IPBBB-24-19954

The Impact of Psychological Treatment on Catastrophization and Pharmacological Response in Chronic Migraine: A Single-Center Experience

Federica Nicoletta Sepe[1*], **Claudia Lanni**[2], **Daniele Michelis**[2] **and Giacomo Lancia**[3]
[1]Department of Emergency Neurology and Stroke Unit, IRCCS C. Mondino Foundation, Pavia, Italy
[2]Department of Neurology, Universitaria SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[3]Department of Basic and Applied Sciences for Engineering (SBAI), Sapienza University, Rome, Italy
Corresponding author: Federica Nicoletta Sepe, Department of Emergency Neurology and Stroke Unit, IRCCS C. Mondino Foundation, Pavia, Italy, E-mail: federica.sepe@mondino.it
Received date: November 14, 2024, Manuscript No. IPBBB-24-19954; **Editor assigned date:** November 18, 2024, PreQC No. IPBBB-24-19954 (PQ); **Reviewed date:** December 02, 2024, QC No. IPBBB-24-19954; **Revised date:** December 09, 2024, Manuscript No. IPBBB-24-19954 (R); **Published date:** December 16, 2024, DOI: 10.36648/2347-5447.12.4.64
Citation: Sepe FN, Lanni C, Michekis D, Lancia G (2024) The Impact of Psychological Treatment on Catastrophization and Pharmacological Response in Chronic Migraine: A Single-Center Experience. Br Biomed Bull Vol.12 No.4: 64.

Supplementary Data

Spearman's test

We utilized Spearman's test [1,2] to investigate the correlation between catastrophization (measured with the Pain Catastrophizing Scale (PCS)) and the Migraine Disability Assessment Score questionnaire (MIDAS), Headache Impact Test (HIT6) and Beck's Inventory Scale (BDI II) scales specifically, we studied correlations at the time T0 (starting of antibody treatment), T1 (3 months later) and T2 (six months later).

Moreover, using the same approach, we studied the correlation level between the PCS subscales helpness, magnification and rumination and the other scales mentioned above (*i.e.,* MIDAS, HIT6 and BDI II). We also considered the correlation levels between the scales utilized .

The significance level α was set to 5%.

However, the simultaneous comparison of tests required adjusting the significance level to avoid the risk of a Type I error.

Thus, we utilized the Bonferroni correct *i.e.*, with n the number of tests involved.

Note that we are interested in testing correlation for three couples of variables (*i.e.*, PCS *vs*. MIDAS, PCS *vs*. HIT6 and PCS *vs*. BDI II) along three distinct time points (*i.e.*, T0, T1 and T2); so we have n=9.

As a result, the adjusted significance level is α_0=0.0055.

For completeness, we report in **Figures 1-3** the complete matrixes of Spearman's coefficients for each variable in our possession along with the p-values matrix; each matrix shows correlation levels at one of the three time-points T0, T1 and T2.

The descriptive statistics of the scale scores are shown in **Supplementary Table 1**.

Supplementary Table 1: Descriptive statistics with standardized moments for PCA, MIDAS, HIT6 and BDI II, at the times T0, T1 and T2.

	Mean	Variance	Skewness	Kurtosis	Tailing
PCS T0	30	97	-0.58	3.75	-6.66
PCS T1	20	49	0.11	1.95	0.38
PCS T2	15	44	0.19	2.94	1.81
HIT6 T0	65	21	0.45	2.55	2.96
HIT6 T1	55	93	-0.43	2.26	-2.33
HIT6 T2	54	110	-0.23	2.89	-0.63
MIDAS T0	67	1135	0.79	3.43	6.29
MIDAS T1	29	349	2.81	2.81	2.38
MIDAS T2	26	557	3.42	3.42	9.11
BDI II T0	20	92	0.38	2.62	2.34
BDI II T1	14	118	1.05	3.16	5.81
BDI II T2	11	75	1.38	7.48	23.91

Wilcoxon's test

We employed Wilcoxon's signed-rank test [3,4] to assess significant differences in scale scores between T0 and subsequent time points, namely, one and T2.

The scales considered are the same as those utilized in the section above (*i.e.,* PCS, MIDAS, HIT6 and BDI II).

Specifically, we conducted one-tailed tests for each pain scale to test the null hypothesis that no significant change occurred in scale scores at the times T1 and T2 compared to T0.

The alternative hypothesis selected was a decrease in scale scores at T1 and T2 compared to T0 (*i.e.,* T1-T0<0 as well as T2-T0<0).

Note that we are interested in testing four variables (*i.e.*, PCS, MIDAS, HIT6 and BDI II) along two intervals of time (*i.e.*, (T0,T1) and (T0,T2),); so, we consider eight tests simultaneously.

As a result, the significance level α=0.05 is then adjusted to through the Bonferroni correctionb**(Supplementary Tables 2-4).**

Supplementary Table 2: Demographic and clinical background details encompassing the entire patient cohort at T0.

Sex	Age	Erenumab	Fremanezumab	Galcanezumab	MIDAS (T0)	HIT6 (T0)	BDI II (T0)	PCS (T0)	Helpness (T0)	Magnification (T0)	Rumination (T0)
F	51	-	X	-	87	72	18	28	7	7	14
F	26	-	X	-	75	72	23	42	22	2	18
F	74	-	X	-	90	76	27	39	17	2	20
F	59	-	X	-	63	71	12	42	18	4	20
F	21	-	X	-	160	65	30	33	15	2	16
F	47	-	X	-	76	44	10	26	8	0	18
F	59	X	-	-	68	60	14	23	11	2	10
F	52	X	-	-	57	63	11	22	7	2	13
F	46	X	-	-	119	68	39	26	12	0	14
F	57	X	-	-	69	72	12	43	21	2	20
F	42	X	-	-	97	67	17	22	8	0	14
M	67	X	-	-	30	63	23	32	12	0	20
F	65	X	-	-	12	60	3	24	14	2	8
F	59	-	-	X	56	67	22	39	17	5	17
M	52	-	-	X	56	64	9	26	9	6	11
F	36	-	-	X	26	62	20	36	18	0	18
F	60	-	-	X	105	70	25	45	23	3	19
M	47	-	-	X	52	63	21	23	13	1	9
F	53	-	-	X	31	64	6	26	10	4	12
F	69	-	-	X	32	68	21	27	10	5	15
F	23	-	-	X	108	76	14	38	21	0	17
F	63	-	-	X	60	59	4	4	2	0	2
M	56	-	-	X	12	60	15	30	14	0	16
F	49	-	-	X	60	68	38	45	21	19	5
F	48	-	-	X	36	68	12	31	15	0	16

Supplementary Table 3: Demographic and clinical background details encompassing the entire patient cohort at T1.

Sex	Age	Erenumab	Fremanezumab	Galcanezumab	MIDAS (T1)	HIT6 (T1)	BDI II (T1)	PCS (T1)	Helpness (T1)	Magnification (T1)	Rumination (T1)
F	51	-	X	-	44	67	12	27	11	2	14
F	26	-	X	-	40	44	30	7	1	4	2
F	74	-	X	-	15	67	21	35	16	2	17
F	59	-	X	-	-	-	-	-	-	-	-

F	21	-	X	-	43	60	7	29	11	0	18
F	47	-	X	-	80	54	8	24	8	0	16
F	59	X	-	-	60	60	6	20	6	1	13
F	52	X	-	-	13	40	1	12	1	0	11
F	46	X	-	-	70	68	38	25	14	0	11
F	57	X	-	-	-	-	-	-	-	-	-
F	42	X	-	-	29	50	15	16	4	2	10
M	67	X	-	-	30	46	11	11	1	1	9
F	65	X	-	-	11	46	9	15	6	2	7
F	59	-	-	X	0	36	6	10	1	0	9
M	52	-	-	X	10	52	3	8	2	1	5
F	36	-	-	X	12	63	6	35	17	0	18
F	60	-	-	X	35	58	15	27	9	0	18
M	47	-	-	X	42	62	14	19	9	1	9
F	53	-	-	X	15	56	3	14	3	2	9
F	69	-	-	X	-	-	-	-	-	-	-
F	23	-	-	X	-	-	-	-	-	-	-
F	63	-	-	X	7	49	9	5	5	0	0
M	56	-	-	X	40	55	19	16	2	2	12
F	49	-	-	X	23	57	37	33	12	6	15
F	48	-	-	X	41	69	13	31	14	1	16

Supplementary Table 4: Demographic and clinical background details encompassing the entire patient cohort at T2.

Sex	**Age**	**Erenumab**	**Fremanezumab**	**Galcanezumab**	**MIDAS (T2)**	**HIT6 (T2)**	**BDI II (T2)**	**PCS (T2)**	**Helplessness (T2)**	**Magnification (T2)**	**Rumination (T2)**
F	51	-	X	-	30	73	11	24	6	4	14
F	26	-	X	-	18	62	9	31	15	0	16
F	74	-	X	-	34	57	15	17	3	2	12
F	59	-	X	-	-	-	-	-	-	-	-
F	21	-	X	-	58	59	4	22	9	0	13
F	47	-	X	-							
F	59	X	-	-	30	62	13	18	6	2	10
F	52	X	-	-	16	57	6	15	3	0	12
F	46	X	-	-	29	56	40	13	3	1	9
F	57	X	-	-	-	-	-	-	-	-	-
F	42	X	-	-	9	36	6	3	0	1	2
M	67	X	-	-	12	36	11	8	0	1	7

F	65	X	-	-							
F	59	-	-	X	0	40	13	10	3	2	5
M	52	-	-	X	4	40	1	10	2	1	7
F	36	-	-	X	6	54	10	15	6	0	9
F	60	-	-	X	12	48	11	8	0	0	8
M	47	-	-	X	62	62	12	20	9	2	9
F	53	-	-	X	10	54	1	14	5	1	8
F	69	-	-	X	-	-	-	-	-	-	-
F	23	-	-	X	-	-	-	-	-	-	-
F	63	-	-	X	90	60	4	17	9	0	8
M	56	-	-	X	50	70	19	23	9	2	12
F	49	-	-	X	22	50	19	20	6	4	10
F	48	-	-	X	10	51	8	15	10	5	0

Jaccard index

The Jaccard Index [5] was employed to quantify the proportion of patients who exhibited both severe catastrophization and severe migraine-induced disability compared to those who did not. To assess this relationship, we defined a subgroup of patients characterized by severe catastrophization (PCS>30) and severe headache-related disability (HIT-6>50, MIDAS>11). Thus, our primary goal was to determine whether patients prone to catastrophizing also experience severe disability due to migraines and *vice versa*. We assessed the Jaccard Index across the entire population and specific subpopulations derived through a stratification process. Stratification was performed based on either the antibody treatment received at the time T0 or by verifying the presence of comorbid depression (BDI II>13, minimal depression). Consider the following example to provide a clearer background about the Jaccard Index. Let n denote the generic patient. Let us define $y^{(n)}_{PCS}$ as a dichotomous variable that takes the value 1 if the patient's PCS score is >30 and 0 otherwise. Similarly, let $y^{(n)}_{MIDAS.}$ Be a dichotomous variable that takes the value 1 if the patient's MIDAS score is >11 and $y^{(n)}_{HIT6}$ takes the value one if the patient's HIT-6 score exceeds 50.

Also, let's consider the sets

the $Y_{PCS}=\{y^{(1)}_{PCS},...,y_{(N)PCS}\}$; $Y_{MIDAS}=\{y^{(1)}_{MIDAS},...,y^{(N)}_{MIDAS}\}$; $Y_{HIT6}=\{y^{(1)}_{HIT6},...,y^{(N)}_{HIT6}\}$.

We denoted by superscript one patient within a generic set containing N individuals.

The Jaccard index for two sets A and B of binary items is defined as,

$$J(A,B)=\frac{(|A\cap B|)}{(|A\cup B|)}$$

The Jaccard index measures similarity between binary sample sets, defined as the number of items with equal binary labels over the number of items considered.

Therefore, $J(Y_{PCS}, Y_{MIDAS})$ informs about the percentage of patients who show either PCS>30 and MIDAS>11 or PCS<30 and MIDAS<11.

For both T0 and T2, we evaluated $J(Y_{PCS}, Y_{MIDAS})$, $J(Y_{PCS}, Y_{HIT6})$ and $J(Y_{HIT6}, Y_{MIDAS})$

Results are shown in **Supplementary Tables 5 and 6**.

Supplementary Table 5: Average Jaccard scores at the time T0 for PCS, HIT6 and MIDAS. Each column reports average association indexes for each stratification (*i.e.*, antibody or binarized Beck's score at T0.

	No stratification	Erenumab	Fremanezumab	Galcanezumab	BDI II score (T0)
MIDAS-HIT6	0.94	0.99	0.99	0.99	0.93
MIDAS-PCS	0.47	0.21	0.75	0.51	0.57
HIT6-PCS	0.47	0.21	0.75	0.51	0.57

Supplementary Table 6: Average Jaccard scores at the time T2 for PCS, HIT6 and MIDAS. Each column reports average association indexes for each stratification (*i.e.,* antibody or binarized Beck's score at T0.

	No stratification	Erenumab	Fremanezumab	Galcanezumab	BDI II score (T0)
MIDAS-HIT6	0.52	0.61	0.99	0.03	0.56
MIDAS-PCS	0.05	0.01	0.25	0.01	0.05
HIT6-PCS	0.47	0.01	0.25	0.51	0.05

Logit-based approach

Using a logit approach involves modeling the relationship between patients' quality of life at T2 and their baseline information at.

The logistic regression model is typically used when the outcome variable is binary or categorical. In this case, the outcome variable Y is defined based on the relative reduction of MIDAS by more than 50% between T0 and T2.

This can be represented as,

$$\text{Y=1 if } \frac{\text{MIDAS (T0)-MIDAS (T2)}}{\text{MIDAS (T0)}} > 0.5; \text{Y=0 otherwise}$$

Here, MIDAS (T0) and MIDAS (T2) denote the MIDAS scores at baseline T0 and follow-up T2, respectively.

Permutation Importance [6] is a technique used to identify the most impactful features in a predictive model. It works by evaluating the change in model performance (*e.g.,* accuracy, AUC) when the values of a feature are randomly permuted while keeping other features unchanged. The decrease in model performance after permutation indicates the importance of that feature in predicting the outcome. The logit model is a regression analysis used to predict the probability of a binary outcome based on one or more predictor variables.

In practice, the probability that patients reduce significantly 50% the value of MIDAS is given,

$$P(Y=1) = \frac{1}{1+\exp(-\beta o - \beta 1 X 1 - \ldots - \beta p Xp)};$$

where β_0 is the intercept, $\beta_1,\ldots,\beta_p$ are the coefficients for predictors $X_1,\ldots,X_p$.

We used to a 250-repeat 4-fold stratified cross-validator to evaluate the Area Under the Curve (AUROC) and Brier's Score (BS) to assess the model's effectiveness. When utilizing the permutation importance method, we determined the resilience of each covariate by assigning importance scores based on the average difference of AUC just before and after permutating a covariate. Note that with the term 250-repeated 4-fold stratified cross-validation approach, we refer to the process we utilized to validate the model. It consists of repeating 250 times a 4-fold split into training and test datasets; usually, 3 folds are utilized to train the model, while the leftover is involved in the validation process. The model is therefore trained and tested through 250 different random configurations derived from the sample population. This method ensured robust assessment and minimized overfitting by repeatedly splitting the data into training and testing sets. To determine the importance of each covariate, we used the permutation importance method. This involved calculating the importance scores by measuring the average change in AUC before and after permuting each covariate see **Figure 4**. This approach allowed us to assess the resilience and significance of each covariate in predicting the outcome.

Sample size

The formulas provided by [7] represent the key to determining the required sample size for inference based on Spearman's test. To apply this method, it is required to specify the punctual values of both the null and alternative hypotheses. Therefore, we assumed to null hypothesis to be H_0:r_0=0 and the alternative hypothesis H_1:r_1=0.65. That is, we want to investigate no correlation (r_0=0) against a moderate (or even stronger) correlation, *i.e.*, r_1=0.65. Thus, the sample size n is given by:

$$n = b + c^2 \left[\frac{z_{\alpha/2} + z_{1-\varphi}}{\Xi(r_0) - \Xi(r_1)}\right]^2$$

where b and c are constants taking values 3 and 1, respectively; α is the significance level and β the test's power; we used Ξ(.) to denote the hyperbolic arctangent.

Note that a regular choice of α=0.10 needs to be adjusted to avoid incurring an increase of Type I errors due to multiple testing. To achieve this, we utilized the Bonferroni correction, so we adopted α=0.011. We also chose a high-power test to exclude the presence of Type II error, so we opted for φ=0.8. We considered the possibility of dropouts during the phase of data acquisition. Thus, we adjusted the sample size through the following formula,

$$n = \frac{1}{1-\delta}$$

where δ denotes the dropout rate; we opted for δ=0.10

Applying both the formulae expressed above, we obtained a population size of 25.

Randomization

We implemented a simple randomization [8] scheme to assign antibody therapy to participants. This method ensured that each participant had an equal probability of receiving the antibody therapy, thereby minimizing selection bias and providing a balanced distribution of treatments across the study groups.

As outlined in the main manuscript, Erenumab was assigned to 6 patients, Fremanezumab to 7 patients and Galcanezumab to 12 patients. Despite assigning Galcanezumab to most patients, the number of doses assigned was equally likely, according to the chi-squared test. We aimed to test the null hypothesis that the antibodies were assigned to patients with equal probability. As described, we utilized a two-tailed chi-squared test with two degrees of freedom, setting a significance level of $\alpha=0.05$. The test yielded a χ^2 statistic of 1.625 and a p-value of 0.4437. Given these results, we do not have sufficient evidence to reject the null hypothesis, indicating that the distribution of antibody assignments is consistent with equal probability.

Scales

Migraine Disability Assessment Test (MIDAS) measures the headache-related disability within the last 3 months in three areas of life: Work/school, household chores and family/social/leisure activities. The MIDAS score is formed by summing the items and ranges from 0 to 270. The disability can be categorized into four grades: (I) little or no disability (MIDAS score 0–5), (II) mild (6–10), (III) moderate (11–20) and (IV) severe disability (>21) [9].

Headache Impact Test-6 (HIT-6) is a six-item self-reported questionnaire used to assess headache-related disability. It assesses headaches' impact on psychological, cognitive, occupational and social functioning over the previous four weeks. Scores range from 36 to 78 and scores above 60 indicate that headache seriously impacts functioning [10].

The Pain Catastrophizing Scale (PCS) was used to measure pain-related catastrophic thoughts. It consists of three subscales: Helplessness (Qs 1-5 and 12), magnification (Qs 6,7 and 13) and rumination (Qs 8-11). Evaluations (0=not at all to 4=always) are made using a five-point Likert scale. The PCS is rated from 0 to 52 points and a higher score corresponds to a higher level of pain-related catastrophic thoughts [11].

The Beck Depression Inventory-II (BDI II) is a 21-item assessment of depression's severity. Each item is graded between 0 and 3 on a four-point Likert-like scale. Higher scores indicate more severe depressive symptoms [12].

Reference

1. Spearman C (1961) The proof and measurement of association between two things. Am J Psychol 15: 72-101. [Crossref] [Google Scholar]
2. Dunn OJ (1961) Multiple comparisons among means. J Am Stat Assoc 56: 52–64. [Crossref] [Google Scholar]
3. Conover WJ (1999) Practical nonparametric statistics. New York John Wiley & Sons United States 350. [Google Scholar]
4. McDonald JH (2014) Wilcoxon signed-rank test. Handbook of Biological Statistics 186-189.

5. Chung NC, Miasojedow B, Startek M, Gambin A (2019) Jaccard/Tanimoto similarity test and estimation methods for biological presence-absence data. BMC Bioinformatics 20: 644. [Crossref] [Google Scholar] [Indexed]
6. Breiman L (2001) Random forests. Machine Learning 45: 5-32. [Google Scholar]
7. May JO, Looney SW (2020) Sample size charts for Spearman and Kendall coefficients. J Biom Biostat 11: 1-7. [Google Scholar]
8. Altman DG, Bland JM (1999) Treatment allocation in controlled trials: Why randomise? BMJ 318: 1209. [Crossref] [Google Scholar] [Indexed]
9. Stewart WF, Lipton RB, Dowson AJ, Sawyer J (2001) Development and testing of the Migraine Disability Assessment (MIDAS) questionnaire to assess headache-related disability. Neurology 56: S20-8. [Crossref] [Google Scholar] [Indexed]
10. Rendas-Baum R, Yang M, Varon SF, Bloudek LM, DeGryse RE, et al. (2014) Validation of the Headache Impact Test (HIT-6) in patients with chronic migraine. Health Qual Life Outcomes 12: 117. [Crossref] [Google Scholar] [Indexed]
11. Darnall BD, Sturgeon JA, Cook KF, Taub CJ, Roy A, et al. (2017) Development and validation of a daily pain catastrophizing scale. J Pain 18: 1139-1149. [Crossref] [Google Scholar] [Indexed]
12. Schotte CK, Maes M, Cluydts R, De Doncker D, Cosyns P (1997) Construct validity of the beck depression inventory in a depressive population. J Affect Disord 46: 115-125. [Crossref] [Google Scholar] [Indexed]