Potential Characteristics for Prediction of the Efficacy of Non-Steroid Anti-Inflammatory Drugs for Migraine Treatment: A Retrospective Cohort Study

Heng-Le Wei
Nanjing Jiangning Hospital: The Affiliated Jiangning Hospital of Nanjing Medical University
Jin-Jin Wang
Nanjing Jiangning Hospital: The Affiliated Jiangning Hospital of Nanjing Medical University
Gang-Ping Zhou
Nanjing Jiangning Hospital: The Affiliated Jiangning Hospital of Nanjing Medical University
Yu-Sheng Yu
Nanjing Jiangning Hospital: The Affiliated Jiangning Hospital of Nanjing Medical University
Hong Zhang (jnyyfsk@126.com)
Jiangning Hospital

Research article

Keywords: Migraine, Non-steroid anti-inflammatory drugs, Logistic regression, Efficacy

Posted Date: June 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-618382/v1

Abstract

Background: Although several special medications for migraine are currently available, non-steroid anti-inflammatory drugs (NSAIDs) are still the first-line pharmacological option. A considerable proportion of migraineurs still be unresponsive to NSAIDs for reasons that remain unknown. The study aimed to develop significant characteristics to predict the efficacy of NSAIDs for patients with migraine.

Methods: In this retrospective study, 567 patients suffering migraine were included and divided into an effective NSAIDs (M-eNSAIDs) group and a noneffective NSAIDs (M-neNSAIDs) group according to the analgesic efficacy at 2 hours after taking NSAIDs. Clinical and neuropsychiatric characteristics were collected and used to build a logistic regression model. And a receiver operating characteristic (ROC) curve was drawn to represent the prediction capability.

Results: Five predictors including education, attack duration, headache impact intensity, anxiety and depression scores were identified to build the logistic regression modal. The area under the curve (AUC) values of each predictor were 0.706, 0.639, 0.560, 0.683 and 0.632, respectively, failing to predict the efficacy of NSAIDs. All five predictors-combined method achieved an acceptable AUC value of 0.834 and a sensitivity of 90.9%.

Conclusions: Despite the insufficient predictive capability of these predictors when analyzed individually, this study developed an effective and convenient method to accurately predict the efficacy of NSAIDs, which would be helpful for developing individualized therapeutic strategies for treatment of migraine.

Introduction

Migraine is a debilitating neural disease that affects patients both mentally and physically. The global prevalence is approximately 15% of the population [1]. In clinical practice, there are scarce evidence-based standard to guide the selection of pharmacological therapies from a variety of choices for migraine. Inappropriate treatment with ineffective drugs could enhance personal trial-and-error risk, economic costs and social burdens. Despite the development of special therapeutic agents for migraine, nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs of the first-line choice for the treatment [2]. NSAIDs are generally used to alleviate the intensity of pain, but may also be ineffective, or associated with a significant risk of unpleasant/intolerable side-effects (such as medication overuse, gastrointestinal disorders) [3, 4]. Inadequate response to NSAIDs treatment in a notable proportion of migraine patients contributes to the large burden of medication-associated disability. For example, migraineurs suffering from ineffective drug therapy tend to excessively use analgesics, which may provoke medication-overuse headache and more frequent headache attacks [5]. Indeed, migraine has high comorbidity with anxiety and depression disorders. A considerable proportion of migraine patients experiencing depression and anxiety comorbidities may develop drug addictions, and even contemplate or attempt suicide [6, 7]. Moreover, a cross-sectional study has also demonstrated that migraine patients with medication overuse headache got higher scores representing anxiety and depression than migraine suffers without drug

overdose [8]. On the other hand, considerable evidence suggests that clinical factors (such as headache frequency and intensity) are involved in the pathogenesis of migraine of the analgesic response [9, 10].

Up to the present, few available studies have attempted to identify how migraine-relative clinical and neuropsychiatric characteristics relate to the efficacy of NSAIDs and few relevant studies with robust evidence have focused on the individual characteristics as predictors to guide the first-line treatment options for migraine [11]. Although some replicable predictors of unsatisfactory clinical outcomes have already been partially identified, clinically meaningful factors for predicting treatment outcomes are absent. Based on the arguments above, the following hypothesis has been proposed that the migraine-related clinical characteristics and psychiatric disorders could affect the efficacy of NSAIDs in migraine. In addition, as a result of similar efficacies with the analgesic agents, the selection of a first-line agent is based on the physician preference. Thus, it is crucial to develop an effective treatment strategy to individualized medication options and enable the choice of optimal first-line therapy for migraine.

To the best of our knowledge, this is the first report that explores the relationship between migraine-related clinical and neuropsychiatric characteristics and the analgesic efficacy of NSAIDs. A logistic regression model and receiver operating characteristic (ROC) curves were established to evaluate their potential roles to predict the efficacy of NSAIDs treatment, and to provide clinical evidence to optimize treatment selection from a series of therapeutic schemes.

Methods

Participants

A retrospective study was carried out of medical records relative to headache patients who came for a visit at the Jiangning Hospital in the period January 2014 to February 2021. Inclusion criteria for patients in the study were: (1) age > 18 years; (2) a diagnosis of episodic migraine according to the clinical criteria provided by the Headache Classification Subcommittee of the International Headache Society [12, 13]; and (3) a history of migraine treatment with NSAIDs. Exclusion criteria consisted of the following: (1) chronic migraine, medication-overuse headaches, and other types of daily persistent headaches; (2) individuals with cardiomyopathy, congenital heart disease, liver failure, renal failure, hepatitis, hemorrhagic diseases and tumors; (3) other malignant diseases. The Affiliated Jiangning Hospital of Nanjing Medical University Ethics Committee approved this study.

Clinical and neuropsychiatric characteristics

Clinical and neuropsychiatric characteristics were assessed by questionnaires. The clinical data includes general demographic features (such as age, sex, education) and migraine-related parameters (such as headache duration, location, intensity, frequency, impact intensity and disabling ability). In detail, the headache intensity was assessed by the visual analog scale (VAS, 0 to 10) [14]. And the Migraine Disability Assessment Scale (MIDAS) [15]and the Headache Impact Test (HIT-6) [16]were used to assess the disability and impact on daily life, respectively. Moreover, the Patient Health Questionnaire (PHQ-9)

[17]and Generalized Anxiety Disorder (GAD-7) [18]were also collected to assess affective symptoms. In general, the complete pain response is rarely achieved and any pain relief is defined as the lesser intensity of pain compared to the pretreatment level. Participants were questioned about headache intensity at 2 hours after NSAIDs treatment and at least 50% pain relief was regarded as a significant outcome.

Statistical analysis

All statistical analyses were performed using SPSS (Version 240.0). The mean ± standard deviation described the continuous variables. The differences in the continuous variables were evaluated using the independent sample *t*-test or the *Mann-Whitney U* test according to the homogeneity of the variance test. The difference in the discrete variables among the sex, location, family history was evaluated using the chi-squared test. Clinical and psychiatric characteristics were assessed for their ability to predict the efficacy of NSAIDs for migraine using the binary logistics regression model. A p value <0.05 was considered statistically significant.

Results

Results of the demographic data

As is shown in **Table 1**, a total of 567 subjects were included in the final analysis. There were no significant differences in age, sex, headache location, family history, headache frequency, headache severity scores and disability scores between the M-eNSAIDs and M-neNSAIDs groups ($p > 0.05$). Results of the univariate analysis showed that patients with M-eNSAIDs had lower disease duration, attack duration, HIT-6 scores, anxiety and depression scores, whereas higher education level, compared with the patients with M-neNSAIDs ($p < 0.05$).

Logistic regression analysis of the efficacy of NSAIDs

Having identified the significant parameters in the education, disease duration, attack duration, HIT-6 scores, GAD-7 scores and PHQ-9 scores, the next process was to adjust for potential confounding variables. The multivariate logical regression model was conducted to identify independent risk factors for evaluating the predictive ability for the efficacy of NSAIDs. If variables were collinear, the variable with the strongest correlation with the outcome was included in the multivariable analysis. In the logistic regression model, the test of parallel lines was not significant. In multivariate analysis, five variables entered into the logistic regression equation (**Table 2**). Such as education, headache attack duration, impact intensity, anxiety and depression scores act as independent risk factors for the efficacy of NSAIDs. The partial regression coefficients were 0.309, -0.042, −0.034, -0.291 and -0.117, respectively. Improving the efficacy of NSAIDs with a decrease in clinical and psychiatric factors indicated that these factors could act as markers to identify patients with M-eNSAIDs from migraineurs with ineffective efficacy. On the other hand, increased education is a beneficial factor to predict the positive efficacy of NSAIDs. Additionally, the present study investigated the combined effects of clinical and neuropsychiatric

characteristics, respectively, on predictive value for the efficacy of NSAIDs in migraine treatment. All area under the curve (AUC), specificity and sensitivity values were displayed in **Table 3.**

ROC curve analysis on the risk factors

The ROC curves detected from each of those variables and combinations of different significant characteristics were drawn **(Fig. 1)**. In detail, the AUC values of the education, attack duration, HIT-6 scores, GAD-7 scores and PHQ-9 scores were 0.706, 0.639, 0.560, 0.683 and 0.632, respectively. Moreover, the AUC value of a combination of the two clinical characteristics (attack duration and HIT scores) was 0.643. Similarly, the AUC value of a combination of the two psychiatric conditions (GAD-7 and PHQ-9 scores) was 0.722. Additionally, the AUC value for detection using a combination of clinical and psychiatric parameters was 0.744, with a diagnostic sensitivity and specificity of 70.5% and 78.4%, respectively. Furthermore, the AUC value of a combination of all significant predictors was 0.834, with a diagnostic sensitivity and specificity of 90.9% and 67.6%, respectively. According to the general standard that AUC values between 0.7 and 0.9 mean a medium level of diagnostic value and these over 0.9 mean a high level of diagnostic value. The study showed all predictors (AUC <0.9) failed to provide a convinced, but moderate diagnostic value.

Discussion

To data, optimal medication selection for migraine remains imprecise. The most common treatment modality is trial-and-error to seek the most effective strategy of migraine treatment. Although several special pharmacological options to treat migraine are currently available, NSAIDs were recommended as the first-line medication treatments. Many migraineurs taking NSAIDs do not achieve complete relief and respond adequately to therapy. Moreover, taking more frequently NSAIDs could develop the risks of medication overuse headache and occurrence of cardiovascular and cerebrovascular events. This traditional trial-and-error approach for drug selection may contribute to treatment failure and unnecessary exposure on patients to insufficient treatment trials, deteriorating patient symptoms and increasing comorbidities. Thus, novel strategies are required to improve treatment selection and success rate from the initiation of treatment. The present study innovatively combined multiple clinical (attack duration and HIT-6 scores) and neuropsychiatric (GAD-7 and PHQ-9 scores) characteristics, based on a logistic regression modal, for the first time to predict the efficacy of NSAIDs treatment for migraine.

As is well-known, migraine is a complex neural disorder with an excited trigeminovascular system due to changes in the central modulating nociceptive inputs [19]. Migraineurs have structural and functional brain alterations between and during migraine attacks that are correlated with clinical characteristics such as duration, severity, disability, frequency of migraine [20-22]. The present study observed that some migraine-related clinical characteristics are risk factors for predicting the analgesic efficacy of NSAIDs. Moreover, some seed-based functional magnetic resonance imaging (fMRI) studies have induced that disrupted functional connectivity patterns in migraine without aura were remarkably correlated with the migraine duration and impact intensity through the functional connectivity analysis and Granger

causality analysis [20, 22]. However, no clear predictive valuation in disease duration was detected in the multivariate logistic regression model, although a significant statistical difference was detected between the two migraine groups in this study. The study presented higher disease duration in patients with M-neNSAIDs than patients with M-eNSAIDs, suggesting that analgesic efficacy of NSAIDs may decline with the progression of migraine. Another possible explanation for the results may be due to the heterogeneity of patient populations, more comprehensive features and advanced algorithms should be further conducted to detect the association between the disease duration and efficacy of NSAIDs for migraine treatment. Moreover, NSAIDs have been proved to be an effective treatment of antinociceptive efficacy to reduce the frequency of attacks and headache severity levels [10]. Besides the well-established role of the trigeminovascular system in migraine pathogenesis, the involvement of other brain phenomena such as cortical spreading depression (CSD) or neurogenic inflammation has become more and more established [23]. It has been hypothesized that the trigeminal sensory afferents were activated by the CSD mechanism, causing migraine attacks [24]. Moskowitz et al [25]demonstrated that inhibiting CSD could benefit migraine prevention in a rat model. The rats with many kinds of analgesic drugs represented less frequent CSD and higher electrical stimulation thresholds, which may result in lower attacks frequency and duration. Then, taking into account the efficacy of NSAIDs modulated by the relevant neural patterns, the attack duration may be indirectly associated with the analgesic efficacy of the selected drug. Thus, the current findings highlighted the role of the clinical characteristics such as attack duration and impact intensity in predicting the analgesic efficacy of NSAIDs and revealing indirectly underlying NSAIDs-related neuromechanism for treating migraine.

Besides the above mentioned, substantial neuroimaging studies have reported that functional impairments with multiple brain networks including the limbic system, are related to the neuropsychological mechanism underlying the chronic pain [26]. Further, some fMRI studies have demonstrated that neural mechanisms of NSAIDs may be involved in the pathophysiological and therapeutic response [27, 28]. On the other hand, anxiety and depression are the common comorbidities associated with chronic pain, which result in aggravation of pain and difficulty of treatment [29]. It has been reported that several neural pathways formed by different brain regions including the limbic system are required for the modulation of psychiatric disorders [30, 31]. Moreover, these relevant regions underlying anxiety and depression disorders are also involved in the trigeminovascular pathway. Additionally, the appearance of detrimental effects in multiple brain networks after NSAIDs applications has been confirmed in many studies [28, 32]. An animal model study [33]demonstrated that NSAIDs interacted with the limbic system exerted analgesic/antinociceptive function on the central neural circuits to achieve the goal of nociceptive relief. Furthermore, it has been generally recognized that changes of limbic-relevant central neural pathways induced by NSAIDs impaired the top-down analgesic modulatory circuits through a quantitative arterial spin labeling (ASL) study [28]. According to the above points, the findings suggested that the activity of the limbic system in migraine can affect analgesic neurophysiological mechanisms of NSAIDs to take effect in the migraine treatment, and that the negative emotions (anxiety and depression) may likely play a key role in the development of tolerance to the antinociceptive effects of NSAIDs.

While self-report and perceptual measures such as questionnaires are convenient and efficient methods to obtain general information [34], few studies have investigated such a relationship between the questionnaire results and efficacy of treatment. The current results demonstrated that many individual clinical and psychiatric characteristics can predict the efficacy of the migraine treatment, but no single feature can support sufficient evidence to predict the therapeutic efficacy of NSAIDs. Thus, observing combinations of multiple potential predictors is necessary. This model based on the combinations with clinical and psychiatric predictors achieved a practical predictive value. In addition, patients with appropriate education levels perform better adherence to self-management strategies and improve the quality of life [35]. The study also considered the education factor, and analyzed different combinations of all predictors for a more effective solution. The combination of clinical, neuropsychiatric and educational factors had the highest predictive effectiveness, which is reliable value for clinical application. Moreover, the accuracy of the combination of anxiety and depression was higher than the accuracy of the clinical characteristics, suggesting that negative emotions could make the design of targeted therapeutic strategies for migraine treatment more extremely difficult and complicated. In general, the current study provided an alternative method to predict the therapeutic efficacy of NSAIDs on migraineurs at an early stage, which may be beneficial for the decision in the therapeutic strategies for migraine.

This study is a preliminary retrospective analysis, and a number of issues influencing the interpretation of our results should be considered. First, as part of the difference between the migraine subgroups lies in the clinical characteristics and neurophysiological mechanisms, additional research is needed to identify subgroups of migraine patients based on unique clinical and neurocognitive profiles and to link these subgroups to effective medication intervention. Second, due to the complexity of the therapeutic mechanism of NSAIDs for migraine, the included characteristics may not be sufficient for all patients, and a more advanced prediction model should be developed. Third, different doses and types of the drugs will likely translate to a different response to the efficacy of medication treatment. A prospective study with a more comprehensive characterization of drugs would be required to further validate these concerns.

Conclusions

In conclusion, this study has examined the relationship between migraine-related characteristics and the efficacy of NSAIDs. Despite some limitations, this study provides a more reliable and practical method based on combinations of clinical predictors and neuropsychiatric assessments to predict the therapeutic effect of NSAIDs in migraine treatment. As an ultimate goal, future studies need to be elaborately designed to develop personalized migraine-specific treatment both at the prophylactic application and acute onset phase.

Abbreviations

AUC: area under the curve; GAD: General Anxiety Disorder; MIDAS: Migraine Disability Assessment Scale; NSAIDs: Non-steroid Anti-inflammatory Drugs; HIT: Headache Impact Test; ICHD: International

Classification of Headache Disorders; PHQ: Patient Health Questionnaire; ROC: receiver operating characteristic; VAS: Visual Analog Scale.

Declarations

Ethics approval and consent to participate

The ethical committee of Nanjing Medical University approved the study.

Consent for publication

Not applicable.

Availability of data and materials

The data will be available upon request from any qualified investigator.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Science and Technology Development Project of Nanjing Medical University (NMUB2020168) and Science and Technology Development Project, Nanjing of China (YKK20202).

Authors' contributions

WHL and WJJ designed and drafted the manuscript. WHL, WJJ and ZGP analyzed the data. YYS and ZH revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all participants in the study.

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Tables

Table 1. Analysis of demographic and neuropsychiatric data.

	M-eNSAIDs	M-neNSAIDs	t/c^2	*p*-value
Age (year)	32.57 ±10.18	32.49±10.51	0.435	0.925
Sex(male/female	84/224	56/203	2.416	0.142
Education (year)	12.75±2.09	11.16±2.75	15.410	**<0.001**
Location (left/right)	189/119	161/98	0.038	0.863
Family history	77/231	70/189	0.301	0.631
Disease duration(year)	9.20±7.89	11.11±7.12	0.574	**0.004**
Frequency (times/month)	6.07±5.48	6.03±4.12	11.793	0.919
Attack duration (hours)	17.36±13.77	24.62±16.69	13.307	**<0.001**
VAS scores	6,36±1.78	6.57±1.48	7.039	0.143
MIDAS scores	41.91±36.26	44.41±33.07	4.811	0.396
HIT-6 scores	61.59±8.17	63.32±7.48	4.696	**0.009**
GAD-7 scores	5.61±2.47	7.62±3.40	18.510	**<0.001**
PHQ-9 scores	5.66±2.49	7.68±4.54	44.851	**<0.001**

NSAIDs: Non-steroid Anti-inflammatory Drugs; M-eNSAIDs: migraine with effective NSAIDs; M-neNSAIDs: migraine with noneffective NSAIDs; VAS: Visual Analogue Scale; MIDAS: Migraine Disability Assessment Scale; HIT: Headache Impact Test; GAD: General Anxiety Disorder; PHQ: Patient Health Questionnaire.

Table 2. Logistic regression analysis of predictors.

	B	S.E.	Wals	Sig.	Exp(B)	95% (CI)
Education	0.309	0.046	44.477	<0.001	1.362	1.244~1.492
Attack duration	-0.042	0.007	34.636	<0.001	0.959	0.946~0.973
HIT-6	-0.034	0.014	5.949	0.015	0.966	0.940~0.993
GAD-7	-0.291	0.037	61.015	<0.001	0.748	0.695~0.804
PHQ-9	-0.117	0.033	12.257	<0.001	0.889	0.833~0.950

All abbreviations are defined in Table 1.

Table 3. AUC comparison of the detection of different combinations of predictors.

Different factors	AUC	Sensitivity	Specificity
Education	0.706	0.909	0.515
Attack duration	0.639	0.682	0.568
HIT-6	0.560	0.932	0.342
GAD-7	0.683	0.773	0.541
PHQ-9	0.632	0.523	0.730
Attack duration + HIT-6	0.643	0.705	0.595
GAD-7 + PHQ-9	0.722	0.818	0.595
Attack duration + HIT-6 + GAD-7 + PHQ-9	0.744	0.705	0.784
Attack duration + HIT-6 + GAD-7 + PHQ-9 + Education	0.834	0.909	0.676

AUC: area under the curve. The other abbreviations are defined in Table 1.

Figures

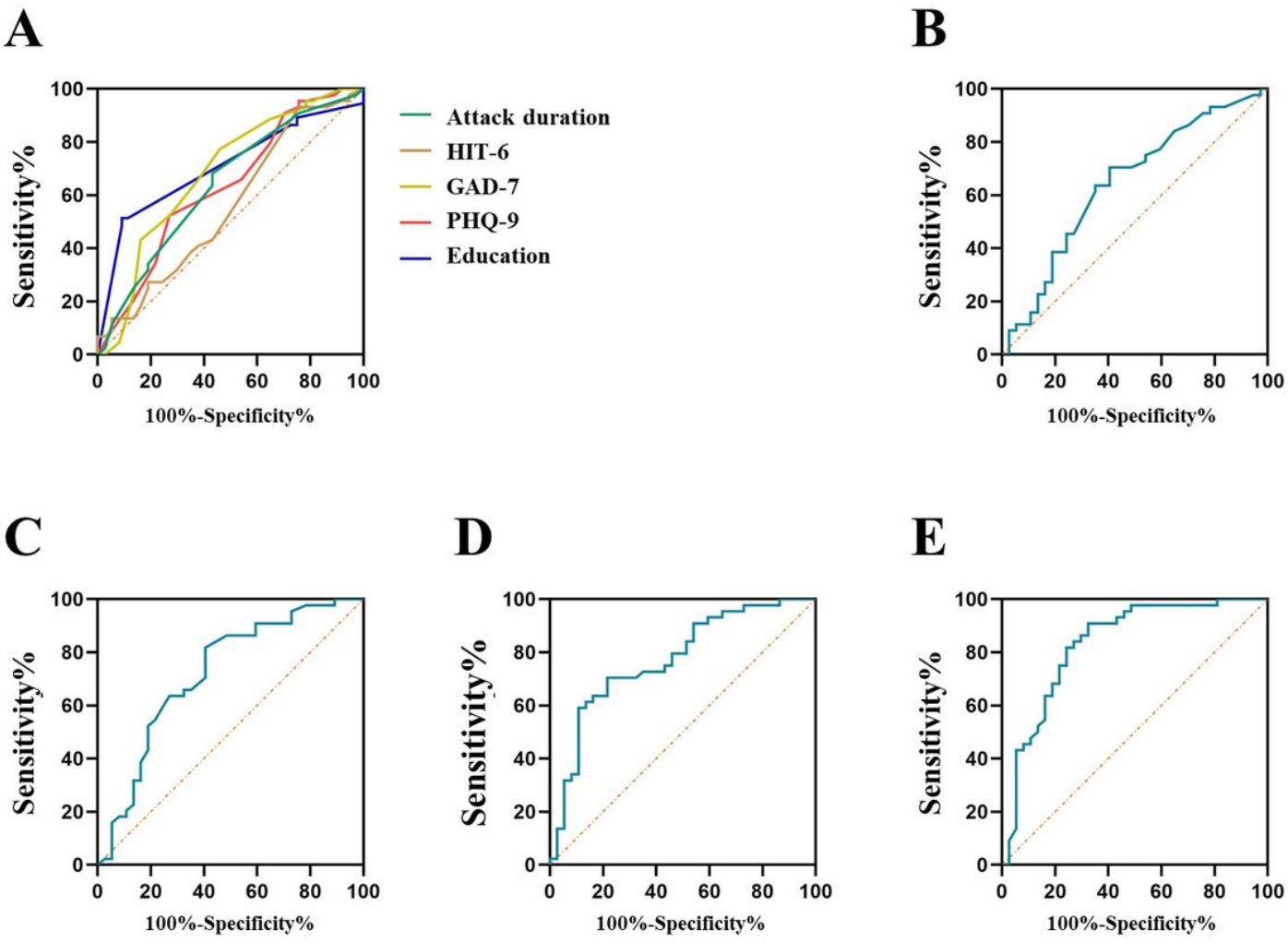

Figure 1

ROC curves of the detection power of different combinations of predictors. (A) ROC curves of single predictors. (B) ROC curve of a combination of attack duration and HIT-6 scores. (C) ROC curve of a combination of GAD-7 and PHQ-9 scores. (D) ROC curve of a combination of clinical and neuropsychiatric predictors. (E) ROC curve of a combination of all five predictors. ROC: receiver operating characteristic. The other abbreviations are defined in Table 1.