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RESEARCH

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Resistant and refractory migraine – two different entities with different comorbidities? Results from the REFINE study

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Abstract

Background Resistant and refractory migraine are commonly encountered in specialized headache centers. Several comorbidities, mostly psychiatric conditions, have been linked to migraine worsening; however, there is little knowledge of the comorbidity profile of individuals with resistant and refractory migraine.

Methods REFINE is a prospective observational multicenter international study involving individuals with migraine from 15 headache centers. Participants were categorized into three groups based on the European Headache Federation criteria: non-resistant and non-refractory (NRNRM), resistant (ResM), and refractory (RefM). We explored the prevalence of 20 comorbidities at baseline in the three groups.

Results Of the 689 included patients (82.8% women), 262 (38.0%) had ResM, 73 (10.4%) had RefM and 354 (51.4%) NRNRM. A higher prevalence of psychiatric comorbidities, trigger points, temporomandibular joint disorders, thyroiditis, and cerebrovascular diseases was observed in the RefM group, followed by ResM and NRNRM. Multiple comorbidities were more common in the RefM group, followed by the ResM group and by the NRNRM group (41.6% vs. 24.5% vs. 14.1% respectively; $p < 0.001$). At the sensitivity analysis, exploring participants with chronic migraine, significant differences among the NRNRM, ResM, and RefM groups were found in the prevalence of anxiety ($p < 0.001$), asthma and rhinitis ($p = 0.013$), bipolar and other psychiatric disorders ($p = 0.049$), cerebrovascular diseases ($p < 0.001$), depression ($p < 0.001$), obesity ($p = 0.002$), thyroiditis ($p < 0.001$), and trigger points ($p = 0.008$).

Conclusion REFINE data indicate that individuals with ResM and RefM have a higher burden of comorbidities than those with NRNRM. It can be postulated that those comorbidities may have an impact on the progression of migraine from a form that is easy to treat to a form that is resistant or refractory to treatments. Longitudinal studies are needed to understand the direction of the association between ResM or RefM and those comorbidities and if proper treatment of comorbidities might help overcome treatment resistance or refractoriness.

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Keywords Migraine, Resistant migraine, Refractory migraine, Comorbidities

Background

Despite advances in migraine treatment, in some individuals with migraine there is a poor response to the available drugs [1, 2]. The difficult-to-treat individuals have been labeled with different definitions and denominations over the years till the most recent definition from the European Headache Federation (EHF) [2–4]. In 2020, the European Headache Federation (EHF) defined two types of difficult-to-treat migraine: resistant migraine (ResM) and refractory migraine (RefM) [5]. Individuals with ResM experience at least 8 debilitating headache days monthly and did not respond to at least 3 classes of migraine preventatives, while those with RefM failed to respond to all available classes of preventive treatments.

An appropriate definition of ResM and RefM might help to identify individuals who are more in need of advanced care and to better understand factors related to the presence of poor response to pharmacological treatments [3, 4].

While there is a good knowledge of comorbidities associated with migraine chronification [6–13], there is little knowledge about comorbidities associated with resistance or refractoriness to preventive treatments and it is unclear whether a particular set of comorbidities may contribute to those conditions. It is worth noting that not all individuals with CM are resistant or refractory to treatment, nor does every individual with ResM or RefM migraine meet the criteria for CM. Identifying specific comorbidities of ResM and RefM is clinically relevant as it might reveal pathophysiological mechanisms associated with migraine and potential adjunct treatment opportunities. In this article, we aimed to describe the specific set of comorbidities of individuals with ResM and RefM.

Methods

Study design

The real-life study on Resistant and Refractory Migraine (REFINE) is a prospective observational multicenter international study that included consecutive individuals referred from 15 headache centers in Western and Eastern Europe, with the University of L'Aquila acting as the coordinating center. The study was observational and no changes in diagnostic and treatment procedures were made. Participants were treated according to the clinicians' decisions and in line with the current guidelines and good clinical practice.

A map of the centers included in the study is reported in Supplementary Fig. 1.

We recruited consecutively participants who were assigned to one of the following groups at baseline:

- participants not meeting the EHF criteria [5] for resistant and refractory migraine (non-resistant and non-refractory group – NRNRM);
- participants meeting the EHF criteria for resistant migraine (resistant group - ResM);
- participants meeting the EHF criteria for refractory migraine (refractory group – RefM; Table 1).

The attribution to each category was performed based on the EHF diagnostic criteria by the staff of each participating center and confirmed by the staff of the coordinating center.

Each center was required to include 50 participants. To include enough subjects with difficult-to-treat migraine (either ResM or RefM), we set a cap of inclusion of 50% of participants with NRNRM corresponding to 25 participants for each center. One year after the beginning of the study, some centers included more than 50 participants to compensate for centers that under-recruited. Despite these efforts, it was challenging for centers to achieve the intended 25% representation of RefM.

Inclusion and exclusion criteria

We applied the following inclusion criteria:

- Individuals referring for either a first or a follow-up visit to one of the centers participating in the project within the study inclusion period;
- Diagnosis of migraine with/without aura or CM according to the ICHD-III diagnostic criteria [14], with or without coexisting tension-type headache;
- Male or female sex;
- Age ≥ 18 years;
- Provided written informed consent;
- Willing to comply with all study procedures and be available for the duration of the study.

Subjects with the following characteristics were not included in the study:

- Presence of any condition which at the physician judgment may preclude the reliability of the collected information;
- Subjects unable to understand the study protocol or unable to provide informed consent and have no legal representative;
- Subjects included in an interventional study on migraine treatment.

Table 1 European Headache Federation criteria for resistant and refractory migraine

Resistant Migraine	Refractory Migraine
A. Established diagnosis of 1.1 Migraine without aura and/or 1.2 Migraine with aura or 1.3 Chronic migraine according to ICHD-III criteria;	A. Established diagnosis of 1.1 Migraine without aura and/or 1.2 Migraine with aura or 1.3 Chronic migraine according to ICHD-III criteria;
B. Debilitating headache for at least 8 days per month for at least 3 months;	B. Debilitating headache for at least 8 days per month for at least 8 months;
C. Failure and/or contraindication to 3 drug classes with established evidence for migraine prevention, given at an appropriate dose for an appropriate duration.	C. Failure and/or contraindication to all classes with established evidence for migraine prevention, given at an appropriate dose for an appropriate duration.

Study procedures

The study comprised a baseline visit and two follow-up visits performed 3–6 and 9–12 months after the baseline visit. Data were collected locally by physicians and/or other healthcare professionals involved in migraine care. At each visit, a paper copy of collected data for each included participant had to be stored at local centers. The paper copy contained demographic information, along with an ID that was unique for each participant and was created upon insertion of the data in the electronic case report form (e-CRF) to keep anonymity. The record ID of each participant was requested to implement the e-CRF at follow-up visits. Only local centers knew the identity of the included participants.

For the present analysis, we used participants' baseline data. At baseline visit, we collected demographic information together with data on headache characteristics, use of migraine-specific drugs, past and present preventive treatments, comorbidities, lifestyle, medical and psychiatric history. Patients were also asked to scales of headache impact, depression and anxiety and insomnia [15–18]. Additionally, data from headache diaries were used to evaluate the frequency and severity of migraine attacks. Details of collected data are reported in Supplementary Table 2.

The prevalence of comorbidities was compared across the three groups of participants with ResM, RefM, and NRNRM. The investigated comorbidities included allergic and respiratory diseases (asthma, rhinitis, urticaria), cardiovascular diseases and hypertension (cardiac diseases, cerebrovascular diseases, hypertension), gastrointestinal and celiac disease, musculoskeletal disorders and chronic pain (neck or back pain, fibromyalgia, TMJ disorders, trigger points), obesity, psychiatric disorders (anxiety, bipolar disorder, depression, sleep disturbances, other psychiatric disorders), rheumatological and other autoimmune disorders. Those comorbidities were predetermined according to those commonly associated with migraine worsening or progression [19–21]. The presence of comorbidities was assessed by the treating physicians according to standard definitions derived from international guidelines and consensus statements. The definitions of comorbidities, their corresponding ICD-10 codes and references for diagnostic criteria are reported in Supplementary Table 3. No mandatory exams or evaluations were requested to exclude asymptomatic comorbidities. We reported the prevalence of each comorbidity, multiple comorbidities, and associations of comorbidities.

Statistical analysis

To report baseline information, we used descriptive statistics. Categorical variables were reported as numbers and proportions, while continuous variables were reported as medians and interquartile ranges (IQRs). We compared the characteristics of the three groups – ResM, RefM, and NRNRM – and their comorbidities via the chi-squared test or Kruskal-Wallis test, as appropriate. To attenuate the possible confounding role of chronic migraine (CM) in comorbidities, we performed a sensitivity analysis on participants with CM. The presence and distribution of multiple comorbidities were also assessed.

As our data are the first on a population of individuals with ResM or RefM defined according to the EHF criteria, we did not pre-specify a sample size. To maintain conservative estimates, we performed non-parametric tests. Due to the exploratory, hypothesis-generating nature of our analyses, p values were reported without correction for multiple comparisons.

Ethical procedures

The study was approved by the Institutional Review Board of the coordinating center with protocol number 45/2020-21 and then approved by local Ethic Committees of all participating centers, wherever applicable. Participants were requested to sign an informed consent before any study procedure.

Results

Of the 689 patients included in the study, 570 (82.8%) were women. The median age was 47 years (IQR 38–56); 73 patients (10.4%) were diagnosed with RefM, 262 patients (38.0%) with ResM and 354 (51.4%) NRNRM. Table 2 reports baseline data referring to the three groups. Participants with RefM and those with ResM had a longer migraine history compared with those with NRNRM (median 34 years, IQR 26–38, vs. 31, IQR 20–40, vs. 24, IQR 16–33; $p<0.001$). The prevalence of CM (83.6% vs. 70.2% vs. 40.1%; $p<0.001$) and of MOH (45.2% vs. 48.1% vs. 19.8%; $p<0.001$) was significantly higher in the RefM and ResM groups compared to the NRNRM group. HIT-6, HADS-A, HADS-D, and

Table 2 Baseline characteristics of the included participants

Characteristic	Overall (*n* = 689)	RefM (*n* = 73)	ResM (*n* = 262)	NRNRM (*n* = 354)	*p* value
Female, n (%)	570 (82.8)	55 (75.3)	224 (85.8)	291 (82.2)	0.237
Age, years (median – IQR)	47 (38–56)	52 (44–60)	50 (40–57)	45 (36–54)	< 0.001
Current smoking, n (%)	101 (14.7)	9 (12.3)	37 (14.2)	55 (15.5)	0.096
Alcohol use, n (%)	303 (44.0)	30 (41.1)	100 (38.3)	173 (48.8)	0.038
Caffeine use, n (%)					0.228
1–2 cups/day	405 (58.9)	45 (61.6)	144 (55.2)	216 (61.0)	
3–4 cups/day	169 (24.6)	14 (19.2)	66 (25.3)	89 (25.1)	
≥5 cups/day	14 (2.0)	-	8 (3.1)	6 (1.7)	
BMI, kg/m^2 (median – IQR)	24 (21–27)	24 (22–26)	24 (21–27)	24 (21–27)	0.512
Age at migraine onset, years (median – IQR)	17 (13–23)	17 (14–21)	16 (13–21)	17 (13–25)	0.113
Migraine duration, years (median – IQR)	27 (18–38)	34 (26–38)	31 (20–40)	24 (16–33)	< 0.001
Chronic migraine, n (%)	387 (56.2)	61 (83.6)	184 (70.2)	142 (40.1)	< 0.001
Medication overuse, n (%)	229 (33.2)	33 (45.2)	126 (48.1)	70 (19.8)	< 0.001
HIT-6 score (median – IQR)	64 (59–67)	66 (63–68)	65 (61–68)	62 (56–66)	< 0.001
HADS-A score (median – IQR)	8 (5–11)	11 (8–15)	9 (6–12)	7 (4–9)	< 0.001
HADS-D score (median – IQR)	6 (3–10)	11 (7–13)	8 (5–10)	5 (2–8)	< 0.001
ISI score (median – IQR)	10 (4–15)	16 (10–18)	12 (5–16)	8 (3–13)	< 0.001

ISI scores were also higher in participants with RefM or ResM compared with those with NRNRM (Table 2).

As reported in Fig. 1, we found a significant difference in several of the considered comorbidities, including depression, anxiety, sleep disturbances, trigger points, TMJ disorders, thyroiditis, cerebrovascular disease, bipolar and other psychiatric disorders among the three groups. All those comorbidities, with the exception of sleep disturbances, were more common in participants with RefM, followed by ResM and then by NRNRM. In the RefM group, 45 participants (62.5%) have at least one psychiatric comorbidity, compared with 121 participants with ResM (46.7%) and 86 with NRNRM (24.3%; $p=0.001$).

Considering multiple comorbidities, 58 participants (80.6%) in the RefM group, 181 (70.4%) in the ResM group, and 201 (56.8%) in the NRNRM group had ≥2 comorbidities ($p=0.001$); 50 participants (69.4%) in the RefM group, 127 (49.4%) in the ResM group, and 306 (44.8%) in the NRNRM group had ≥3 comorbidities ($p=0.001$); and 40 participants (55.6%) in the RefM group, 90 (35%) in the ResM group, and 212 (31%) in the NRNRM group had ≥4 comorbidities ($p=0.001$; Fig. 2). No clear pattern of association between comorbidities emerged across the three groups (Supplementary Table 4).

In the sensitivity analysis performed on 387 participants with CM (61 RefM, 184 ResM, 142 NRNRM), there was a significant difference across the three groups for depression, anxiety, bipolar and other psychiatric disorders, cerebrovascular diseases, trigger points, asthma, rhinitis and thyroiditis (Fig. 3). In all those cases, the RefM group had the highest prevalence of comorbidities, followed by the ResM and NRNRM groups.

Discussion

One of the aims of the REFINE study was to field test the EHF definitions of RefM and ResM, marking the first consensus to differentiate these two conditions. Individuals with ResM have a challenging condition that may still respond to effective migraine-specific preventive treatments, while those with RefM might host a dysfunction in brain circuits that favor resistance to any known preventive treatment [22]. In our study, the differing burden of comorbidities between RefM and ResM supports the clinical relevance of this distinction.

Referring to specific comorbidities, we found that psychiatric conditions were particularly more prevalent in participants with RefM and ResM compared with those with NRNRM. To our knowledge, the association between psychiatric comorbidities and response to preventive migraine treatments has not been systematically assessed. Literature suggests that individuals with psychiatric comorbidities develop a poorer response to treatments such as onabotulinumtoxinA if compared to those without psychiatric comorbidities [23]; The results regarding the effectiveness of migraine-specific treatments, such as monoclonal antibodies targeting the CGRP pathway, are controversial. On one hand, some studies suggest that these treatments are equally effective in individuals with and without psychiatric comorbidities; on the other hand, real-life studies indicate that psychiatric comorbidities, including depression, may predict a poor response to anti-CGRP monoclonal antibodies [19, 24]. Given the high prevalence of psychiatric comorbidities among patients with RefM and ResM, there is a critical need for integrated care approaches that address both psychiatric symptoms and migraine simultaneously. Such multidisciplinary strategies could potentially improve treatment outcomes especially for individuals with RefM.

Other comorbidities that were more prevalent in participants with RefM and ResM compared with those with

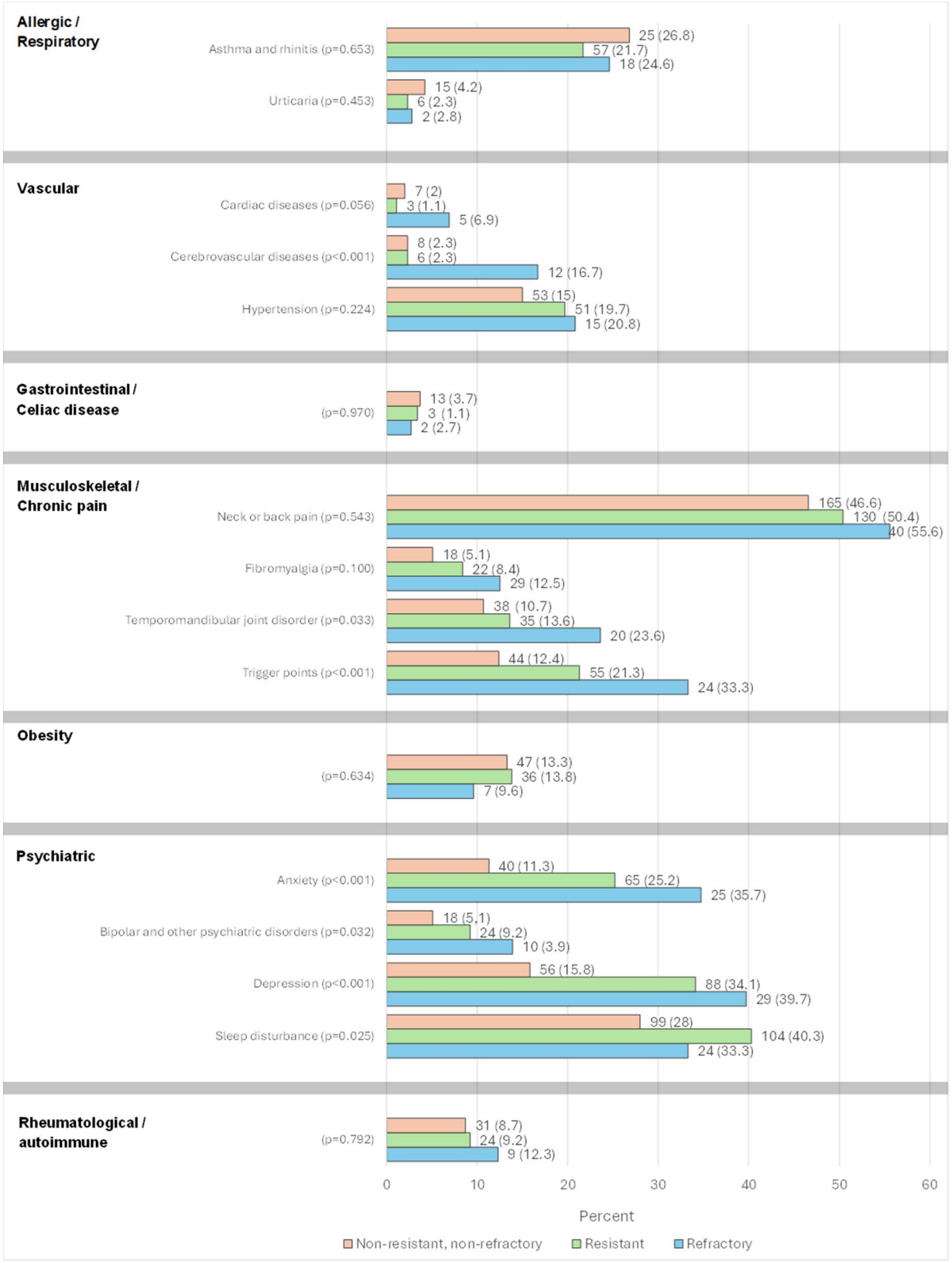

Fig. 1 Prevalence of comorbidities according to the diagnosis of resistant, refractory, or non-resistant migraine in the overall REFINE cohort

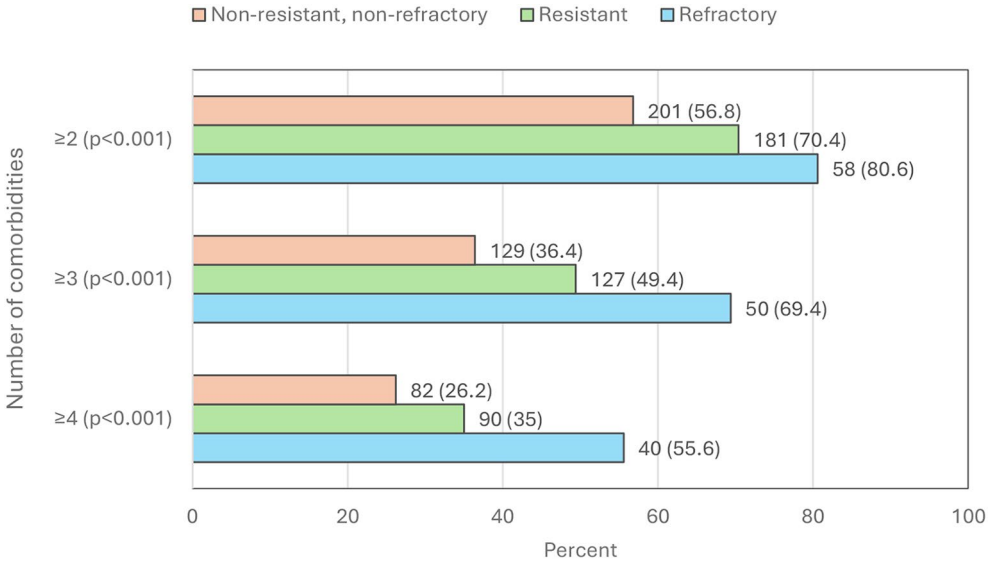

Fig. 2 Prevalence of multiple comorbidities

NRNRM included cerebrovascular diseases, the presence of trigger points, TMJ disorders, and thyroiditis. The relationship between migraine and the presence of myofascial trigger points is controversial [25, 26]. Their presence can contribute to increased muscle tension and pain, which may interfere with the efficacy of standard migraine preventive treatments. Similarly, TMJ disorders might be more prevalent in participants with RefM compared with the other participants' groups due to shared neural pathways and central sensitization [27–29]. The trigeminal nerve, involved in both conditions, can exacerbate pain when TMJ disorders are present [30, 31].

The association between RefM and cerebrovascular diseases or thyroiditis has no clear explanation. Both cerebrovascular diseases [32] and thyroid disorders [33, 34] have been found in comorbidity with migraine. However, it has not been assessed to date whether those comorbidities are associated with a decreased response to migraine preventive treatments. It should be noted that the prevalence of individuals with cerebrovascular diseases or thyroiditis was low, which limits the generalizability of our findings.

Even though statistical significance was not observed for all comorbidities, we can still discern a trend indicating that some conditions are more prevalent among individuals who do not respond effectively to pharmacological treatments. It is important to note that many of these conditions, such as autoimmune and rheumatological diseases, fibromyalgia, cardiac disease, hypertension, and neck or back pain, are other forms of chronic pain, which might contribute to their association with resistance to migraine treatment. Specifically, these conditions are more common in individuals with ResM or RefM compared to those with NRNRM.

Our analysis of the prevalence of multiple comorbidities among the three groups provides additional insight into these patterns. We observed that individuals with RefM had a significantly higher frequency of having more than 4 comorbidities (41.6%) compared to those with ResM (24.5%) and NRNRM (14.1%). This difference highlights that individuals with RefM not only experience a greater number of comorbid conditions but also face a more complex clinical picture that could contribute to their refractoriness to treatment. In contrast, while individuals with ResM also showed a higher prevalence of multiple comorbidities compared to NRNRM, their comorbidity burden was less pronounced than in the RefM group.

Two of our findings deserve particular attention. Firstly, we noted a trend in the prevalence of comorbidities, which was highest in participants with RefM, followed by those with ResM and by those with NRNRM. Secondly, we found that even after selecting the population with CM, many differences among RefM, ResM, and NRNRM persisted.

The gradient or continuum in the prevalence of comorbidities – maximum in the RefM group, intermediate in the ResM group, and minimum in the NRNRM group – suggests that ResM might be considered as an intermediate stage between NRNRM and RefM. The progression from NRMRM to ResM and then to RefM might reflect not only an increasing difficulty in achieving treatment efficacy, but also a corresponding increase in the number and/or severity of associated comorbidities. This gradient emphasizes the need for differentiated clinical strategies that address both the response to treatment and comorbidities for these different groups of individuals. The observed continuum might indicate distinct underlying

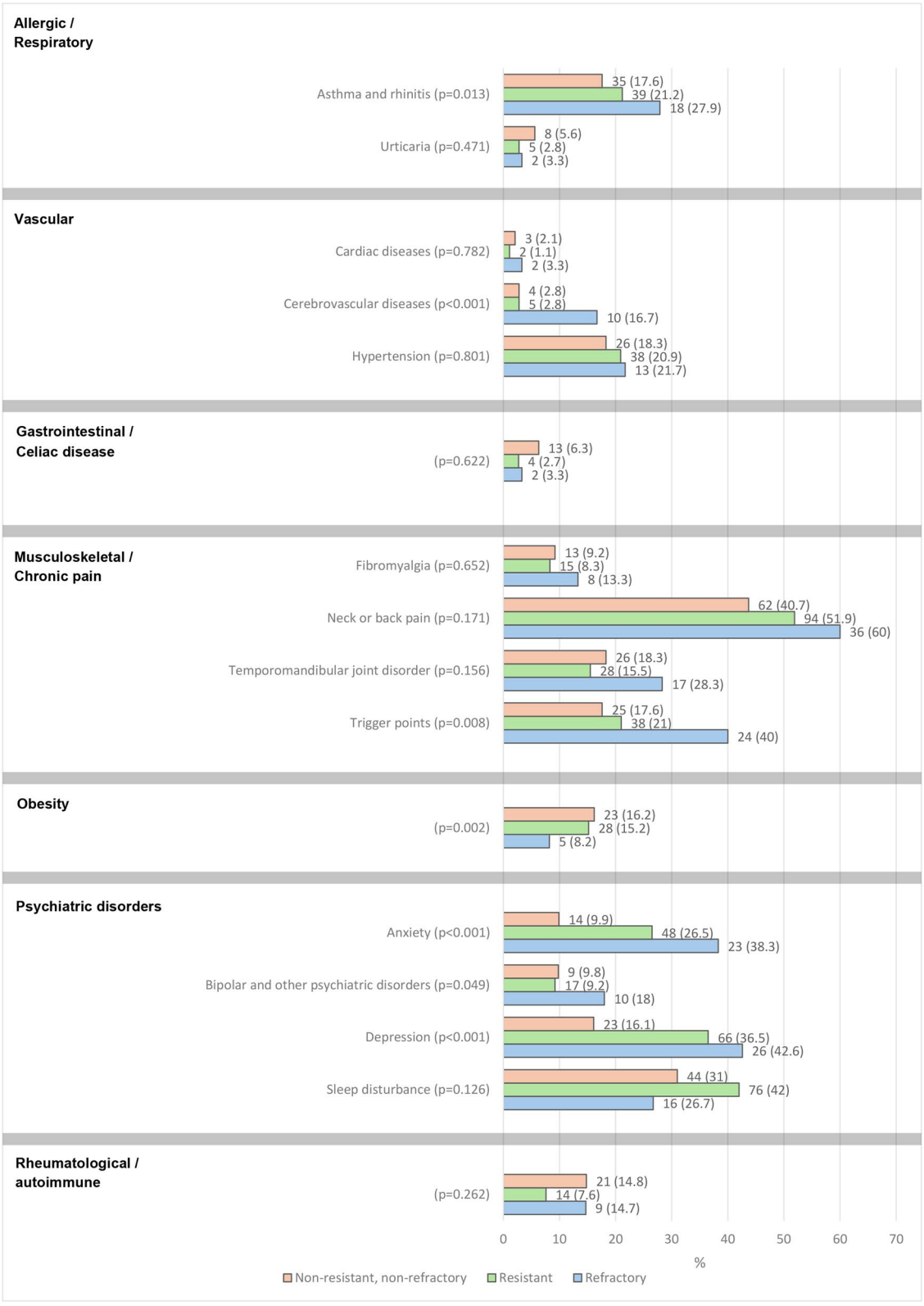

Fig. 3 Prevalence of comorbidities according to the diagnosis of resistant, refractory, or non-resistant migraine in the subset of participants with chronic migraine

pathophysiological mechanisms or represent different stages in the disease progression from NRNRM to ResM and RefM. Understanding the biological basis of this gradient could inform the development of personalized treatment strategies that target specific pathophysiological processes at different stages of disease progression.

Referring to the second major finding of our study, we noted a clear distinction between chronicity and resistance – or refractoriness – to preventive treatments. Several comorbidities, particularly psychiatric conditions, are associated with the progression of migraine from episodic to chronic [35–37]. A previous cross-sectional study performed on 194 individuals with CM showed a high prevalence of comorbidities and especially mental (34%), circulatory (18%), and endocrine conditions (13%), with 32% of individuals reporting multiple comorbidities [38]. In line with those results, our sensitivity analysis performed in individuals with CM found a prevalence of 57.8% for psychiatric comorbidities, 21.9% for vascular comorbidities, and 14.5% for endocrine conditions, while 71.5% of individuals with CM had multiple comorbidities. However, it is unknown whether those comorbidities are also associated with resistance or refractoriness to preventive treatments. To identify the specific set of comorbidities of individuals with RefM or ResM by avoiding the confounding given by the presence of CM, we conducted a sensitivity analysis considering only participants with CM. In this analysis, the prevalence of psychiatric disorders, cerebrovascular diseases, obesity, trigger points, asthma, rhinitis, and thyroiditis still was most frequent in ReFM followed by ResM and lastly NRNRM. Interestingly, in the sensitivity analysis obesity emerged as a significantly associated factor, particularly more prevalent in the NRNRM group. This finding deserves further exploration as it contrasts with the association between obesity and CM and gives further evidence to the difference between CM and difficult-to-treat migraine [39, 40].

Our data are the first to report the prevalence of comorbidities specifically associated with ResM and RefM. We used data from a large prospective, multicenter study performed in tertiary headache centers among European headache experts. However, the study also has some limitations. Firstly, while we provided a definition of comorbidities to strive for consistency, however there may still be differences in interpretation and application by each clinician, which might limit the reliability of the findings. Additionally, given the multicenter nature of the study, there may be variability in the diagnostic criteria and management approaches used across the different centers. Such variability could potentially influence the study results, introducing heterogeneity in the data. To mitigate this, we standardized the study protocols as much as possible and provided detailed guidelines to ensure consistency across centers. We also adopted very broad definitions of comorbidities which might have led to the loss of diagnostic details especially for sleep disturbances. Secondly, our study only reported baseline cross-sectional data and therefore was not designed to test causal relationships. As a result, we cannot state that the comorbidities significantly associated with RefM or ResM are causal factors in the genesis of resistance or refractoriness to preventive treatments. Thirdly, our analyses did not allow us to identify any pattern or cluster in comorbidities, many of which could be linked to each other especially in participants with multiple comorbidities and identify specific profiles of comorbidities in individuals with ResM or RefM. Fourth, the REFINE study did not collect data on the severity or treatment of migraine comorbidities, which could have influenced their overall impact. Several studies suggest that effective migraine prevention improves psychiatric comorbidities [41–44]; however, to the best of our knowledge, there is no study proving that the treatment of comorbidities improves migraine. Besides, there is poor and conflicting evidence on the relationship between comorbidities such as the psychiatric ones and response to migraine prevention [23, 45]. Fifth, although we could perform a sensitivity analysis to rule out the influence of CM on our population, we could not assess the impact of other potential confounders on migraine comorbidities, such as age, sex, or medication overuse. A subgroup analysis in individuals with episodic migraine was not feasible due to the too low number of participants with RefM who were episodic. Finally, since this study was performed in tertiary headache centers, we cannot draw conclusions that can be extended to the general population, which would require a population-based study design.

Conclusions

Our data showed that RefM and ResM have a different prevalence of some comorbidities. Therefore, although needing confirmation in larger cohort studies, our findings indicate that the definition of RefM and ResM as two distinct clinical entities is reasonable. NRNRM, RefM, and ResM are on a continuum of increasing prevalence of several comorbidities, especially the psychiatric ones. Future research should focus on elucidating the underlying mechanisms that connect comorbidities with ResM or RefM. Understanding these mechanisms could potentially guide the development of targeted therapeutic approaches – both pharmacological and non-pharmacological – that consider the high disease burden and the complexity of managing multiple pharmacological treatments for both migraine and associated comorbidities.

Abbreviations

NRNRM	Non-Resistant and Non-Refractory Migraine
ResM	Resistant Migraine
RefM	Refractory Migraine

EHF	European Headache Federation
CM	Chronic Migraine
e-CRF	electronic Case Report Form
IQRs	Interquartile Ranges
TMJ disorders	Temporomandibular Joint Disorders
CGRP	Calcitonin Gene Related Peptide
HADS	Hospital Anxiety and Depression Scale
HIT	Headache Impact Test
MIDAS	Migraine Disability Assessment Test
ISI	Insomnia Severity Index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-024-01910-3.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions
SS, VC, and ZK conceived the study and supervised the project. RO and CR drafted the initial manuscript. CR, VC, AO, SA, OŠ, JP, WWG, LA, GN, DBN, AMV, MG, JV, GI, SB, and MC, collected the data. VC, AO, SA, MB, OŠ, RG, CL, JP, PM, WWG, IPM, DM, LA, GN, AO, DBN, PPR, AMV, MPP, MG, KR, JV, MSR, FV, GI, MW, SB, MC, ZK, SS, reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
P.M. serves as the Editor-in-Chief of *The Journal of Headache and Pain*.

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