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A nomogram for the prediction of response to anti-CGRP mAbs: the CGRP score

Marina Romozzi[1,2*], Ammar Lokhandwala[3], Catello Vollono[1,2], David García-Azorín[4], Giulia Vigani[5], Francesco De Cesaris[5], Claudia Altamura[6,7], Fabrizio Vernieri[6,7], Paolo Calabresi[1,2], Sonia Di Tella[8†] and Luigi Francesco Iannone[9,10†]

Abstract

Introduction Real-world studies have explored potential predictors of response to anti-calcitonin gene related peptide (CGRP) monoclonal antibodies (mAbs), though results have remained inconsistent. Machine learning (ML) algorithms are becoming increasingly relevant in migraine research, offering a data-driven approach to identifying predictors of response to preventive treatments. To maximize their potential, a clinically applicable and user-oriented framework is needed to promote the use of these algorithms in research and, eventually, as supportive tools in clinical practice.

Methods This prospective cohort study included adults with migraine treated with anti-CGRP mAbs (anti-ligand and receptor) at two headache centers. Responders were defined as patients achieving ≥ 50% reduction in monthly headache days (MHDs) at 12 months. A logistic regression model was trained (80%) and tested (20%) using 11 baseline variables, including age, sex, migraine subtype, medication overuse, MHDs, and disability scores. Model performance was evaluated using accuracy, precision, recall, and F1-score. A nomogram was created for future research and clinical application. The model was then validated against an external test cohort treated with anti-CGRP mAbs.

Results Among 429 patients, 310 completed twelve months of treatment, with 236 (55.0%) classified as responders. The external test set included 109 patients. The ML model achieved an overall average weighted F1-score of 70.5% between the two test sets, with good performance in identifying "responders" (precision: 0.75, recall: 0.84, F1-score: 0.79). The model yielded predictions with an overall accuracy of 74% when tested against an external test cohort. Chronic migraine status, older age, and lower baseline MHDs were associated with higher response likelihood. Medication overuse and frequent analgesic use were negatively associated with response. The nomogram provided a clinically interpretable tool to estimate response probability, providing a total score named "CGRP Score" (**C**GRP mAbs **G**lobal **R**esponse **P**rediction).

[†]Sonia Di Tella and Luigi Francesco Iannone share senior co-authorship.

*Correspondence:
Marina Romozzi
marinaromozzi@gmail.com

Full list of author information is available at the end of the article

Conclusion This ML-based predictive score achieved a good performance in identifying responders to anti-CGRP mAbs. The nomogram has the potential to be a practical, user-friendly tool for supporting clinical decision-making after validation.

Keywords Migraine, Response, Predictors, Monoclonal antibodies, Calcitonin gene-related peptide, Machine-learning

Introduction

The monoclonal antibodies (mAbs) against the calcitonin gene-related peptide (CGRP) pathway are specific drugs approved for the prophylactic treatment of migraine (anti-CGRP mAbs) that have demonstrated consistent effectiveness and safety in randomized clinical trials (RCTs) and real-world studies [1]. Due to the expected increasing use of anti-CGRP mAbs, their cost, the reimbursement criteria imposed by national health services in several countries, and the potential long treatment cycles needed, there is a growing interest in identifying response predictors in order to personalize treatment approaches.

Real-world studies have attempted to identify response predictors to anti-CGRP mAbs with inconsistent results [2]. Machine learning (ML) algorithms are also increasingly used in migraine medicine to identify predictors of response to preventive treatments, including anti-CGRP mAbs, from a high amount of data through data-driven learning, slightly improving the prediction performances [3–6]. A clinically applicable and user-oriented framework should be adopted to encourage the use of these algorithms in research to explore factors associated with drug response and, in the future, as supportive tools in clinical practice. Two recent ML algorithms in migraine were coupled with an online software platform featuring a user-friendly interface to facilitate their use and improve familiarization with these novel tools [4, 5]. However, a straightforward and practical ML-based scoring system, comparable to a paper-and-pencil tool, for predicting clinical response to anti-CGRP mAbs has yet to be developed.

Herein, we aimed to create, using an ML-based model, a score to predict 12-month response to anti-CGRP mAbs in patients with migraine using demographic and clinical baseline variables as predictors and to create a nomogram applicable in clinical settings.

Methods

In this observational analytic study with prospective cohort design, all consecutive patients treated with anti-CGRP mAbs (anti-ligand or receptor) over a period of 12 months at two tertiary outpatient headache centers (Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome and Careggi University Hospital in Florence) were evaluated. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and is part of the *Registro Italiano Cefalee* (RICe) study, which was approved by the local Ethics committee (CEAVC *Studio RICe*, *14591_oss* and subsequent amendments *2022–609*).

Study participants, patients selection, and study variables

The study population included patients with migraine treated with anti-CGRP mAbs (erenumab 70–140 mg monthly; galcanezumab 240 mg first dose and 120 mg monthly; or fremanezumab 225 mg monthly) from 1 December 2019 to 1 February 2023. Participants were included if they were older than 18 years, signed the informed consent, had a diagnosis of migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria [7], and started a preventive therapy with an anti-CGRP mAb according to the Italian prescription and reimbursement policies. Patients were excluded if they did not show compliance in completing the paper headache diary (patients with more than one missing key baseline variable were excluded from the analysis) or to the treatment. We also recruited an external test cohort, including patients treated with anti-CGRP mAbs prospectively recruited from a third tertiary headache center (Fondazione Policlinico Campus Bio-Medico in Rome) at different times, specifically from 1 February 2023 to 1 March 2025.

Patients completed a paper headache diary three months before the anti-CGRP mAb prescription and throughout the treatment period at months 3, 6, 9, and 12. This diary recorded the number of monthly headache days (MHDs) and the use of acute medication, including the total number of analgesics per month (AMNs) and number of days per month when at least one analgesic was used (AMDs). Additionally, Headache Impact Test (HIT-6) questionnaire (monthly) and the Migraine Disability Assessment (MIDAS) questionnaire (quarterly). Because the study aimed to predict the response to anti-CGRP mAbs, only baseline demographic and clinical variables were considered. Dropouts from the treatment and reasons for discontinuation throughout the treatment period (months 3, 6, 9, and 12) were recorded.

Response rates were assessed based on reductions in MHDs at month 12; patients with ≥ 50% reduction of MHDs were classified as responders. Reduction in MHDs at month 12 of > 30%, > 50%, > 75% and 100% was also calculated [8].

Statistical analysis

Considering the study's exploratory nature, no sample size was calculated a priori. A sample size > 400 was considered adequate based on prior studies [5]. Demographic and baseline characteristics were summarized descriptively, namely mean ± standard deviation [SD] for continuous variables and number (percentage) for categorical data. The normality assumption was assessed using the Shapiro–Wilk test. A two-tailed p value < 0.05 was considered significant for all variables. All data were analyzed using SPSS software version 26.0 (IBM Corp. SPSS Statistics, Armonk, NY, USA).

Machine learning model and nomogram generation

To select the model to work with, logistic regression model, support vector machine, linear support vector machine, gradient boosting, and random forest model were trained and tested against each other. Each model was put through a model pipeline as described in the next paragraph. To ensure the best model was selected, the hyperparameters of the models were tuned at the time of training. The models were then tested against a held-out validation set. This validation set was generated by a 20% split of the entire training dataset and was held out prior to training and was not exposed to the model at any point. The best model was selected based on the weighted F1-score obtained by running the models against this validation set. Out of the models tested, the logistic regression model and the random forest model were found to be the most performant, with the random forest model being approximately 2% more accurate than the logistic regression model. However, despite the slightly better performance, we decided to select the logistic regression model as we prioritized its ease of interpretability and clear relationship between predictors and outcome of the model for our goal to develop a useful tool to use in a clinical setting, such as a nomogram.

The model was created as a model pipeline where numeric missing data were imputed using the k-nearest-neighbors algorithm to get the mean value of the five nearest neighbors. Then, the data was standardized by removing the mean and scaling to unit variance using Scikit-learns StandardScalar method. Then, the model was run through a sequential backward feature selector to train the model on the most significant variables associated with anti-CGRP mAbs treatment response. Finally, a logistic regression model was trained using a training set and then tested and evaluated against a test set to evaluate model accuracy. Hyperparameters of the model were tuned using a grid search cross-validation at the time of training and set to optimize for the average weighted F1-score of the model (harmonic mean of the precision and recall that reflects the accuracy of classification models) [6]. The model was trained to classify patients into responders and non-responders based on the reduction in MHDs ≥ 50% at month 12 compared to baseline. For patients who dropped out earlier than the 12-month period for any reason, the last recorded total MHDs were carried forward and used to calculate the patient's response for month 12 (Last Observation Carried Forward).

The model was given 11 baseline demographical and clinical variables chosen according to prior literature [5], clinical relevance and accessibility in all clinical settings: sex, age, years from onset of migraine, migraine diagnosis (episodic migraine (EM) or chronic migraine (CM)), medication overuse status at baseline, migraine with aura, baseline MHDs, AMDs, AMNs, MIDAS, and HIT-6 score. The variables age and years from onset were recoded and inserted in the model as ordinal variables. For age, the following ranges, based on quartiles, were used: 18–35, > 35–52.5, > 52.5–70, and > 70 years. Similarly, for years from onset, the ranges were as follows: 0–18 years, > 18–35 years, > 35–52.5 years, > 52.5–70 years, and > 70 years. The dataset was split into 80%-20% sets to train and test the models, respectively. The data was split in a stratified fashion to maintain the proportion of responders to non-responders in the training set and the test set. The models were fitted, as described above, using the training data, and accuracy measures were evaluated based on the results obtained by running the model against the test data (internal test set). The model was then further tested against an external cohort (external test set).

Analysis was performed following the recent guidelines for ML in migraine research [6].

Once the model was trained, the coefficients associated with each input feature and the model intercept were noted. The model, with the recorded coefficients and intercept, was recreated in RStudio, and a nomogram was generated using the nomogram *function*, available as part of the RMS library, which mapped the logistic regression coefficients to a graphical representation. The nomogram allows clinicians to estimate the probability of the outcome (treatment response) by aligning predictor values to points on the scale. The *datadist* function from the RMS library was applied to the dataset to define the ranges and distributions of each predictor variable, which controlled the scale and appearance of the nomogram. The probability thresholds used in the nomogram were carefully selected to enhance clinical interpretability and decision-making. The probability distribution of patient response in the nomogram was calculated using the cumulative logistic distribution function. Customized cutoffs at 0.001, 0.01, followed by a sequence from 0.1 to 0.9 in increments of 0.5, and additional high confidence points at 0.95, 0.99, and 0.999, ensure a clear

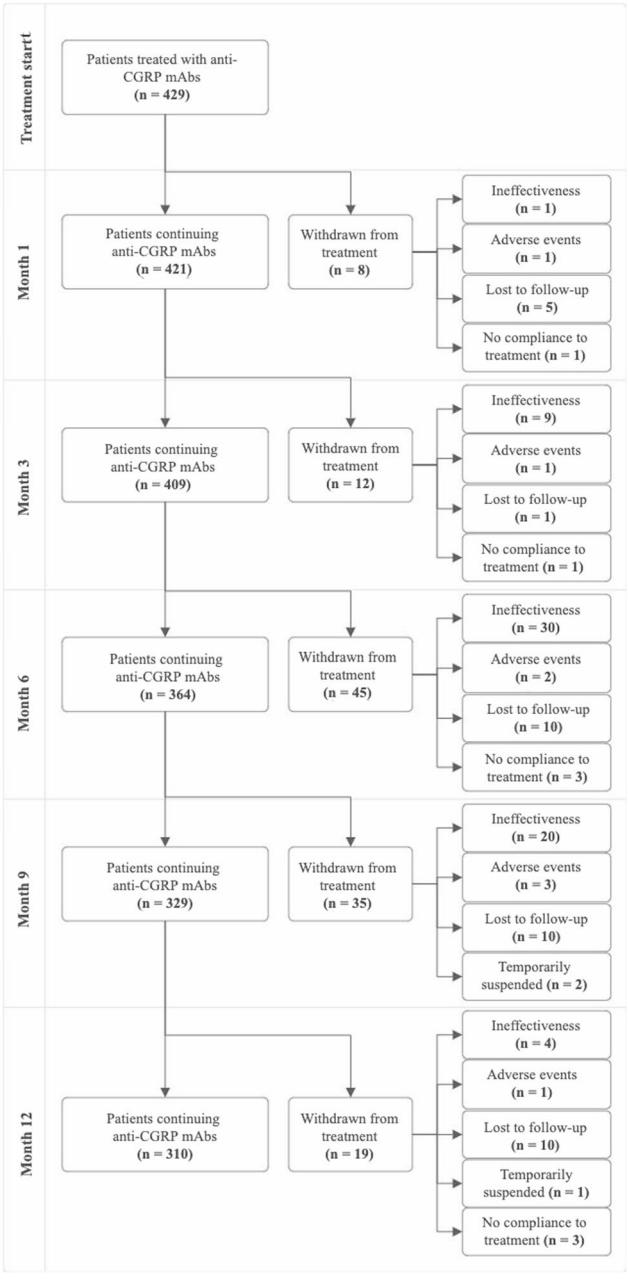

Fig. 1 Flowchart of patients with reasons for withdrawal

representation of risk probabilities across the spectrum, facilitating precise stratification of patient outcomes.

We used the scikit learn library to plot the ROC curves from the estimator and used that to calculate the AUC ROC score.

The data processing, analysis, and machine learning models were developed in Python (v3.6.1) using the Scikit-Learn (v1.2.2) library. Python's pandas and NumPy libraries were also used. The generated model was then exported to RStudio (version 2024.09.0), where the nomogram was created using R's RMS library.

Table 1 Comparison of baseline demographic and clinical characteristics between the study and validation cohorts.

	Study cohort (*n* = 429)	External cohort (*n* = 109)	Group comparison (*p* value)
Age [years]	47.8 ± 13.4	49.8 ± 10.8	0.204#
Sex female, n (%)	346 (81.0)	92 (84.0)	0.369°
Age at onset	31.9 ± 14.5	29.6 ± 12.3	0.272#
Aura, n (%)	40 (9.3)	9 (8.3)	0.730°
Chronic migraine, n (%)	374 (87.0)	65 (59.6)	< 0.001°
Medication overuse, n (%)	331 (77.2)	55 (50.5)	< 0.001°
Monthly headache days	22.5 ± 7.2	17.5 ± 9.9	< 0.001#
Number of analgesics per month	31.2 ± 29.2	17.4.4 ± 9.9	< 0.001#
Days with acute medication use	18.9 ± 8.9	16.6 ± 7.6	0.004#
MIDAS	84.7 ± 59.3	73.5 ± 40.7	0.614#
HIT-6	67.5 ± 6.3	66.7 ± 6.4	0.262#

Values are reported as mean ± SD if not otherwise specified. Percentages are expressed on column total. HIT-6, headache impact test-6; MIDAS, migraine disability assessment; SD, standard deviation; #, Mann-Whitney U test; °, chi-squared, (χ^2) test

Model validation

Once the model was trained and tuned, we prepared an external test dataset to validate it against. The model was never exposed to this dataset during training. The data was encoded similarly to the internal data and then evaluated using the model pipeline, which imputed missing data using the same K nearest neighbor algorithm, scaled the data, and then tested it against the fitted model. The precision, recall, and F1-score were recorded for a comprehensive overview of the model's performance.

Results

Cohort characteristics

Overall, 429 patients were eligible for the study. Figure 1 reports the flowchart of the study and the patients who withdrew treatment with anti-CGRP mAbs throughout the 12-month treatment course; 310 patients completed 12 months of treatment. Table 1 provides an overview of the demographic and clinical features of the entire study sample at baseline. Overall, 236 patients (55.0%) were classified as 50% responders after 12 months of treatment (Supplementary Table 1).

Model development

The classification model achieved an overall average weighted F1-score of 70.5% across the two test sets, with good performance in identifying "responders" (precision: 0.75, recall: 0.84, F1-score: 0.79). The model also attained an area under the receiver operating characteristic curve (AUC-ROC) of 0.72. Table 2 summarizes the efficiency parameters of the model.

The logistic regression model identified predictors of response (≥ 50%) or non-response (< 50%) to anti-CGRP

Table 2 Model performance score for the prediction of response to monoclonal antibodies against calcitonin gene-related peptide (anti-CGRP mAbs) at 12 months.

Class label	Precision		Recall		F1-score		Support	
	Internal Test cohort (*n* = 86)	External cohort (*n* = 109)	Internal Test cohort (*n* = 86)	External cohort (*n* = 109)	Internal Test cohort (*n* = 86)	External cohort (*n* = 109)	Internal Test cohort (*n* = 86)	External cohort (*n* = 109)
Non-responders	0.78	0.30	0.39	0.30	0.52	0.30	27	20
Responders	0.66	0.84	0.84	0.84	0.74	0.84	59	89
Macro avg	0.73	0.57	0.65	0.57	0.65	0.57	86	109
Weighted avg	0.72	0.74	0.7	0.74	0.67	0.74	86	109

Table 3 Coefficients calculated by the model for each feature at baseline.

Variables at baseline	Coefficients
Sex	– 0.175
Age	0.251
Years from onset	– 0.178
Migraine diagnosis (EM or CM)	0.385
Medication overuse	– 0.076
Aura	– 0.118
Monthly headache days	– 0.181
Days with acute medication use	– 0.089
Number of analgesics per month	– 0.408
MIDAS	– 0.020
HIT-6	– 0.017

A higher value coefficient corresponds to a higher correlation between the feature value and a positive outcome. A negative value indicates an inverse correlation to the positive outcome

EM, episodic migraine, CM, chronic migraine; HIT-6, headache impact test-6; MIDAS, migraine disability assessment score

mAb treatment. Age had a positive correlation (0.251), suggesting that patients with older age may have a higher probability of benefiting from treatment in this model, while sex had a negative correlation (– 0.175), suggesting that females are more likely to have a positive outcome. The feature migraine with aura demonstrated a negative effect (– 0.118), suggesting that patients with migraine aura tend to be slightly less likely to respond. Among the features, chronic migraine showed the strongest positive associations (coefficient of 0.385), suggesting that patients with CM are more likely to respond to treatment.

Baseline MHDs (– 0.181), medication overuse status at baseline (– 0.076), and AMNs (– 0.408) and AMDs (– 0.089) had a negative correlation and were negatively associated with treatment response. Table 3 reports all the model coefficients.

Nomogram development

As illustrated in Fig. 2, the nomogram features scales corresponding to the minimum and maximum values for each input feature and the reading instructions. The patient's specific value for each feature is identified on the corresponding scale, and the points associated with that value are recorded using a ruler. This process is repeated for all relevant features. After calculating the points for each feature, they are summed and marked on the "total points" scale with a maximum corresponding to 480 points. After obtaining the total score, a straight line is then drawn from the "total points" scale to the "responder" scale to estimate the likelihood of being a responder to treatment.

If the total points fall between the 0.5 and 0.9 range (or above), the patient is predicted to be a responder to anti-CGRP mAbs, with the probability corresponding to the value on the "responder" scale. For example, a total of 0.5 indicates a 50% chance of a response, while 0.9 corresponds to a 90% chance of response.

We named the score the "CGRP Score," derived from the acronym **C**GRP mAbs, **G**lobal **R**esponse **P**rediction. Figure 3 illustrates an exemplary patient and the corresponding scores and interpretation, showing how the nomogram can be used to predict treatment response. Supplementary Table 2 provides the corresponding values for each variable, along with the sum of these values, which is then converted into a probability of response to treatment.

External test set

The model was then validated against an external validation dataset (external test set) of 109 patients undergoing treatment with anti-CGRP mAbs. Accounting for patient drop-off, 99 patients completed 12 months of treatment.

The demographic and clinical characteristics of the external test cohort are reported in Table 1. Performance scores across all models for the external test cohort are detailed in Table 2. The weighted F1-score was found to be 0.74.

Discussion

The present study applied ML algorithms using baseline demographic and clinical variables to evaluate treatment response to anti-CGRP mAbs at 12 months, which yielded high accuracy. Furthermore, we developed a nomogram that represents a "pen and pencil tool" that can be used to rapidly obtain a predictive response score (namely, the "CGRP" score). We also validated the model on an external cohort, achieving good performances.

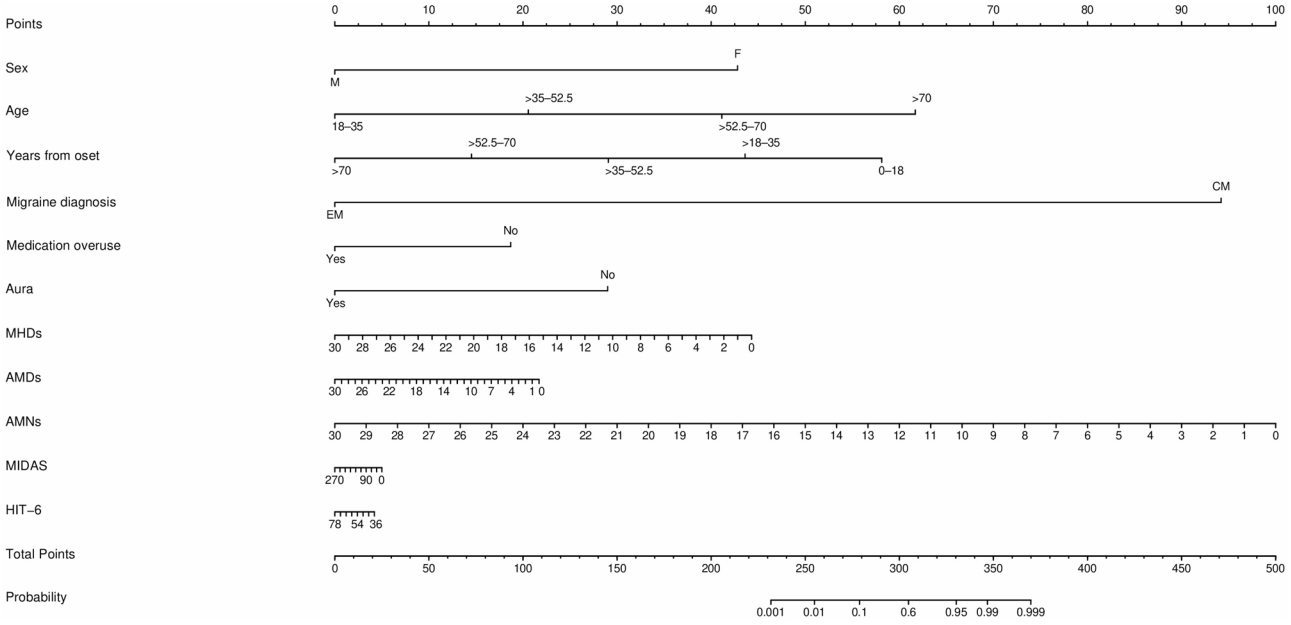

Fig. 2 Nomogram. The nomogram is used to manually obtain a prediction of response to anti-CGRP monoclonal antibodies (mAbs). To use the nomogram, each predictor variable is aligned with its respective point scale at the top of the figure. For each variable, locate the patient's value on its axis and draw a straight vertical line upward until it intersects the "Points" scale. The number of points where the line meets the scale represents the contribution of that variable to the overall score. Repeat this process for all variables in the model, then sum the points to obtain the Total Points. Finally, locate the Total Points value on the "Total Points" axis at the bottom of the nomogram, draw a vertical line downward to the "Probability" scale, and read the predicted probability of the outcome (predicted response probability to anti-CGRP mAbs at 12 months)

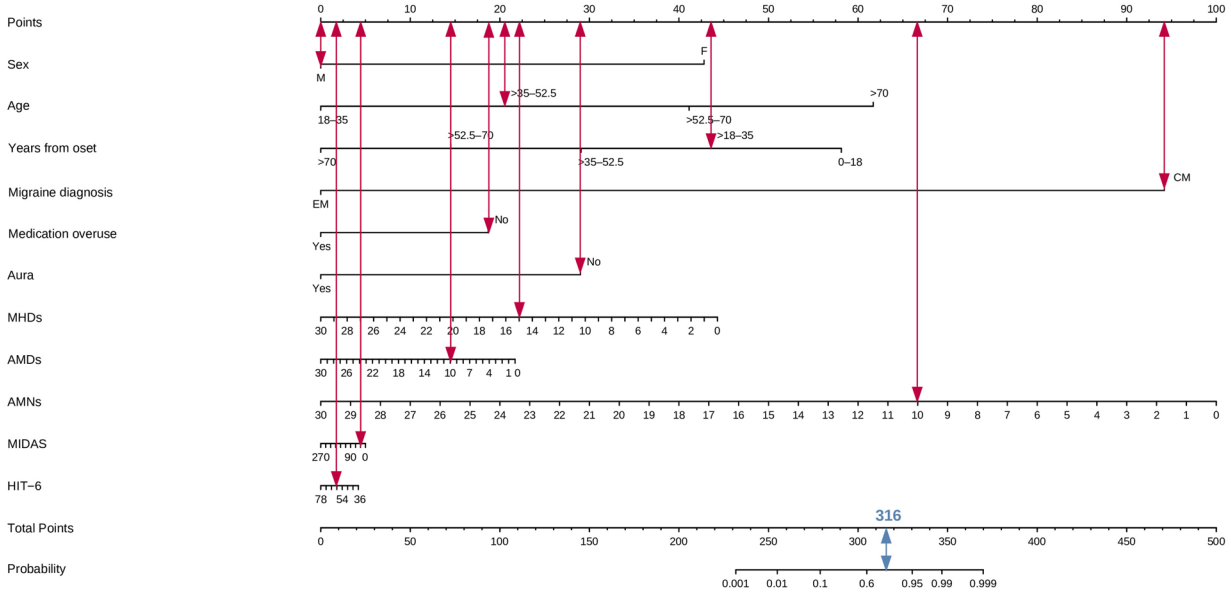

Fig. 3 Nomogram reporting an exemplary patient and the corresponding scores and interpretation. Consider a male patient with the following characteristics: the patient is a 36-year-old man, which places him within the age range of 35–52 years, corresponding to 21 points on the nomogram. His years from onset are 20, which falls within the 18–35 years range, adding another 44 points. The patient has a diagnosis of chronic migraine (CM), which gives him 94 points. He does not have medication-overuse headache, so he earns 19 points, and he also does not have a diagnosis of migraine with aura, corresponding to 29 points. The patient reports 15 monthly headache days, which results in 22 points, and he has 10 days with acute medication use, adding 14 points. He uses 10 analgesics per month (total number of analgesics), contributing a significant 67 points. With a MIDAS score of 30, he receives 4 points, and finally, his HIT-6 score of 60 corresponds to 2 points. After summing the points for each variable, his total score reaches 316, corresponding to a probability of 0.821, or an 82% chance of being a responder to treatment with anti-CGRP monoclonal antibodies.

ML algorithms are increasingly used to support migraine diagnosis, treatment prognosis, and treatment response [3, 9–11]. A limited number of studies employed ML approaches to predict treatment response to anti-CGRP mAbs. Gonzalez-Martinez et al. developed the first ML model for predicting response to anti-CGRP mAbs and proposed a predictive tool including five variables [4]. The model yielded an accuracy of over 70% in each model developed [4]. However, demographic variables, data on migraine characteristics, history and diagnosis, and information on acute medication were not included, and response at three months was used to predict response, which may limit the model's applicability.

A second online tool was recently developed to incorporate a broader range of variables and stratify responses to anti-CGRP mAbs at multiple time points (3, 6, and 12 months), utilizing predictors as early as the first month [5].

Including all preventive treatments for migraine, Chiang et al. conducted an ML analysis involving 145 variables to predict treatment responses to various migraine preventive therapies, including anti-CGRP mAbs. The model showed superior predictive performance for anti-CGRP mAbs compared to other non-specific preventive treatments. According to the Authors, this is likely due to the migraine-specific nature of CGRP mAbs and the models being developed using detailed migraine characteristics. The analysis incorporated a wide range of variables such as migraine characteristics, triggers, and family history [12]. However, the study does not clearly specify the follow-up duration at which the treatment response was evaluated [12].

In principle, every clinical tool or algorithm should be designed and developed to be easily reproducible and straightforward to interpret, enabling its use in time-constrained clinical settings and by individuals without specialized training. Predictive scores are valuable tools in this context, as they synthesize complex information into ready-to-use formats. Health authorities endorse some of these scores for use in primary care settings [13].

To date, no predictive score has been developed specifically to assess treatment responses to anti-CGRP mAbs. In migraine management, standardized severity and disability scores are widely used, serving not only as measures of disease burden but also, in some cases, as guides for clinical and treatment decisions. For instance, in Italy, the MIDAS score is employed as a criterion for prescribing anti-CGRP mAbs and for evaluating the continuation of treatment [14, 15].

Given the high cost of anti-CGRP mAbs, it is essential to optimize their use by identifying patients most likely to benefit from treatment and those who may require a more intensive therapeutic approach. In this context, combination strategies, such as the concurrent use of agents with different mechanisms of action (e.g., onabotulinumtoxinA and anti-CGRP mAbs), integration with traditional oral preventives, or extended treatment durations, should be considered to support both personalized care and efficient allocation of healthcare resources [16].

The model developed in this study utilizes a streamlined set of variables that are routinely assessed in clinical practice, enhancing its practicality. Additionally, the nomogram potentially offers a straightforward visual tool that may support clinical decision-making, allowing a realistic integration into clinical practice without the need for computational resources.

This study has some strengths and limitations. It is a multicenter study with a substantial sample size and prospectively collected data, with careful collection of migraine-related variables and disability and severity questionnaires validated on an external cohort. One limitation of our approach is that the nomogram-based score relies only on baseline data to predict the 12-month treatment response. However, this was an intentional design choice aimed at simplifying the tool and enabling an early estimation of a patient's likelihood of response. Furthermore, the use of the Last Observation Carried Forward method may introduce bias, although it ensures that early discontinuations due to lack of efficacy are incorporated into the model. Additionally, the model was built using a dichotomous outcome (≥50% reduction in MHDs), which, while commonly used and standardized in both clinical trials and real-world studies, may not fully capture the complexity of migraine treatment and response. We highlight the need for future models to incorporate multiparametric and individualized definitions of response, including multi-tiered response definitions (e.g., ≥30%, ≥50%, ≥75% reduction of MHDs) and the incorporation of patient-reported outcomes [17]. Lastly, relevant baseline characteristics, such as comorbidities—particularly psychiatric ones—that may influence the response to anti-CGRP mAbs were not considered.

Conclusion

We developed the first ML-based score using a nomogram to predict the response to anti-CGRP mAbs with good prediction performances. The ML model provides a foundation for iterative refinement in identifying variables associated with treatment response to anti-CGRP mAbs. The derived nomogram offers a reproducible scoring system with the potential for manual application in clinical practice. However, prospective validation of the nomogram as a clinical decision-support tool remains necessary.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-02138-5.

Supplementary Material 1

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Author contributions
M.R., A.L. and L.F.I had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. M.R., A.L., S.D.T, and L.F.I. wrote the main manuscript text, and M.R., A.L., S.D.T prepared the figures. All Authors critically reviewed the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Data availability
Data supporting the findings in the present study are reported in the article and in the supplementary materials. The data collected and analyzed for the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
LFI received fees and Honoraria for advisory boards and speaker panels from Teva, Eli Lilly, Lundbeck, Pfizer, Organon and AbbVie. CV received fees, Honoraria for advisory boards, support for attending meetings and/or travel and speaker panels from Teva, Eli Lilly, Lundbeck, Pfizer, and AbbVie. MR received support for attending meetings and/or travel from AbbVie and Lundbeck. PC received fees, Honoraria for advisory boards, support for attending meetings and/or travel and speaker panels from AbbVie, Bayer Schering, Bial, Biogen-Dompè, Biogen-Idec, Eisai, Genzyme, Lundbeck, Lusofarmaco, Merck-Serono, Novartis, Prexton, Teva, UCB Pharma, and Zambon. Other authors have no conflicting interests relevant to the manuscript.

Author details
[1]Dipartimento Universitario di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Neurologia, Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[3]Drexel University, Philadelphia, USA
[4]Headache Unit, Department of Neurology, Hospital Universitario del Río Hortega, Valladolid, Valladolid, Spain
[5]Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Florence, Italy
[6]Unità Cefalee e Neurosonologia, Fondazione Policlinico Campus Bio-Medico, Via Alvaro del Portillo, 200, Rome, Italy
[7]Neurologia, Dipartimento di Medicina e Chirurgia, Università Campus Bio-Medico di Roma, Rome, Italy
[8]Dipartimento di Psicologia, Università Cattolica del Sacro Cuore, Milan, Italy
[9]Digital and Predictive Medicine, Pharmacology, Clinical Metabolic Toxicology-Headache Center and Drug Abuse, AOU Policlinico di Modena, Modena, Italy
[10]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

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