW	LOW
Chen	2021	HIGH	LOW	LOW	LOW
Chong	2021	HIGH	LOW	LOW	LOW
Chong	2017	HIGH	LOW	LOW	LOW
deTomasso	2003	HIGH	LOW	LOW	LOW
Frid	2020	UNCLEAR	LOW	LOW	LOW
Garcia-Chimeno	2017	HIGH	LOW	UNCLEAR	UNCLEAR
Holsteen	2020	LOW	LOW	LOW	LOW
Jorge-Hernandez	2014	HIGH	LOW	UNCLEAR	UNCLEAR
Katsuki	2020	LOW	LOW	LOW	LOW
Khayamnia	2019	LOW	LOW	UNCLEAR	LOW
Krawczyk	2012	UNCLEAR	LOW	LOW	LOW
Kwon	2020	UNCLEAR	LOW	LOW	LOW
Li	2020	HIGH	UNCLEAR	UNCLEAR	low
Meng	2018	HIGH	LOW	UNCLEAR	UNCLEAR
Rocca	2021	LOW	UNCLEAR	LOW	LOW
Sarsam	2020	HIGH	LOW	UNCLEAR	UNCLEAR
Schwedt	2015	HIGH	LOW	LOW	LOW
Sedghi	2016	HIGH	LOW	LOW	LOW
Simić	2020	UNCLEAR	UNCLEAR	LOW	UNCLEAR
Simić	2021	UNCLEAR	UNCLEAR	LOW	LOW
Subasi	2019	HIGH	LOW	LOW	LOW
Taufique	2021	HIGH	LOW	UNCLEAR	LOW
Tu	2020	HIGH	LOW	LOW	LOW
Wu	2015	HIGH	UNCLEAR	UNCLEAR	UNCLEAR
Yang	2018	HIGH	LOW	LOW	LOW
Zhang	2016	HIGH	LOW	LOW	LOW
Zhu	2019	HIGH	LOW	UNCLEAR	LOW

First Author	Year	Patient Selecti	Index Test	Reference Standard
Akben	2016	LOW	LOW	LOW
Akben	2012	LOW	LOW	LOW
Alkan	2011	LOW	LOW	LOW
Bellotti	2007	LOW	LOW	UNCLEAR
Cao	2018	LOW	LOW	LOW
Celik	2017	HIGH	LOW	LOW
Celik	2015	HIGH	LOW	LOW
Chen	2021	LOW	LOW	LOW
Chong	2021	LOW	LOW	LOW
Chong	2017	LOW	LOW	LOW
deTomasso	2003	LOW	LOW	LOW
Frid	2020	LOW	LOW	LOW
Garcia-Chimeno	2017	LOW	LOW	UNCLEAR
Holsteen	2020	LOW	LOW	LOW
Jorge-Hernandez	2014	LOW	LOW	UNCLEAR
Katsuki	2020	HIGH	LOW	LOW
Khayamnia	2019	HIGH	LOW	UNCLEAR
Krawczyk	2012	LOW	LOW	LOW
Kwon	2020	UNCLEAR	LOW	LOW
Li	2020	LOW	LOW	UNCLEAR
Meng	2018	UNCLEAR	LOW	UNCLEAR
Rocca	2021	LOW	LOW	LOW
Sarsam	2020	UNCLEAR	LOW	UNCLEAR
Schwedt	2015	LOW	LOW	LOW
Sedghi	2016	LOW	LOW	LOW
Simić	2020	UNCLEAR	LOW	LOW
Simić	2021	LOW	LOW	LOW
Subasi	2019	LOW	LOW	LOW
Taufique	2021	LOW	LOW	UNCLEAR
Tu	2020	LOW	LOW	LOW
Wu	2015	UNCLEAR	LOW	UNCLEAR
Yang	2018	LOW	LOW	LOW
Zhang	2016	LOW	LOW	LOW
Zhu	2019	LOW	LOW	UNCLEAR

(a)



(b)

Fig. 3: *Methodological quality summary table and graph. (a) Risk of bias (left) and applicability concerns (right) summary: review authors' judgements about each domain for each included study. (b) Proportion of studies with LOW, UNCLEAR and HIGH risk of bias and applicability concerns as assessed by QUADAS-2 tool.*

diagnose primary headache disorders using the Multiple Fuzzy C-Means Clustering algorithm. Its accuracy was compared with other conventional models, and was the highest at 97.2% (in the diagnosis of migraine) (Table II).

In another study by Simiae *et al* (2020)[40] a hybrid fuzzy clustering approach created by combining the fuzzy partition method and maximum likelihood estimation clustering algorithm was used to diagnose primary headache disorders using selected clinico-demographic attributes. An accuracy of 77.4% was achieved (Table II).

AI in Radiological Diagnosis of Migraine

10 studies used AI models to diagnose migraine based on imaging modalities. The median accuracy was 88.85% (range 81.25 to 100%) (Table III).

Chong *et al* (2017)[41] obtained resting state functional connectivity (RSFC) data in the "eyes closed" state for the 108 individuals in their study. A total of 33 known pain-processing brain areas were selected. Pre-processing using principal component analysis (PCA) and subsequent classification using diagonal quadratic discriminate analysis (DQDA) found that six regions (bilateral amygdala, right middle temporal, posterior insula, middle cingulate, and left ventromedial prefrontal brain regions) had the highest contribution in discrimination between migraineurs and healthy controls. Their best accuracy was 86.1% (Table III).

Chen *et al* (2021)[42] performed dynamic amplitude of low-frequency fluctuations (dALFF) analyses on 42 subjects. In the migraineurs, significantly decreased dALFF was observed in certain brain regions (the bilateral anterior insula, bilateral lateral orbitofrontal cortex, bilateral medial prefrontal cortex, bilateral anterior cingulate cortex, and left middle frontal cortex). SVM was used for classification, giving an accuracy of 83.33% (Table III).

Rocca *et al* (2021)[43] collected a total of 268 T2 and T1 weighted brain MRI scans from patients of multiple sclerosis, migraine and other mimics of the former. The final trained model was compared with two expert neuroradiologists. An accuracy of 92.9% was attained using Convolutional Neural Network (CNN) (Table III).

Tu *et al* (2020)[44] conducted a multi-level study using linear SVM for identifying an fMRI marker for differentiating between migraineurs and healthy controls (HCs), assessing its generalisability, validating it by differentiating between migraine and other chronic pain disorders, and for assessing its response with treatment, respectively. Accuracies of 91.4%, 84.2% and 73.1% were obtained in the three diagnostic studies respectively (Table III).

Yang *et al* (2018)[45] used AlexNet and Inception module-based GoogleNet CNN models to diagnose and classify migraine based on the pre-processed resting-state fMRI data and the three indices ALFF, Regional Homogeneity (ReHo) and Regional Functional Correlation Strength (RFCS) extracted from it. GoogleNet CNN model was found to have a higher accuracy of 99.25% (Table III).

In the study conducted by Zhang *et al* (2016)[46], along with fMRI (ALFF, ReHo and RFCS) data, gray matter maps were also created using sMRI. 116 features were selected for each map and fed to a multi-kernel SVM model. An accuracy of 83.67% was obtained (Table III).

Schwedt *et al* (2015)[47] used 4 classifiers (Table III) to classify migraineurs into chronic and episodic and differentiate them from HCs, as well as to test the currently used threshold of 15 headache days/month for differentiating chronic from episodic migraine. Using sMRI scans and PCA, principal components for the cortical area, thickness, and volume features were used as input data. DQDA was found to have the highest accuracy of 86.3% (HC vs chronic migraine) in all the classification schemes.

Li *et al* (2020)[48] used a new method based on neighbourhood rough set and PCA for feature extraction from resting state functional MR scans. KNN model was most accurate (100%) at binary classification (migraine vs HC) (Table III).

Jorge-Hernandez *et al* (2014)[49] and Meng *et al* (2018)[50] performed feature extraction based on graph theory using fMRI (T1, EPIBOLD) and magnetoencephalogram (MEG) as input variables respectively. After feature extraction, the images were classified into migraineurs vs HCs. In the study by Jorge-Hernandez *et al*, multiple ML algorithms were evaluated (Table III) and the highest accuracy was achieved using ANN (92.86%). In the study by Meng *et al*, an accuracy of 81.25% was achieved using CNN.

Two studies (Garcia-Chimeno *et al* and Chong *et al*) (Table III) employed both clinical data and MRI scans as features for classification and diagnosis of migraine. Garcia-Chimeno *et al* (2017)[51] recruited HCs, subjects with sporadic migraine and chronic migraine with medication overuse. They were administered a set of questionnaires assessing the extent of pain, mental health and IQ, and diffusion tensor MRI. They used three classification algorithms (Table I) and then employed four feature selection algorithms to improve classification accuracy, taking it as high as 98% with SVM and NB.

Chong *et al* (2021)[52] also used a combination of clinical questionnaires and imaging data (T1-weighted and diffusion tensor MRI) for classification, achieving an average accuracy of 97.1% for identifying migraineurs using an LR algorithm (Table III).

Risk of Bias and Applicability Assessment

QUADAS-2 has four domains for risk of bias assessment (patient selection, index test, reference standard and flow and timing) and three for applicability concerns (patient selection, index test, reference standard) (Fig. 3).

There were a total of four studies (11.8%) with an overall low risk of bias – three of these however, had a high applicability concern in the patient domain[29,30,32]. Holsteen *et al*[31] was the only study which had an overall low-risk of bias as well as low applicability concerns.

Twenty-three out of the 34 studies had 'high'-risk of bias in the patient selection domain as per QUADAS-2, the most frequent cause being a case-control study design. Not mentioning the sampling method or an objective inclusion/exclusion criteria also increase the risk of bias in this domain, as well as raise applicability concerns. Applicability concerns for the present review was considered 'high' in the patient domain if subjects less than 18 years old were included[29,30,32,33].

The studies that did not mention the validation method used for their models were given 'unclear' risk of bias in the index test domain[19-22,38-40,43,48]. Applicability concerns in the index test domain were low for all 34 studies.

The studies that did not mention a recognised reference criteria were considered having 'unclear' risk of bias and applicability concern in the reference standard domain since subjects may have been misdiagnosed as having migraine patients[22,27,28,33,36,39,48-51].

Risk of bias in the flow and timing domain was considered 'unclear' if all subjects were not administered a reference standard or if it was not the same for all[22,36,39,40,49-51].

Discussion

Headache is the most common presenting neurological symptom in primary care[7]. Migraine is a significant contributor to global disease burden and disability. It has a complex pathophysiology which includes channelopathies as well as various neurovascular phenomena and poses a diagnostic dilemma for physicians owing to its varied and non-specific clinical presentation. Some radiological features like small regions of cerebral infarcts and white matter hyperintensities are also seen in other neurological conditions.

AI can help to identify medical data from multiple sources[15]. In recent times, several new diagnostic questionnaires have been validated, e.g., ID Migraine[53], HUNT-4[54], a web-based questionnaire by Min Kim[55] *et al,* etc. Feature selection algorithms can help select clinical attributes from such questionnaires and modalities most relevant in the diagnosis of migraine, as done in the study by Garcia-Chimeno *et al*[51]. AI can reduce inter-observer and intra-observer variation, and save time and effort.

To our knowledge, this is the first systematic review reporting the use of AI in the diagnosis of migraine in adults. Thirty-four papers were included in this review spanning close to a hundred AI models. A meta-analysis was not possible due to marked heterogeneity in study design, input data and reporting of performance parameters.

Two studies in this review reported a best accuracy of 100%- Khayamnia *et al*[33] using clinical attributes in SVM and Li *et al*[48] using fMRI in kNN. In comparison, the highest accuracy among studies using EEG was 93.3% by Akben *et al* (2012)[19]. The two studies (Chong *et al*[52] and Garcia-Chimeno *et al*[51]) which used both clinical data and MRI scans for classification of migraine got accuracies as high as 97.06% and 98% respectively.

The median accuracy achieved by the studies included in this review was highest for those employing radiological data (92.13%) and lowest for those using clinical attributes (81%) for diagnosing migraine. However, it must be noted that all studies with low-risk of bias used clinical data for diagnosis. This highlights the need for developing and training of more models using clinico-demographic or questionnaire-based data since that is the primary mode of migraine diagnosis currently[8] and also the most viable diagnostic avenue to be pursued; considering patient convenience and expenses incurred, and the lack of availability of other modalities; especially in low-resource settings.

There is increasing interest in the possible applications of AI in the field of medicine. However, its application comes with challenges. Most studies in this review employed relatively small data sets whereas the development of an accurate algorithm relies on larger ones. Thus, we recommend use of bigger, more diverse data sets. Additionally, the AI models developed should be open source to make external validation possible. These measures will boost accuracy and ensure generalisability. Further, systematic and uniform reporting should be ensured to minimise omission of important information. Appropriate study designs should be employed to reduce risk of bias and increase reliability of the conducted studies. The need of the hour is to develop a model for the integration of AI in workflow. Such recommendations were made by only two studies in our review[27,36].

AI models have the potential to minimise inequalities in healthcare. However, developing countries face a unique challenge in terms of the application of this new technology in low-resource settings. Training of clinicians would also be required to be able to use this technology effectively. In order to address these issues and other potential challenges, more studies need to be conducted in such settings, with use of indigenous datasets.

There also exist ethical concerns regarding ownership and use of the data for developing AI models. These concerns should be addressed by developers of the software and all stakeholders.

Strengths of this review

All English-language peer-reviewed articles from across the world were included in this review. Clinical setting for patient selection was not a bar in the inclusion or exclusion of a study. Many types of models (Fig. 1) using various types of input data were assessed. Risk of bias for the included studies was assessed using the standardised QUADAS-2 tool.

Limitations of this review

A quantitative synthesis of results was not possible due to the heterogeneity, high-risk of bias and small sample size of a significant number of studies included in this review. Accuracy was chosen as the primary outcome measure as other metrics were reported infrequently. However, accuracy may be influenced by the quality of the dataset. We excluded studies that were not in the English language and thus may have missed out on some potentially significant findings reported in these articles. Rarer forms of migraine and subjects below the age of 18 years, though a small subset, were not included in our review.

Other uses of AI in Migraine

AI has also been employed in other aspects of migraine like delineation of pathophysiology, prognostication, pharmacotherapy and cost analysis[56–58]; but these studies were beyond the scope of the present systematic review.

Conclusion

This review aims to highlight recent advances in the diagnosis of migraine using machine learning. It is a step towards building comprehensive data driven diagnostic models for migraine. Future studies should use larger, more diverse samples to achieve greater accuracy and generalisability while paying attention to ethical implications. Concerted efforts are necessary to ensure that these models progress from their current experimental status to the point of deployment in actual clinical settings to improve patient care.

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