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Longitudinal assessment of migraine burden in resistant and refractory migraine – Data from the prospective REFINE study

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Abstract

Background Some individuals with migraine fail to respond adequately to preventive treatments, bearing most of migraine burden. The European Headache Federation (EHF) classifies these individuals into resistant migraine (ResM) or refractory migraine (RefM) according to treatment failures, debilitating headache days, and disease duration. We investigated the evolution of these categories over six months in patients treated at tertiary headache centers and whether they accurately reflect disability and burden.

Methods Participants from the multicenter, prospective REFINE study were classified into three categories of treatment responsiveness, namely RefM, ResM, and non-refractory non-resistant migraine (NRNRM). The primary objective was to determine the trajectories of category changes over six months. Secondary outcomes included changes in the 6-item Headache Impact Test (HIT-6), Headache-Attributed Lost Time (HALT), and Hospital Anxiety and Depression Scale (HADS-A and HADS-D) scores.

Results Overall, 489 participants were included with a median age of 45 years (IQR = 36–53); 389 participants (79.7%) were female; 256 (52.4%) had NRNRM, 178 (36.4%) ResM, and 55 (11.2%) RefM. At follow-up, 200/256 (78.1%) NRNRM remained stable, while 56/256 (21.9%) progressed to ResM. Among those with ResM, 98/178 (55.1%) remained stable, 72/178 (40.5%) improved to NRNRM, and 8/178 (4.5%) worsened to RefM. Among participants with RefM, 37/55 (67.3%) remained stable, while 18/55 (32.7%) improved to NRNRM. Participants with RefM and ResM presented significantly higher scores at baseline than those with NRNRM. Over time, HIT-6, HALT, and HADS-A scores improved

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substantially in the overall cohort ($p < 0.001$, $p < 0.001$, and $p = 0.006$, respectively). Improvements were observed in participants with ResM across all scores and HIT-6 and HALT for NRNM, but no improvement was noted in participants with RefM.

Conclusions Over six months, ~40% of ResM and ~30% of RefM individuals improved to NRNM, while ~20% of NRNM developed treatment resistance after receiving care in tertiary headache centers. Participants with ResM had a better prognosis than those with RefM. While both ResM and RefM reflect high migraine disability burden, they might present relevant differences in their management and prognosis.

Keywords Headache, Chronic migraine, Intractable, Anti-CGRP, Monoclonal antibodies, Gepants, Disability, Validation

Introduction

Migraine is one of the leading causes of disability globally [1–3]. Over the past decade, the introduction of new migraine-specific medications has changed the management of migraine, significantly improving the overall quality of life of migraineurs [4, 5]. Nonetheless, a subgroup of individuals with migraine still fails to respond adequately to preventive migraine treatments, arguably enduring most of the burdensome effects of migraine [6]. Treatment failure can occur due to several factors, including ineffectiveness, intolerance, or contraindication [6]. These individuals may have distinctive underlying pathogenic mechanisms or may represent a different stage of migraine progression, therefore requiring tailored management strategies [6–11].

Various definitions of difficult-to-treat migraine have been proposed, yet none has gained wide acceptance and has been widely adopted in clinical practice [12–14]. In 2020, the European Headache Federation (EHF) proposed updated definitions of resistant (ResM) and refractory migraine (RefM) [15] which identified two different degrees of difficult-to-treat migraine. Notably, EHF criteria account for the recent introduction of calcitonin gene-related peptide (CGRPs) antagonists to define treatment resistance/refractoriness.⁴ Despite the large consensus and the potential clinical novelties of the EHF definitions, their criteria still require validation in real-world studies, and no longitudinal assessment has been conducted to assess the evolution from one category of treatment responsiveness to another (e.g., how many patients progressed from ResM to RefM over a specific interval). We aimed to investigate the evolution of these categories over six months in patients who received care at tertiary headache centers and determine whether they accurately reflect the individuals' disability burden.

Methods

Standard protocol approvals, registrations, and patient consents

Ethics approval was obtained from the Institutional Review Board and/or relevant Ethics Committees at all participating centers (protocol number from coordinating center: 45/2020-21). Participants or their authorized representatives provided written informed consent.

Study cohort and study design

REFINE is a prospective, multicenter, observational study conducted from 2020 to 2022 across 15 European tertiary headache centers in Austria, Estonia, Germany, Greece, Italy, Lithuania, Poland, Portugal, Spain, and Turkey [16]. The study included consecutive adult individuals with a diagnosis of episodic or chronic migraine according to the International Classification of Headache Disorders (ICHD)-III diagnostic criteria [17]. Individuals unable to reliably collect information for the study or included in interventional research were excluded. Participants were classified into three categories of treatment responsiveness according to the EHF criteria [15]: (i) RefM (failure and/or contraindications of all classes of migraine preventives and $\geq$ eight debilitating headache days/month for at least 6 months), (ii) ResM (failure and/or contraindications of ≥ 3 classes of migraine preventives and $\geq$ eight debilitating headache days/month for at least 3 months), and (iii) non-refractory non-resistant migraine (NRNM) which included participants not meeting the definitions of either ResM or RefM (Fig. 1). A debilitating headache was defined as a headache causing serious impairment in daily living activities despite the use of pain-relief medications with established efficacy. Drug failure was defined as a lack of effectiveness due to persistent headache despite an appropriate dose and duration or a lack of tolerability due to side effects. As participants fulfilling the criteria for RefM also satisfy those for ResM, participants were included in the ResM category only if they also did not meet the criteria for RefM. Recruitment was stratified according to those three categories to balance the final cohort and allow comparisons. Nevertheless, participants were recruited consecutively within each of the RefM, ResM, and NRNM categories.

Participants received treatment at the discretion of the treating physicians and local clinical protocols. Clinical status and variables of interest were collected for each participant at two time points, i.e., at baseline and after 6 months. Data collected included demographics, medical history, lifestyle, headache characteristics, and migraine-specific treatments. Headache diaries were used to assess the severity and frequency of headache attacks. The following migraine-related disability scales and anxiety/depressive scales were collected systematically at each

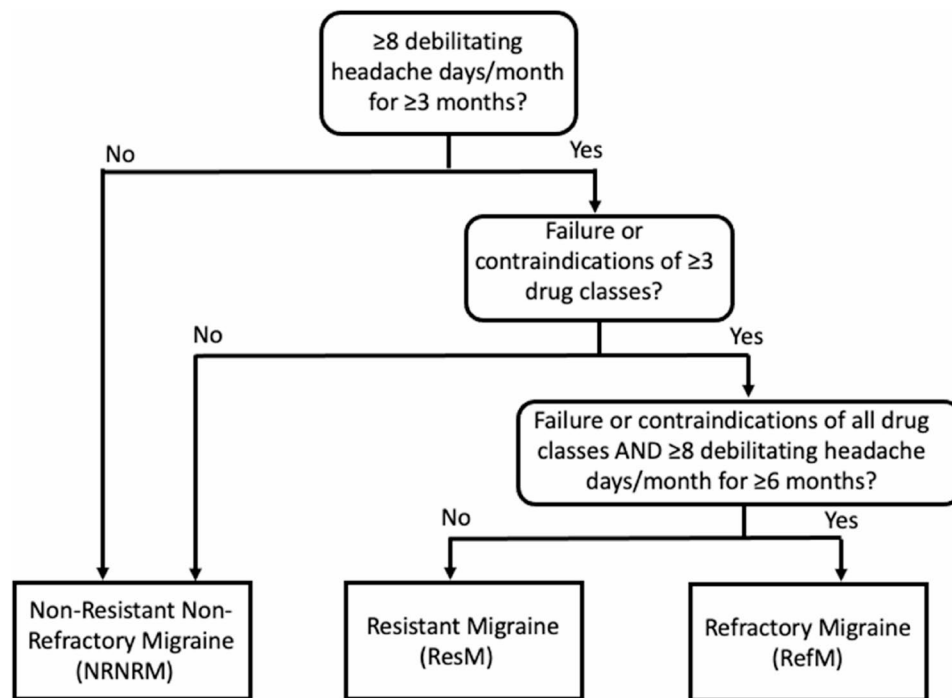


Fig. 1 Diagnostic flowchart to classify treatment responsiveness of migraine individuals

time point: the 6-item Headache Impact Test (HIT-6), Headache-Attributed Lost Time (HALT), and Hospital Anxiety and Depression Scale (HADS-A and HADS-B). At follow-up, participants were re-classified into one of the three categories of treatment responsiveness, according to their preventive treatment history during the previous six months. Specifically, participants reporting less than eight monthly disabling headache days after the prescription of preventive medication were re-classified into the NRNRM category. In contrast, those developing new treatment failures progressed from the NRNRM to the ResM or from the ResM to the RefM category (Fig. 2).

To evaluate how different medications were used in the three categories of NRNRM, ResM, and RefM, we assessed prescriptions for onabotulinumtoxinA and monoclonal antibodies targeting the CGRP pathway. These medications were specifically analyzed because they are injectable treatments typically prescribed to patients who do not respond to oral migraine medications. We did not include oral preventive migraine medications in this analysis, as at the time of the survey they were all non-specific – gepants were not yet in use during the recruitment period.

Objectives and outcomes

The primary objective of the study was to determine the number and proportions of participants with NRNRM, ResM, and RefM at baseline and follow-up. Secondly, we assessed the changes in the 6-item Headache Impact Test (HIT-6), Headache-Attributed Lost Time (HALT),

and Hospital Anxiety and Depression Scale (HADS-A and HADS-D) scores between baseline and after 6 months, stratified by baseline category of treatment responsiveness – NRNRM, ResM, or RefM. Moreover, we classified participants according to change in category into (i) improvement (i.e., participants changing from ResM or RefM to NRNRM), (ii) worsening (i.e., participants changing from NRNRM to ResM/RefM or from ResM to RefM), and (iii) no changes (i.e., participants who maintained their baseline status).

Statistical analysis

For the present study, we only included participants who had completed the follow-up.

Continuous variables were presented as medians and interquartile ranges (IQR), while categorical variables were reported as counts and percentages. Demographics, medical history, headache characteristics, and scale scores were reported as descriptive statistics. Comparisons across categories of treatment responsiveness were performed using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. As all our analyses were exploratory, no adjustment was performed for multiple comparisons and no formal sample size calculation was performed for these analyses.

Participants' characteristics potentially associated with category worsening or improvement with p -value < 0.1 in univariable comparisons were entered in two multivariable logistic regression models – one for characteristics associated with improvement and one for those

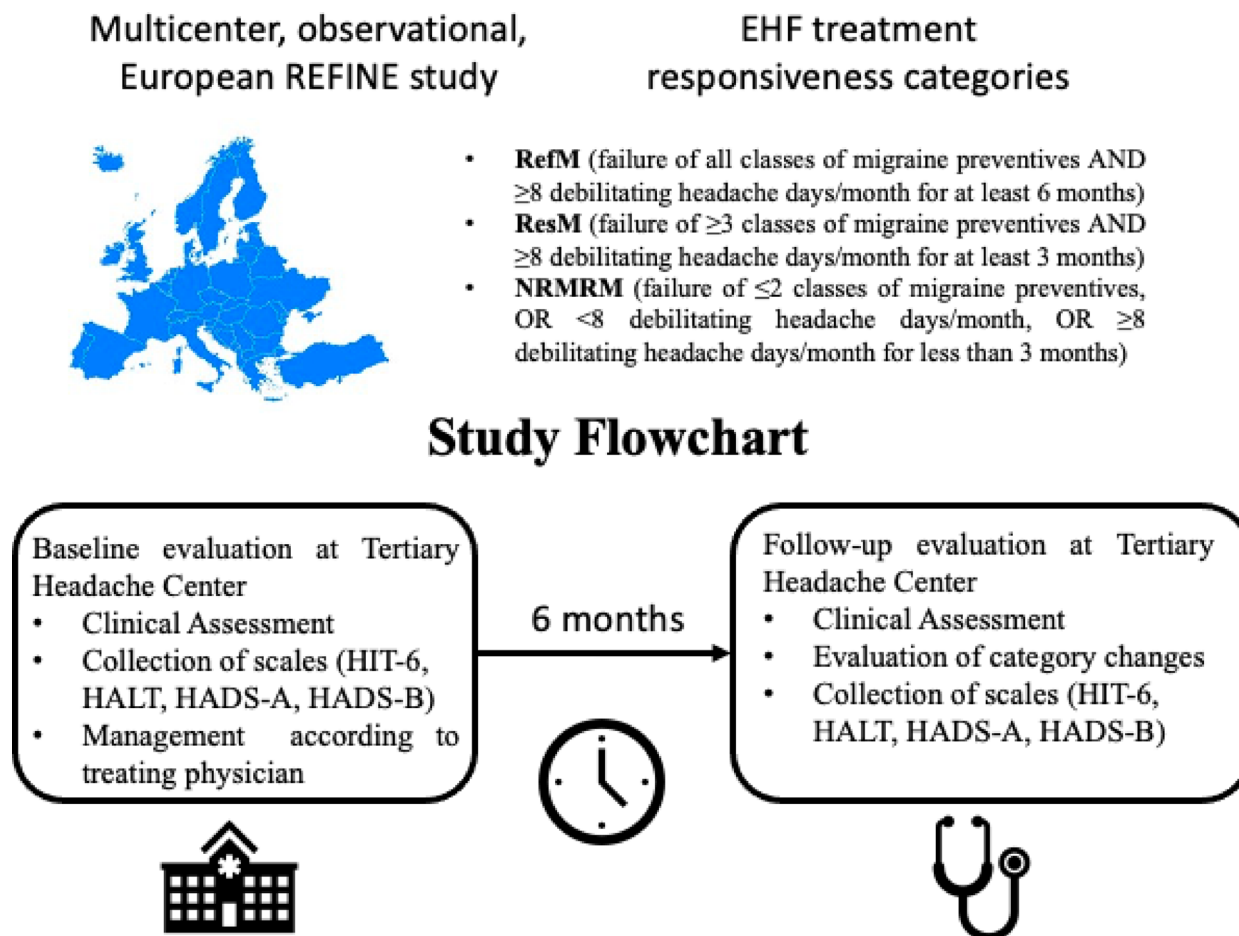


Fig. 2 Study design and Flowchart. *Patient can revert from RefM to NRMRM as a novel class medication results in a drop of debilitating headache days per month below a certain threshold (8 days/month) RefM: refractory migraine. ResM: resistant migraine. NRMRM: non-refractory, non-resistant migraine. EHF: European Headache Federation. HIT-6: 6-item Headache Impact Test. HALT: Headache-Attributed Lost Time. HADS: Hospital Anxiety and Depression Scale

associated with worsening – with the outcomes as a dependent variable. Effect size estimates derived from logistic regression models were reported as adjusted odds ratio (aOR) with 95% confidence intervals (95%CI). The aORs reported in this study represent the odds ratios for developing the outcomes (improvement or worsening) versus participants who had no change, with no change as the reference category. Participants with RefM at baseline, who could not further worsen their treatment responsiveness category during follow-up, were excluded from the model on worsening, while those with NRMRM at baseline, who could not further improve during follow-up, were excluded from the model on improvement.

All calculated P-values were two-tailed. Statistical significance was assumed at $p < 0.05$. The statistical analysis was performed with R (Version 4.2.2).

Results

Baseline characteristics

Out of 689 initial participants, 489 (71.0%) completed the 6-month follow-up. Compared with participants who completed follow-up, those lost to follow-up had a higher proportion of females (90.5% vs. 79.7%; $p = 0.003$), were older (median age 49 years, IQR 39–57; $p = 0.006$), had a higher number of monthly migraine days during the previous three months (median 13, IQR 9–20, vs. 11, IQR 7–18; $p < 0.001$), lower scores of the HIT-6 (median 62, IQR 58–66, vs. 64, IQR 60–68; $p = 0.002$) and HALT questionnaire (median 24, IQR 14–48, vs. 40, IQR 13–78; $p < 0.001$; Supplementary Table 1).

The median age of the 489 participants with complete follow-up was 45 years (IQR=36–53), and 389 (79.7%) were female. At baseline, 256 participants (52.4%) were diagnosed with NRMRM, 178 (36.4%) with ResM, and 55 (11.2%) with RefM. Compared with participants with NRMRM, those with RefM and ResM were older, had a longer migraine duration and frequency, a higher

Table 1 Baseline sociodemographic and clinical characteristics of individuals included in the study

Characteristic	Overall (n = 489)	NRNRM (n = 256)	ResM (n = 178)	RefM (n = 55)	p value
Female, n (%)	389 (79.7)	201 (78.5)	149 (83.7)	39 (70.9)	0.208
Age, years (median – IQR)	45 (36–53)	42 (34–51)	48 (37–56)	42 (34–51)	< 0.001
Current smoking, n (%)	82 (16.8)	39 (15.2)	27 (15.2)	16 (29.1)	0.090
Alcohol use, n (%)*	225 (46.1)	132 (51.6)	68 (38.2)	25 (45.5)	0.026
Caffeine use, n (%)					0.174
1–2 cups/day	290 (59.4)	160 (62.5)	99 (55.6)	31 (56.4)	
3–4 cups/day	118 (24.2)	62 (24.2)	45 (25.3)	11 (20.0)	
≥ 5 cups/day	10 (2.0)	4 (1.6)	6 (3.4)	-	
BMI, kg/m ² (median – IQR)	24 (21–27)	24 (21–28)	24 (21–27)	24 (23–26)	0.646
Age at migraine onset, years (median – IQR)	17 (13–23)	17 (13–23)	16 (13–24)	17 (15–22)	0.212
Migraine duration, years (median – IQR)	26 (16–35)	22 (14–32)	28 (18–39)	32 (24–36)	< 0.001
Monthly migraine days (median – IQR)	11 (7–18)	8 (4–15)	13 (10–20)	15 (10–19)	< 0.001
Chronic mi- graine, n (%)	275 (57.2)	98 (38.3)	124 (69.7)	53 (96.4)	< 0.001
Medication overuse, n (%)	172 (35.2)	58 (22.7)	87 (37.6)	27 (49.1)	< 0.001
HIT-6 score, median (IQR)	64 (60–68)	63 (57–66)	66 (62–68)	66 (65–68)	< 0.001
HALT score, median (IQR)	40 (13–78)	19 (7–49)	60 (33–87)	98 (59–140)	< 0.001
HADS-A score, median (IQR)	8 (5–12)	7 (4–10)	9 (6–12)	13 (9–15)	< 0.001
HADS-D score, median (IQR)	6 (3–10)	5 (2–8)	8 (5–11)	12 (9–14)	< 0.001

*Either habitual or abuse

BMI: Body Mass Index. HIT-6: 6-item Headache Impact Test. HALT: Headache-Attributed Lost Time. HADS: Hospital Anxiety and Depression Scale

prevalence of chronic migraine and medication overuse, and had higher scores of the HIT-6, HALT, HADS-A, and HADS-D scales, as shown in Table 1.

Longitudinal assessment and evolution of migraine treatment categories

After the six-month follow-up, 284/489 participants (58.1%) were diagnosed with NRNRM, 160/489 (32.7%) with ResM, and 45 (9.2%) with RefM. Among the 256 participants diagnosed with NRNRM at baseline, 200/256 (78.1%) remained in the same category, whereas 56/256 (21.9%) worsened to ResM at follow-up. Among the 178 participants diagnosed with ResM at baseline, 98/178 (55.1%) remained in the same category, 72/178 (40.4%) improved to NRNRM, and 8/178 (4.5%) worsened to

RefM at follow-up. Among the 55 participants with RefM at baseline, 37/55 (67.3%) remained in the same category, while 18/55 (32.7%) improved to NRNRM. Figure 3 shows the participants' change in categories over the follow-up period.

Longitudinal assessment of migraine-related burden across categories

The HIT-6 score improved over time in the overall population (baseline: 64 [IQR = 60–68], follow-up: 61 [IQR = 55–65]; $p < 0.001$). Participants with RefM were the only group in which no improvement in the HIT-6 score was observed over time (baseline 66 [IQR = 65–68], follow-up: 65 [IQR = 58–68], $p = 0.054$). A statistically significant improvement in the HALT score was observed in the NRNRM (baseline: 19 [IQR = 7–49], follow-up: 15 [IQR = 5–40]; $p = 0.038$) and in the ResM group (baseline: 60 [IQR = 33–87], follow-up: 33 [IQR = 15–60]; $p < 0.001$), while an improvement in the HADS-A (baseline: 9 [IQR = 6–12], follow-up: 7 [IQR = 4–11]; $p = 0.005$) and HADS-D scores (baseline: 8 [IQR = 5–11], follow-up: 6 [IQR = 3–10]; $p = 0.038$) was present only in the ResM category. Changes in scores at the different time points for each category are reported in Fig. 4 and in Supplementary Table 2.

The changes in the prescription of injectable preventive medications are reported in Fig. 5. The proportion of participants with ResM who were prescribed monoclonal antibodies targeting the CGRP pathway increased from 21.3% before baseline to 43.8% after baseline. In comparison, those drugs had already been prescribed before baseline in 63.6% of participants with RefM. The proportion of participants with ResM who received a prescription for OnabotulinumtoxinA also increased between baseline and after six months (from 24.7 to 32.0%). In comparison, most participants with RefM (85.5%) had already been prescribed OnabotulinumtoxinA at baseline. In line with monoclonal antibodies targeting the CGRP pathway, OnabotulinumtoxinA prescriptions increased in participants with NRNRM and ResM while decreasing in those with RefM (Fig. 5).

Factors associated with improvement and worsening of treatment responsiveness status

In the multivariable analysis, improvement in treatment responsiveness status was significantly associated with the presence of trigger points (adjusted OR 1.17 [95%CI = 1.05–1.30]) and a higher number of prior treatment failures (adjusted OR 1.05 [95%CI = 1.03–1.07] per each additional treatment failure) (Table 2). Conversely, worsening of treatment responsiveness status was significantly associated with fewer baseline monthly migraine days (adjusted OR 1.00 [95%CI = 1.00–1.01] per each additional day) and a lower number of prior treatment

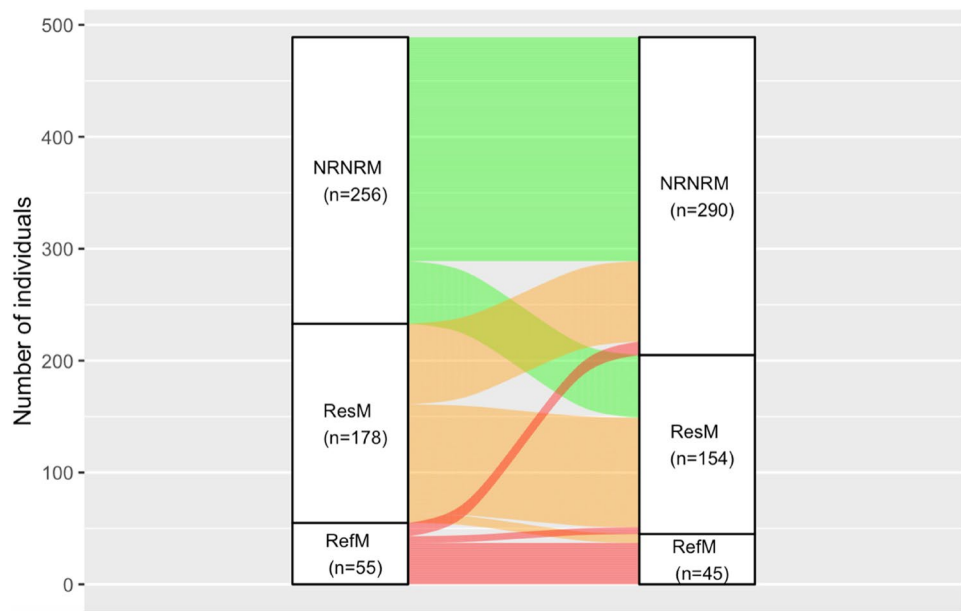


Fig. 3 Alluvial plot showing the transition from one diagnosis to the other during follow-up in the present study. Data refer to participants with complete follow-up. NRNRM: Non-refractory, Non-resistant Migraine. ResM: Resistant Migraine. RefM: Refractory Migraine

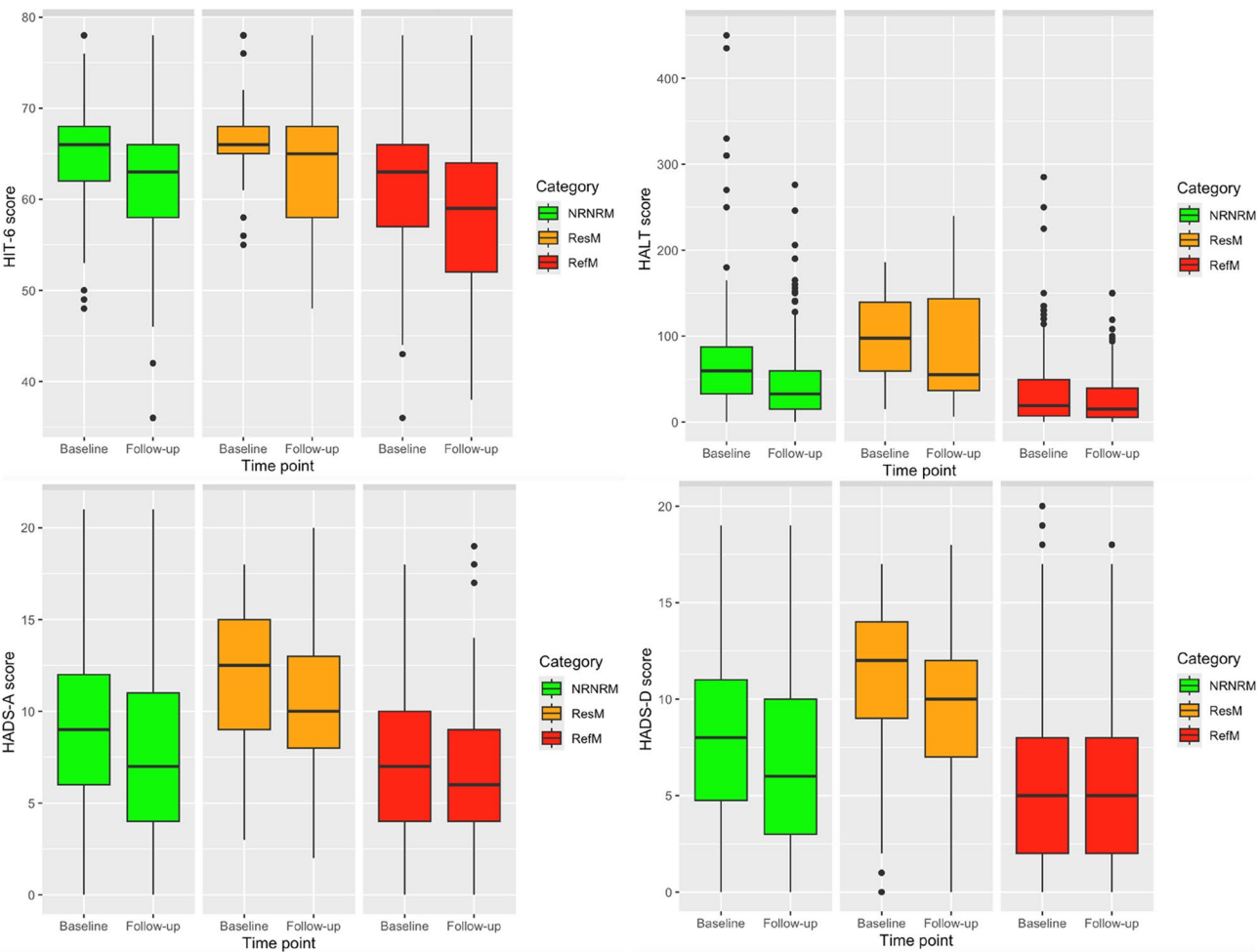


Fig. 4 Baseline and follow-up outcomes according to treatment response categories following the European Headache Federation proposal [15].

Table 2 Independent predictors of improvement of treatment responsiveness status from baseline characteristics

Characteristic	Improve- ment (n = 90)	No change (n = 145)	OR (95% CI - univariate)	p value (univariate)	OR (95% CI - multivariate)	p value (multi- variate)
Female, n (%)	74 (82.2)	118 (81.4)	1.06 (0.53–2.10)	0.871	-	-
Age, years (median – IQR)	46 (36–54)	49 (40–56)	-	0.223	-	-
Contraceptive use, n (%)*	11 (14.9)	19 (16.1)	0.91 (0.41–2.04)	0.819	-	-
Menopause, n (%)*	26 (35.1)	39 (33.1)	1.10 (0.59–2.02)	0.767	-	-
Current smoking, n (%)	21 (23.3)	25 (17.2)	1.46 (0.76–2.80)	0.254	-	-
Alcohol use, n (%)**	40 (44.4)	49 (33.8)	1.57 (0.91–2.69)	0.103	-	-
Caffeine use, n (%)				0.078		
1–2 cups/day	53 (58.9)	82 (56.6)			1.09 (0.97–1.22)	0.304
3–4 cups/day	25 (27.8)	28 (19.3)			1.12 (0.99–1.27)	0.141
≥5 cups/day	3 (3.3)	3 (2.1)			1.13 (0.85–1.51)	0.084
Illicit drug use, n (%)	-	-	-	-	-	-
Comorbidities, n (%)						
Cardiovascular disease	1 (1.1)	3 (2.1)	0.53 (0.05–5.22)	0.999	-	-
Cerebrovascular disease	3 (3.5)	9 (6.3)	0.52 (0.14–1.99)	0.382	-	-
Hypertension	16 (17.8)	31 (21.5)	0.80 (0.41–1.56)	0.512	-	-
Fibromyalgia	5 (5.6)	16 (11.1)	0.48 (0.17–1.35)	0.238	-	-
Neck/back pain	55 (61.1)	74 (51.4)	1.31 (0.76–2.27)	0.137	-	-
Trigger points	29 (32.2)	29 (20.1)	1.91 (1.05–3.50)	0.041	1.17 (1.05–1.30)	0.006
Temporomandibular joint dysfunction	19 (21.1)	18 (12.5)	1.90 (0.94–3.86)	0.096	1.00 (0.88–1.13)	0.057
Rheumatological disease	6 (6.7)	10 (6.9)	0.97 (0.34–2.76)	0.731	-	-
Asthma	6 (6.7)	9 (6.3)	1.08 (0.37–3.16)	0.437	-	-
Rhinitis	14 (15.6)	25 (17.4)	0.89 (0.43–1.82)	0.857	-	-
Depression	39 (43.3)	53 (36.8)	1.31 (0.77–2.25)	0.338	-	-
Anxiety	25 (27.8)	44 (30.6)	0.89 (0.50–1.59)	0.480	-	-
Bipolar disorder	1 (1.1)	3 (2.1)	0.53 (0.05–5.22)	0.999	-	-
Other psychiatric disorders	10 (11.1)	11 (7.6)	1.53 (0.62–3.77)	0.357	-	-
Thyroiditis	21 (23.3)	21 (14.6)	1.53 (0.62–3.77)	0.168	-	-
Urticaria	1 (1.1)	3 (2.1)	0.53 (0.05–5.22)	0.999	-	-
Gastrointestinal disease	2 (2.2)	2 (1.4)	1.63 (0.23–11.80)	0.638	-	-
Celiac disease	1 (1.1)	-	-	0.382	-	-
Other autoimmune diseases	1 (1.1)	6 (4.2)	0.26 (0.03–2.19)	0.302	-	-
Sleep disturbances	29 (32.2)	59 (41.0)	0.70 (0.40–1.22)	0.425	-	-
Previous preventive treatment failures (median – IQR)	4 (3–6)	5 (3–7)	-	0.085	1.05 (1.03–1.07)	< 0.001
BMI, kg/m ² (median – IQR)	23 (21–27)	24 (21–27)	-	0.396	-	-
Age at migraine onset, years (median – IQR)	16 (13–21)	16 (13–23)	-	0.664	-	-
Migraine duration, years (median – IQR)	26 (18–36)	29 (20–38)	-	0.460	-	-
Migraine days*** (median – IQR)	11 (10–20)	15 (10–22)	-	0.012	1.00 (1.00–1.01)	0.109
Chronic migraine, n (%)	58 (64.4)	121 (82.9)	0.37 (0.20–0.69)	0.001	0.95 (0.87–1.04)	0.256
Medication overuse, n (%)	38 (42.2)	77 (53.1)	0.65 (0.38–1.10)	0.105	-	-
HIT-6 score, median (IQR)	65 (62–68)	66 (64–68)	-	0.193	-	-
HALT score, median (IQR)	67 (35–88)	64 (37–111)	-	0.313	-	-
HADS-A score, median (IQR)	9 (6–13)	11 (8–13)	-	0.361	-	-
HADS-D score, median (IQR)	8 (6–12)	9 (5–12)	-	0.827	-	-

*Proportions are reported on the total of women in each group

**Either habitual or abuse

***During the previous three months

BMI: Body Mass Index. CGRP-mAbs: monoclonal antibodies targeting the calcitonin gene-related peptide pathway. HIT-6: 6-item Headache Impact Test. HALT: Headache-Attributed Lost Time. HADS: Hospital Anxiety and Depression Scale

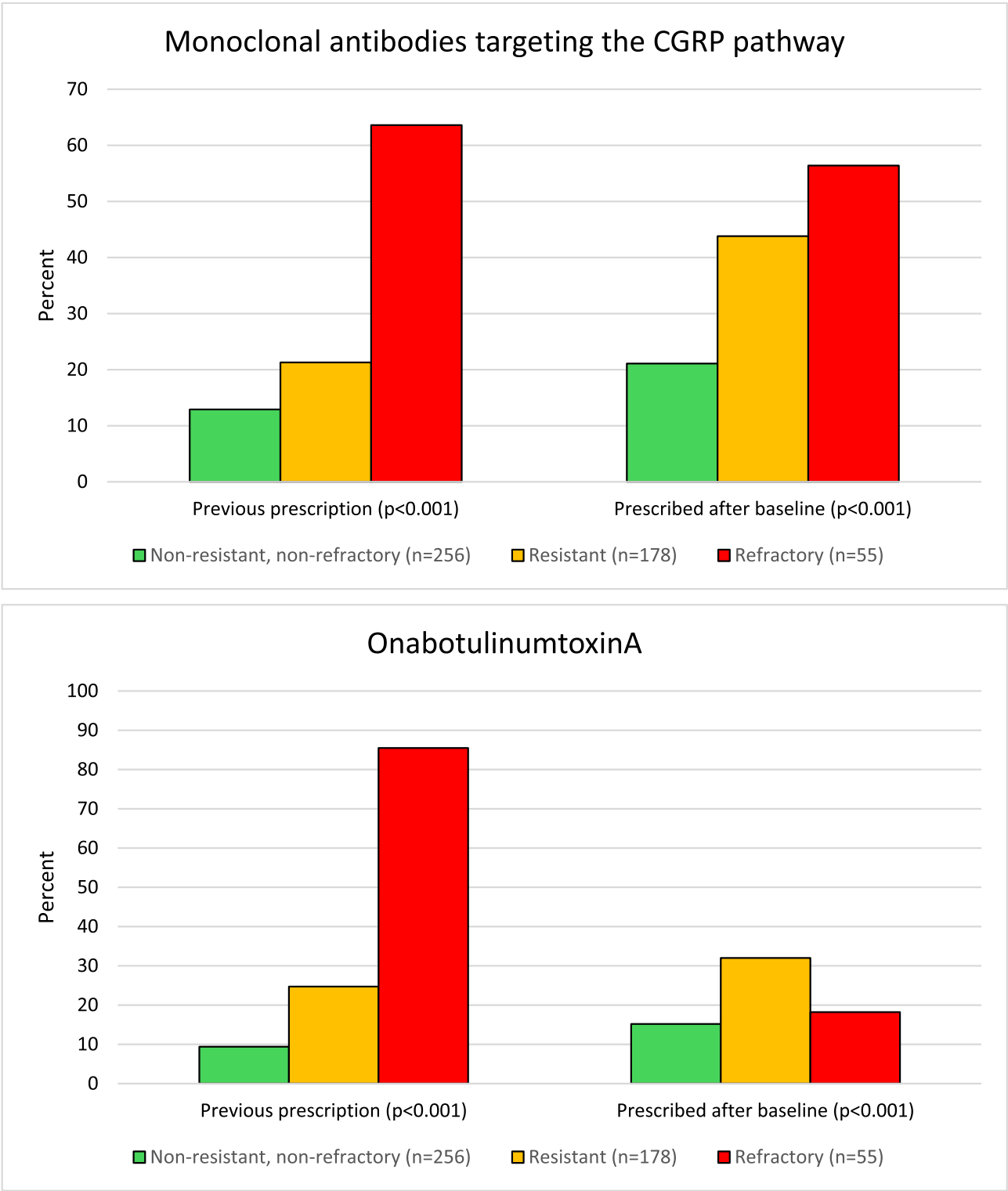


Fig. 5 Prescriptions of injectable treatments for migraine prevention in participants with non-resistant and non-refractory, resistant, and refractory migraine over the study period. Data refers to the 489 participants with complete follow-up. Participants' categories are those attributed at baseline. The graphs reflect treatments that were prescribed at least once in their migraine history, rather than prescriptions at a specific time point. CGRP: calcitonin gene-related peptide

failures (adjusted OR 0.97 [95%CI=0.96–0.99] per each additional treatment failure) (Table 3).

Discussion

In our multicenter prospective cohort study, which longitudinally assessed individuals with NRNM, ResM, and RefM as defined by the EHF categories, we found that (i) more participants with ResM improved their treatment responsiveness condition to NRNM compared to those with RefM; (ii) participants with ResM or RefM had a higher disability burden compared with those with NRNM, (iii) disability levels in RefM remained relatively stable over time, whereas ResM showed the most significant improvement, and (iv) presence of trigger points, number of treatment failures and baseline monthly migraine days were the only independent predictors of changes of treatment responsiveness status.

This is the first real-life longitudinal study reporting the change in categories of treatment responsiveness in tertiary headache centers. We found that approximately 40% of participants with ResM reverted to NRNM, while two out of every three participants with RefM remained in their category. Our finding confirms the difference between ResM, which can improve if individuals are prescribed effective migraine prevention, and RefM, in which some specific mechanisms might determine the ineffectiveness of preventive treatments [6]. In our study, participants with RefM had a heavy and relatively stable migraine burden, while those with ResM experienced a decrease in the migraine burden. It is also relevant that no group of participants experienced increased migraine disability burden. Notably, most participants with ResM were prescribed monoclonal antibodies targeting the CGRP pathway or OnabotulinumtoxinA for the first time when entering the REFINE study follow-up, which might have been important in overcoming resistance to preventive treatments.

As we showed that ResM and RefM are associated with a higher migraine disability burden compared with NRNM, we confirmed that individuals with these difficult-to-treat migraine states experience a disease-related disability that extends beyond the simple lack of response to preventive treatments. Our data contribute to identifying characteristics typical of individuals with ResM and RefM, which deserve further exploration as they might be associated with mechanisms underlying resistance or refractoriness to preventive treatments [6]. Our findings also highlight the importance of timely recognition and treatment of ResM, as this condition is more prone to respond to treatments. On the other hand, it is also important to correctly identify individuals with RefM as they might represent suitable candidates for research on the mechanisms of migraine and candidates for combination treatments and/or non-pharmacological treatments

[6, 18]. These findings could inform headache specialists and policy decision-makers to streamline referral processes for individuals with ResM and RefM to specialist care. Our data validate the effectiveness of a classification system that differentiates ResM from RefM, enabling clinicians to provide specialist care to individuals most likely to benefit.

A lower number of prior treatment failures and fewer baseline monthly migraine days, indicating a lower overall migraine burden, were associated with worsening in treatment responsiveness status. While these findings may seem counterintuitive, they likely reflect features of individuals with non-refractory migraine who can still worsen toward a severe migraine responsiveness status. Conversely, individuals with RefM cannot worsen further. On the other hand, a higher number of prior treatment failures and the presence of trigger points were associated with improved treatment responsiveness status. While the former might still be interpreted with the same conceptual framework, it might also be partially explained by the widespread use of anti-CGRP monoclonal antibodies as a last resource—after all or most other classes of drugs have failed [6]. Notably, trigger points might represent a clinically meaningful treatment responsiveness marker consistent with previous literature [19].

The severity and burden of migraine have historically been assessed based on the frequency of headache attacks by distinguishing individuals with episodic migraine from those with chronic migraine [3, 17]. However, this classification provides only a snapshot of a highly dynamic condition, does not account for the intensity of the attacks, and offers limited insights into the predictive response to future therapies [20–22]. A classification framework based on treatment responsiveness might better reflect migraine history and provide complementary information to the standard frequency-based definition, thereby enhancing management strategies [23].

The main strength of our study is that it represents the first one to provide a longitudinal assessment of individuals with ResM and RefM over six months. Additional strengths include its multicenter prospective design and the adoption of a standardized definition of ResM and RefM established by a large international consensus. However, our study has also some limitations. First, the proportions among categories were unbalanced, with RefM being relatively underrepresented. Second, due to the observational nature of the study, participants received heterogeneous management after baseline, depending on local protocols and clinical practice. This might have had an impact on the change from ResM to RefM, as some participants classified as ResM might have remained in their category only due to an insufficient number of drug trials within the six-month-period.

Table 3 Independent predictors of worsening of treatment responsiveness status from baseline characteristics

Characteristic	Worsening (n = 64)	No change (n = 318)	OR (95% CI - univariate)	p value (univariate)	OR (95% CI - multivariate)	p value (multi- variate)
Female, n (%)	52 (81.3)	258 (81.1)	1.02 (0.93–1.11)	0.904	-	-
Age, years (median – IQR)	44 (36–53)	44 (34–52)	-	0.649	-	-
Contraceptive use, n (%)*	7 (13.4)	48 (18.6)	0.90 (0.78–1.04)	0.534	-	-
Menopause, n (%)*	15 (28.8)	54 (20.9)	1.02 (0.93–1.12)	0.102	-	-
Current smoking, n (%)	8 (12.5)	48 (15.1)	0.91 (0.80–1.04)	0.224	-	-
Alcohol use, n (%)*	29 (45.3)	138 (43.4)	1.08 (0.63–1.85)	0.002	0.94 (0.88–1.00)	0.059
Caffeine use, n (%)				0.750	-	-
1–2 cups/day	41 (64.1)	188 (59.1)			-	-
3–4 cups/day	12 (18.8)	80 (25.2)			-	-
≥5 cups/day	1 (1.6)	6 (1.9)			-	-
Illicit drug use, n (%)	-	3 (0.9)	-	-	-	-
Comorbidities, n (%)						
Cardiovascular disease	1 (1.6)	5 (1.6)	0.99 (0.11–8.65)	0.999	-	-
Cerebrovascular disease	2 (3.1)	8 (2.5)	1.25 (0.26–6.03)	0.732	-	-
Hypertension	15 (23.4)	56 (17.7)	1.38 (0.72–2.64)	0.279	-	-
Fibromyalgia	6 (9.4)	18 (5.7)	1.72 (0.66–4.53)	0.060	1.07 (0.93–1.22)	0.358
Neck/back pain	29 (45.3)	161 (50.8)	0.81 (0.47–1.39)	0.644	-	-
Trigger points	14 (21.9)	43 (13.6)	1.79 (0.91–3.51)	0.216	-	-
Temporomandibular joint dysfunction	9 (14.1)	34 (10.7)	1.37 (0.62–3.01)	0.328	-	-
Rheumatological disease	2 (3.1)	24 (7.6)	0.40 (0.09–1.72)	0.229	-	-
Asthma	7 (10.9)	26 (8.2)	1.38 (0.57–3.33)	0.706	-	-
Rhinitis	8 (12.5)	60 (18.9)	0.61 (0.28–1.36)	0.334	-	-
Depression	12 (18.8)	77 (24.3)	0.72 (0.37–1.42)	0.588	-	-
Anxiety	10 (15.6)	55 (17.4)	0.89 (0.42–1.85)	0.864	-	-
Bipolar disorder	1 (1.6)	7 (2.2)	0.70 (0.09–5.83)	0.999	-	-
Other psychiatric disorders	-	14 (4.4)	-	-	-	-
Thyroiditis	7 (10.9)	38 (12.0)	0.90 (0.38–2.13)	0.712	-	-
Urticaria	3 (4.7)	11 (3.5)	1.37 (0.37–5.07)	0.762	-	-
Gastrointestinal disease	1 (1.6)	4 (1.3)	1.25 (0.14–11.34)	0.446	-	-
Celiac disease	-	4 (1.3)	-	-	-	-
Other autoimmune diseases	1 (1.6)	7 (2.2)	0.71 (0.09–5.83)	0.999	-	-
Sleep disturbances	17 (26.6)	110 (34.7)	0.68 (0.38–1.25)	0.353	-	-
Previous preventive treatment failures (median – IQR)	1 (0–3)	3 (0–4)	-	0.001	0.97 (0.96–0.99)	0.001
BMI, kg/m ² (median – IQR)	25 (22–30)	24 (21–27)	-	0.038	1.01 (1.00–1.02)	0.060
Age at migraine onset, years (median – IQR)	18 (14–25)	16 (13–22)	-	0.247	-	-
Migraine duration, years (median – IQR)	24 (14–37)	24 (15–35)	-	0.240	-	-
Monthly migraine days (median – IQR)	15 (8–24)	10 (5–17)	-	0.007	1.00 (1.00–1.01)	0.002
Chronic migraine, n (%)	37 (57.8)	158 (49.5)	1.40 (0.81–2.40)	0.226	-	-
Medication overuse, n (%)	26 (40.6)	96 (30.2)	1.58 (0.91–2.75)	0.102	-	-
HIT-6 score, median (IQR)	64 (60–68)	64 (58–67)	-	0.293	-	-
HALT score, median (IQR)	48 (18–76)	28 (10–60)	-	0.149	-	-
HADS-A score, median (IQR)	8 (4–11)	7 (5–11)	-	0.523	-	-
HADS-D score, median (IQR)	5 (3–9)	5 (2–9)	-	0.539	-	-

*Proportions are reported on the total of women in each group

**Either habitual or abuse

***During the previous three months BMI: Body Mass Index. CGRP-mAbs: monoclonal antibodies targeting the calcitonin gene-related peptide pathway. HIT-6: 6-item Headache Impact Test. HALT: Headache-Attributed Lost Time. HADS: Hospital Anxiety and Depression Scale

NNRM: Non-refractory, Non-resistant Migraine. ResM: Resistant Migraine. RefM: Refractory Migraine

CGRP: calcitonin gene-related peptide

Supplementary Table 1 Comparisons between baseline sociodemographic and clinical characteristics of participants with and without study follow-up

Third, almost half of the initial participants were lost to follow-up, and participants lost to follow-up had different characteristics from those who were followed-up (Supplementary Table 1). The proportion of participants lost to follow-up might have introduced selection bias and limited the generalizability of our findings; nevertheless, the REFINE study had an observational design with no compulsory procedure and did not adopt strategies to enhance participants' adherence to follow-up. Fourth, our purely observational study design could not allow to assess the exact contribution of each medication and especially injectable treatments – i.e., onabotulinumtoxinA and CGRP-mAbs – to migraine prevention. Finally, migraine follows a naturally fluctuating course that is highly individualized and sometimes seasonally patterned, such as holidays, work/school routines, or weather changes. Therefore, treatment responsiveness categories might partially reflect these natural fluctuations rather than the results of management.

Conclusions

We found that many individuals with ResM who receive care in tertiary headache centers and are treated with migraine-specific preventive medication can revert their resistance to treatment, while individuals with RefM tend to have a stable condition. The categories of ResM and RefM have a high migraine burden and reflect the treatment responsiveness of individuals, providing complementary information to the standard frequency-based definition (i.e., chronic and episodic migraine) to inform management. Timely recognition and treatment of individuals with ResM and identification of those with RefM are crucial to managing those conditions. Longer observational studies are warranted to draw definite conclusions about the natural history of ResM and RefM.

Abbreviations

EHF	European Headache Federation
CGRP	Calcitonin Gene-related Peptide
HADS	Hospital Anxiety and Depression Scale (HADS)
HALT	Headache-Attributed Lost Time (HALT)
HIT-6	6-item Headache Impact Test
RefM	Refractory Migraine
ResM	Resistant Migraine
NRNM	Non-Refractory Non-Resistant Migraine

Supplementary Information

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Supplementary material 1.

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Author contributions

SS, VC, and ZK conceived the study and supervised the project. UP and RO drafted the initial manuscript. All authors contributed to data collection, reviewed the manuscript for content, and approved the final version of the manuscript.

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Data availability

The corresponding author will grant access to the study data upon reasonable request and after approval by the REFINE executive committee.

Declarations

Consent for publication

Participants or their authorized representatives provided written informed consent.

Competing interests

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Ethical approval and consent to participate

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