

# Screening for bipolar disorder among migraineurs: the impact of migraine–bipolar disorder comorbidity on disease characteristics

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**Purpose:** The aim of this study was to evaluate the prevalence of comorbid bipolar disorder (BD) among migraineurs and the impact of migraine–BD comorbidity on disease characteristics.

**Patients and methods:** A total of 120 adult patients diagnosed with migraine at a single tertiary care center were included in this cross-sectional study. Data on sociodemographic and migraine-related characteristics, family history of psychiatric diseases, comorbid psychiatric diseases, and first-episode characteristics were recorded. Mood Disorders Diagnosis and Patient Registration Form (SCIP-TURK), Mood Disorder Questionnaire (MDQ), and Hypomania Checklist-32-Revised (HCL-32-R) were applied to all patients by experienced clinicians, and clinical diagnoses were confirmed using Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I). Migraine Disability Assessment Scale (MIDAS) was used to evaluate the headache-related disability. Study parameters were compared between migraineurs with and without comorbid BD.

**Results:** The diagnosis of comorbid BD was confirmed in 19.2% of migraineurs. A significantly higher percentage of patients with comorbid BD than those without comorbid BD had family history of BD (39.1% vs 6.2%,  $P < 0.001$ ), suicide attempt (30.4% vs 5.2%,  $P < 0.001$ ), and physical abuse (52.2% vs 26.8%,  $P = 0.019$ ). MIDAS scores were significantly higher (50.6 [43.2] vs 33.8 [42.7],  $P = 0.0422$ ) in migraineurs with comorbid BD than in those without comorbid BD. Multivariate logistic regression model revealed that a positive family history of type I BD (odds ratio [OR], 14.42; 95% confidence interval [CI], 2.94–70.73;  $P = 0.001$ ) and MIDAS scores  $> 30$  (OR, 3.69; 95% CI, 1.12–12.19;  $P = 0.032$ ) were associated with 14.42 times and 3.69 times increased likelihood of BD, respectively.

**Conclusion:** Our findings revealed comorbid BD in a remarkable percentage of migraineurs and a higher likelihood of having BD in case of a positive family history of type I BD and MIDAS scores  $> 30$ . Comorbid BD was associated with a higher rate for a family history of BD, suicide attempt, and childhood physical abuse as well as aggravated migraine-related disability among migraineurs. Migraineurs with and without comorbid BD showed similar sociodemographic and migraine disease characteristics as well as similar high rates for comorbid anxiety and first-episode depression.

**Keywords:** migraine, bipolar disorder, comorbidity, suicide attempt, MIDAS, depression

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## Introduction

Migraine is a common episodic incapacitating neurological disorder and a significant public health problem characterized by unilateral throbbing headaches accompanied often with nausea, phonophobia, and/or photophobia.<sup>1–3</sup> Migraine is frequently associated with several psychiatric comorbidities, while timely recognition of these comorbidities

is important given their adverse effects on migraine course along with the similar impact of poorly treated migraine on the outcome of comorbid psychiatric illness.<sup>4–7</sup>

Bipolar disorder (BD) is a chronic mood disorder that affects 2%–4% of the general population and is characterized by cyclic occurrence of elevated (manic: type I or hypomanic: type II) and depressed mood states.<sup>8,9</sup> While most of the previous studies focused on the comorbidity of migraine with depression or anxiety disorders, recent epidemiologic and clinical evidence indicates the possibility of migraine–BD comorbidity with threefold increase in migraine prevalence shown among patients with BDs.<sup>10–14</sup>

Migraine is suggested to have an impact on the clinical course of BD, leading to earlier onset of BD, higher prevalence of comorbid anxiety disorders, and atypical symptoms of depression.<sup>10,12,15,16</sup> However, limited data are available on the prevalence of BD among migraineurs and the impact of BD on the clinical course of migraine disease.<sup>14,17,18</sup>

The present study was therefore designed to evaluate the prevalence of comorbid BD among migraineurs and the impact of migraine–BD comorbidity on disease characteristics.

## Patients and methods

### Study population

A total of 120 adult patients diagnosed with migraine based on the International Classification of Headache Disorders, third revision (ICHD-3; beta) diagnostic criteria (2) upon their admission to the Neurology and Headache Outpatient Clinic at Erenköy Mental and Neurological Diseases Training and Research Hospital, Istanbul were included in this cross-sectional study. Being illiterate; presence of any neurologic disorders other than headache and any disorder that may cause secondary headache including trauma, infection, cerebrovascular disease, glaucoma, sinusitis, tumor, and craniocervical dystonia; past history of sequela from a neurologic disease or head trauma; and presence of dementia or other organic mental disorders, mental retardation, and substance dependence or substance abuse were the exclusion criteria. As shown in the study flowchart (Figure 1), of 580 patients admitted to the outpatient clinic with a complaint of headache between January 2015 and August 2015, 393 patients had primary headache and 175 out of 393 patients had migraine. Of 175 patients with migraine enrolled into the study, 45 patients were excluded due to comorbidity of

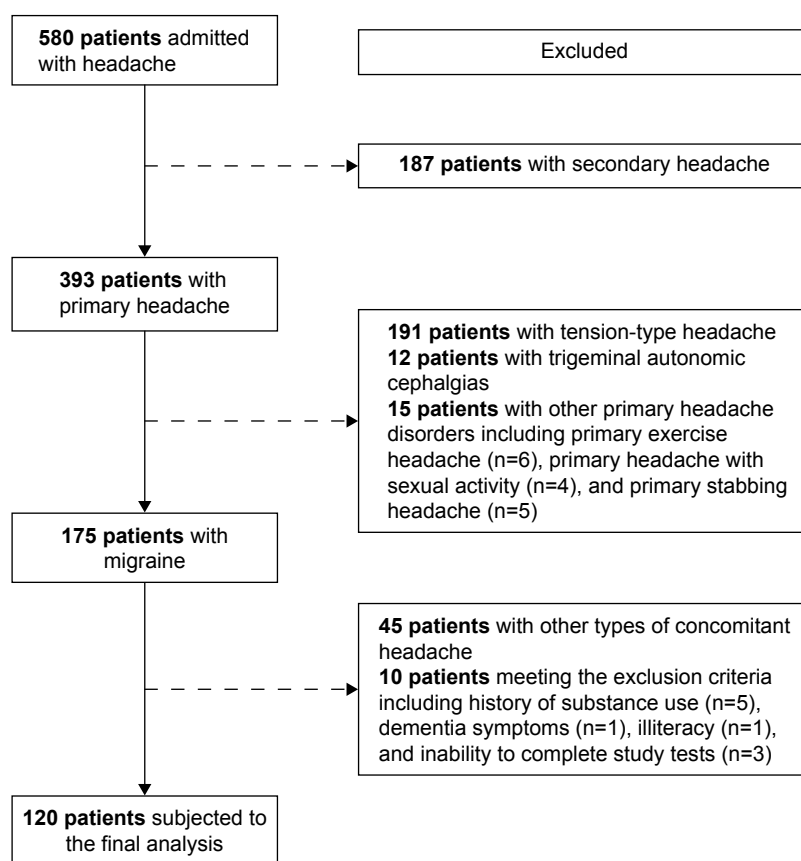


Figure 1 Study flowchart.

other headache types and 10 patients were excluded since they met the exclusion criteria, including history of substance use (n=5), dementia symptoms (n=1), illiteracy (n=1), and inability to complete study tests (n=3). Accordingly, 120 patients with migraine were subjected to the final analysis.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the ethics committee of Erenköy Mental and Neurological Diseases Training and Research Hospital.

## Assessments

Data on sociodemographic characteristics (age, gender, marital status, educational level, employment, socioeconomic status), caffeine intake, smoking and alcohol consumption, migraine characteristics (disease duration [months], episode frequency, episode duration [hours], severity score, aura, prodromal symptoms, change in side, triggering factors, accompaniments), family history of psychiatric diseases, comorbid psychiatric diseases, and first-episode characteristics were recorded in each patient. Mood Disorders Diagnosis and Patient Registration Form (SCIP-TURK), Mood Disorder Questionnaire (MDQ), and Hypomania Checklist-32-Revised (HCL-32-R) were applied to all patients by experienced physicians, and clinical diagnoses were confirmed by the same psychiatry specialist in all patients via Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I). Detailed information about characteristics of the first episode was obtained retrospectively during assessment with questionnaires and clinical interview in each patient. Migraine Disability Assessment Scale (MIDAS) was used to evaluate the headache-related disability. Study parameters were compared between migraineurs with and without comorbid BD. In addition, estimators of having bipolar disease were analyzed via univariate and mutually adjusted multivariate logistic regression analyses.

## SCID-I

The SCID-I is a semi-structured interview developed by First et al<sup>19</sup> in 1997, comprising six structured modules to diagnose both current and lifetime Axis-I psychiatric disorders based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria along with the duration of disorder, family history, and the presence of physical diseases. The Turkish adaptation and reliability of SCID-I was performed by Ozkurkcuoglu et al<sup>20</sup> in 1999.

## Diagnostic and Monitoring Form for Mood Disorders (SCIP-TURK)

SCIP-TURK is a 111-item semi-structured scale developed by Ozerdem et al<sup>21</sup> in 2004 and consists of four modules that provide data on patient characteristics (sociodemographic features, medical background, family history, smoking, alcohol, and drug use) and characteristics of BD (age at onset and the type and severity of the first episode [postpartum onset, seasonality, or depression subtype], the number and duration of episodes, suicide attempts, social support and stories of childhood trauma or abuse, and the treatments).

## MDQ

MDQ is a self-report instrument developed by Hirschfeld et al<sup>22</sup> in 2000 to screen lifetime history of manic and/or hypomanic symptoms. MDQ includes 13 yes/no questions mainly derived from *DSM-IV* in the first sub-item, and the second sub-item asks whether several of any reported manic or hypomanic symptoms or behaviors were experienced during the same period of time or associated with functional impairment related. The total score is the sum of overall scores for each item marked as yes (1 point) or no (0 point). The Turkish version of the MDQ has been validated by Konuk et al<sup>23</sup> in 2007, and an optimal cut-off point was reported to be a score of  $\geq 7$  as associated with best scores of sensitivity (0.64) and specificity (0.77).

## HCL-32-R

HCL-32 is an eight-item self-report instrument to screen lifetime history of manic and/or hypomanic symptoms and to identify BD-sensitive individuals. Participants are requested to focus on “the high periods” and to indicate whether specific thoughts or emotions were present during this state. HCL-32 assesses symptoms in greater detail than *DSM-IV*-based structured clinical interview, including questions on general well-being (first two items) and 32 yes/no questions on manic and/or hypomanic symptoms (third item), effect of symptoms on life (fourth item) and other people (fifth item), duration of symptoms (sixth item), and the presence of (seventh item) and days per year (eighth item) with such mood period. The optimal cutoff point for HCL-32 was reported to be a score of  $\geq 14$  for the original form developed by Angst et al<sup>24</sup> in 2005. The Turkish version of HCL-32 was adapted by Vahip et al<sup>25</sup> in 2016, and the optimal cutoff point was reported to be a score of 14/15.

## MIDAS

The MIDAS, a five-question tool to quantitatively evaluate the headache-related disability in terms of the number of

days in the past 3 months and activity limitations due to migraine, was developed by Stewart et al<sup>26</sup> in 2001 and validated and checked for reliability for Turkish by Ertas et al<sup>27</sup> in 2004. The score obtained is graded based on the number of days with >50% loss in productivity as follows: grade I (0–5 days), indicative of little or no disability; grade II (6–10 days), mild disability; grade III (11–20 days), moderate disability; and grade IV (>21 days), severe disability.

## Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 20.0; IBM Corporation, Armonk, NY, USA). Chi-square ( $\chi^2$ ) test and Fisher's exact or Fisher–Holton–Freeman test were used for the comparison of categorical data, while Mann–Whitney *U* test was used for the analysis of numerical data. The estimators of having bipolar disease were evaluated by using univariate logistic regression; the ones with significant effect were evaluated using mutually adjusted multivariate logistic regression. Data were expressed as median (interquartile range [IQR]) and percent (%) where appropriate.  $P < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

The diagnosis of comorbid BD was confirmed in 23 patients (19.2%; in 18 [78.3%] females and 5 [21.7%] males). No significant difference was noted in migraine patients with (median [IQR] age: 38.0 [15.0] years; 78.3% were females) and without (median [IQR] age: 41.0 [15.0] years; 84.5% were females) comorbid BD in terms of demographic characteristics. With no significant difference between patients with versus without comorbid BD, most of the migraineurs were university graduates (52.2% and 43.3%, respectively), employed (60.9% and 50.5%, respectively), and married (52.2% and 67.0%, respectively) subjects with moderate-to-high socioeconomic status (69.6% and 60.8%). The rates for smoking (60.9% vs 49.5%) and alcohol consumption (60.9% vs 46.4%) were also similar among migraine patients with respect to the presence of comorbid BD (Table 1).

### Migraine characteristics

No significant difference was noted among migraineurs with and without comorbid BD in terms of median disease duration (180.0 vs 132.0 months), latest (4.0 vs 3.0 episodes) and previous month (5.0 vs 4.0 episodes) episode frequency, episode duration (10.0 vs 14.0 hours) and severity score (8.0 for each; Table 2).

**Table 1** Characteristics of migraineurs with and without comorbid BD

| Patient characteristics     | Migraineurs    |                   | P-value            |
|-----------------------------|----------------|-------------------|--------------------|
|                             | With BD (n=23) | Without BD (n=97) |                    |
| Age (years), median (IQR)   | 38.0 (15.0)    | 41.0 (15.0)       | 0.377 <sup>a</sup> |
| Gender (female), n (%)      | 18 (78.3)      | 82 (84.5)         | 0.534 <sup>b</sup> |
| Educational status, n (%)   |                |                   |                    |
| Primary school              | 7 (30.4)       | 28 (28.9)         | 0.809 <sup>c</sup> |
| Secondary school            | 4 (17.4)       | 27 (27.8)         |                    |
| University                  | 12 (52.2)      | 42 (43.3)         |                    |
| Employment, n (%)           |                |                   |                    |
| Employed                    | 14 (60.9)      | 49 (50.5)         | 0.371 <sup>c</sup> |
| Unemployed                  | 9 (39.1)       | 48 (49.5)         |                    |
| Marital status, n (%)       |                |                   |                    |
| Married                     | 12 (52.2)      | 65 (67.0)         | 0.182 <sup>c</sup> |
| Single/divorced/widowed     | 11 (47.8)      | 32 (33.0)         |                    |
| Socioeconomic status, n (%) |                |                   |                    |
| Low–moderate                | 7 (30.4)       | 38 (39.2)         | 0.436 <sup>c</sup> |
| Moderate–high               | 16 (69.6)      | 59 (60.8)         |                    |
| Caffeine intake, n (%)      | 7 (30.4)       | 12 (12.4)         | 0.052 <sup>b</sup> |
| Smoking, n (%)              | 14 (60.9)      | 48 (49.5)         | 0.326 <sup>c</sup> |
| Alcohol consumption, n (%)  | 14 (60.9)      | 45 (46.4)         | 0.212 <sup>c</sup> |

**Notes:** <sup>a</sup>Mann–Whitney *U* test. <sup>b</sup>Fisher's exact test. <sup>c</sup> $\chi^2$  test.

**Abbreviations:** BD, bipolar disorder; IQR, interquartile range.

No significant difference was noted in the rate of migraine with aura (73.9% vs 54.6%), presence of aura-related clinical difference (47.8% vs 38.1%), type of aura (visual in 65.2% vs 44.3%), presence (78.3% vs 60.8%) and type (psychic in 52.2% vs 43.3%) of prodromal symptoms, and change in side (69.6% vs 72.2%) with respect to comorbid BD (Table 2).

Emotional stress (100.0% and 93.8%) was the most common triggering factor, while photophobia (100.0% and 93.8%), phonophobia (91.3% and 96.9%), and nausea (95.7% and 88.7%) were the most commonly observed accompaniments similarly in patients with and without BD. Apart from significantly higher rates of alcohol consumption (47.8% vs 23.7%,  $P=0.021$ ) as a trigger and osmophobia (73.9% vs 49.5%,  $P=0.035$ ) as an accompaniment in patients with comorbid BD than in those without comorbid BD, the two groups were similar in terms of migraine triggers and accompaniments (Table 2).

### Past history and comorbid psychiatric diseases

Migraineurs with versus without comorbid BD were similar in terms of family history of psychiatric disease in first-degree relatives (73.9% vs 74.2%), while a significantly higher percentage of patients with comorbid BD than those without co-morbid BD had a family history of BD (39.1% vs 6.2%,  $P < 0.001$ ), type I BD (34.8% vs 4.1%,  $P < 0.001$ ) in particular (Table 3).



**Table 2** Migraine characteristics in migraineurs with and without comorbid BD

| Migraine characteristics         | Migraineurs       |                      | P-value <sup>a</sup>       |
|----------------------------------|-------------------|----------------------|----------------------------|
|                                  | With BD<br>(n=23) | Without<br>BD (n=97) |                            |
|                                  | Median<br>(IQR)   | Median<br>(IQR)      |                            |
| Disease duration (months)        | 180.0 (156.0)     | 132.0 (168.0)        | 0.669                      |
| Episode frequency                |                   |                      |                            |
| Latest                           | 4.0 (5.0)         | 3.0 (4.0)            | 0.973                      |
| Previous month                   | 5.0 (7.0)         | 4.0 (5.0)            | 0.149                      |
| Episode duration (hours)         | 10.0 (18.0)       | 14.0 (44.0)          | 0.486                      |
| Severity score                   | 8.0 (2.0)         | 8.0 (2.0)            | 0.326                      |
|                                  | <b>n (%)</b>      | <b>n (%)</b>         | <b>P-value<sup>b</sup></b> |
| Migraine with aura               | 17 (73.9)         | 53 (54.6)            | 0.092                      |
| Aura-related clinical difference | 11 (47.8)         | 37 (38.1)            | 0.394                      |
| Type of aura                     |                   |                      |                            |
| Visual                           | 15 (65.2)         | 43 (44.3)            | 0.072                      |
| Auditory                         | 5 (21.7)          | 13 (13.4)            | 0.335                      |
| Sensory                          | 1 (4.3)           | 19 (19.6)            | 0.118                      |
| Motor                            | 4 (17.4)          | 12 (12.4)            | 0.506                      |
| Other                            | 1 (4.3)           | 1 (1.0)              | 0.348                      |
| Prodromal symptoms               |                   |                      |                            |
| Any                              | 18 (78.3)         | 59 (60.8)            | 0.117                      |
| Psychic                          | 12 (52.2)         | 42 (43.3)            | 0.442                      |
| Motor                            | 1 (4.3)           | 2 (2.1)              | 0.475                      |
| Gastrointestinal                 | 6 (26.1)          | 18 (18.6)            | 0.399                      |
| Others <sup>c</sup>              | 2 (8.7)           | 16 (16.5)            | 0.520                      |
| Change in side                   | 16 (69.6)         | 70 (72.2)            | 0.804                      |
| Triggering factors               |                   |                      |                            |
| Emotional stress                 | 23 (100.0)        | 91 (93.8)            | 0.594                      |
| Physiologic tiredness            | 19 (82.6)         | 64 (66.0)            | 0.121                      |
| Seasonal alteration              | 19 (82.6)         | 75 (77.3)            | 0.780                      |
| Hunger                           | 18 (78.3)         | 87 (89.7)            | 0.162                      |
| Menstruation                     | 17 (73.9)         | 61 (62.9)            | 0.319                      |
| Alcohol                          | 11 (47.8)         | 23 (23.7)            | <b>0.021</b>               |
| Posture changes                  | 5 (21.7)          | 16 (16.5)            | 0.549                      |
| Others                           | 12 (52.2)         | 55 (56.7)            | 0.694                      |
| Accompaniments                   |                   |                      |                            |
| Nausea                           | 22 (95.7)         | 86 (88.7)            | 0.458                      |
| Vomiting                         | 16 (69.6)         | 62 (63.9)            | 0.610                      |
| Phonophobia                      | 21 (91.3)         | 94 (96.9)            | 0.244                      |
| Photophobia                      | 23 (100.0)        | 91 (93.8)            | 0.594                      |
| Dizziness                        | 21 (91.3)         | 86 (88.7)            | 1.000                      |
| Insomnia                         | 21 (91.3)         | 81 (83.5)            | 0.520                      |
| Vertigo                          | 9 (39.1)          | 32 (33.0)            | 0.577                      |
| Osmophobia                       | 17 (73.9)         | 48 (49.5)            | <b>0.035</b>               |
| Allodynia                        | 19 (82.6)         | 69 (71.1)            | 0.263                      |
| Others                           | 1 (4.3)           | 4 (4.1)              | 1.000                      |

**Notes:** <sup>a</sup>Mann-Whitney U test. <sup>b</sup> $\chi^2$  test and Fisher's exact test. <sup>c</sup>Yawning, chills, polyuria, and somnolence. Values in bold indicate statistical significance ( $P < 0.05$ ).

**Abbreviations:** BD, bipolar disorder; IQR, interquartile range.

Comorbid psychiatric diseases were evident in majority of migraineurs with no significant difference between patients with and without comorbid BD (91.3% vs 81.4%). Anxiety disorder was the most common comorbid psychiatric disorder similarly in migraineurs with and without BD (43.5% and

**Table 3** Psychiatric diseases in migraineurs with and without comorbid BD

| Psychiatric diseases                  | Migraineurs       |                      | P-value          |
|---------------------------------------|-------------------|----------------------|------------------|
|                                       | With BD<br>(n=23) | Without<br>BD (n=97) |                  |
|                                       | n (%)             | n (%)                |                  |
| Family history of psychiatric disease |                   |                      |                  |
| Any relative                          | 18 (78.3)         | 81 (83.5)            | 0.549            |
| First-degree relatives                | 17 (73.9)         | 72 (74.2)            | 0.975            |
| BD                                    | 9 (39.1)          | 6 (6.2)              | <b>&lt;0.001</b> |
| Type I                                | 8 (34.8)          | 4 (4.1)              | <b>&lt;0.001</b> |
| Type II                               | 1 (4.3)           | 2 (2.1)              | 0.475            |
| Unipolar depression                   | 13 (56.5)         | 62 (63.9)            | 0.510            |
| Suicide attempt                       | 2 (8.7)           | 17 (17.5)            | 0.524            |
| Comorbid psychiatric disorder         |                   |                      |                  |
| Any                                   | 21 (91.3)         | 79 (81.4)            | 0.358            |
| Cyclothymia                           | 0 (0.0)           | 0 (0.0)              | 1.000            |
| Dysthymia                             | 0 (0.0)           | 4 (4.1)              | 1.000            |
| Schizophrenia                         | 0 (0.0)           | 0 (0.0)              | 1.000            |
| Panic disorder                        | 4 (17.4)          | 12 (12.4)            | 0.506            |
| Alcohol use disorder                  | 2 (8.7)           | 3 (3.1)              | 0.244            |
| Suicide attempt                       | 7 (30.4)          | 5 (5.2)              | <b>0.002</b>     |
| Eating disorder                       | 1 (4.3)           | 0 (0.0)              | 0.192            |
| Social phobia                         | 2 (8.7)           | 10 (10.3)            | 1.000            |
| Obsessive compulsive disorder         | 4 (17.4)          | 7 (7.2)              | 0.219            |
| Hypochondriasis                       | 1 (4.3)           | 3 (3.1)              | 0.578            |
| Posttraumatic stress disorder         | 2 (8.7)           | 6 (6.2)              | 0.648            |
| Dissociative disorder                 | 4 (17.4)          | 12 (12.4)            | 0.506            |
| Specific phobia                       | 5 (21.7)          | 37 (38.1)            | 0.138            |
| Generalized anxiety disorder          | 0 (0.0)           | 13 (13.4)            | 0.071            |
| Somatoform disorder                   | 0 (0.0)           | 8 (8.2)              | 0.351            |
| Anxiety disorder                      | 10 (43.5)         | 61 (62.9)            | 0.089            |
| History of childhood abuse            |                   |                      |                  |
| Any                                   | 17 (73.9)         | 69 (71.1)            | 0.790            |
| Sexual                                | 4 (17.4)          | 20 (20.6)            | 1.000            |
| Physical                              | 12 (52.2)         | 26 (26.8)            | <b>0.019</b>     |
| Emotional                             | 13 (56.5)         | 64 (66.0)            | 0.395            |
| Legal                                 | 5 (21.7)          | 13 (13.4)            | 0.335            |

**Notes:**  $\chi^2$  test—Fisher's exact test. Values in bold indicate statistical significance ( $P < 0.05$ ).

**Abbreviation:** BD, bipolar disorder.

62.9%), while suicide attempt (30.4% vs 5.2%,  $P=0.002$ ) and history of physical abuse (52.2% vs 26.8%,  $P=0.019$ ) were significantly more common among migraineurs with comorbid BD than in those without comorbid BD (Table 3).

### First-episode characteristics

Apart from a higher prevalence of associated psychotic characteristics (21.7% vs 4.3%,  $P=0.021$ ) and higher likelihood of spontaneous relief (34.8% vs 31.4%,  $P=0.022$ ) in patients with comorbid BD than in those without comorbid BD, no significant difference was noted in first-episode characteristics with respect to comorbid BD among migraineurs. Similarly, in migraineurs with and without comorbid BD, first-episode depression (91.4% and 72.2%, respectively), presence of a life event (87.0% and 94.3%,

respectively), moderate episode severity (52.2% and 51.4%, respectively), and management of episode via use of antidepressants (47.8% and 67.2%, respectively) were the prominent first-episode characteristics (Table 4).

## MDQ, HSL-32-R, and MIDAS scale scores

MDQ and HSL-32-R confirmed the likelihood of comorbid BD in 91.3% and 100.0% of patients with BD, while albeit in a significantly lower percentage of patients, they also revealed positive results in 2.1% ( $P<0.001$ ) and 70.1% ( $P=0.003$ ) of patients without BD, respectively. Median (IQR) MIDAS scores were significantly higher (37.0 [61.0] vs 19.0 [28.0],  $P=0.042$ ) in migraineurs with comorbid BD than in those without comorbid BD (Table 5).

## Univariate and multivariate logistic regression analyses for estimators of having bipolar disease

Univariate analysis revealed caffeine intake ( $P=0.039$ ), alcohol as trigger ( $P=0.025$ ), osmophobia as accompaniment ( $P=0.025$ ), family history of type I BD ( $P<0.001$ ), previous suicide attempt ( $P=0.001$ ), physical abuse in childhood ( $P=0.022$ ), and MIDAS scores  $>30$  ( $P=0.014$ ) to be significantly

**Table 4** First-episode characteristics in migraineurs with and without comorbid BD

| Characteristics            | Migraineurs       |                      | P-value      |
|----------------------------|-------------------|----------------------|--------------|
|                            | With BD<br>(n=23) | Without<br>BD (n=97) |              |
|                            | n (%)             | n (%)                |              |
| First episode              |                   |                      |              |
| Mania                      | 1 (4.3)           | 0 (0.0)              | 0.059        |
| Mixed                      | 1 (4.3)           | 0 (0.0)              |              |
| Depression                 | 21 (91.4)         | 70 (72.1)            |              |
| Presence of a life event   | 20 (87.0)         | 66 (94.3)            | 0.358        |
| Severity of episode        |                   |                      |              |
| Mild                       | 2 (8.7)           | 9 (12.9)             | 0.944        |
| Moderate                   | 12 (52.2)         | 36 (51.4)            |              |
| Severe                     | 9 (39.1)          | 25 (35.7)            |              |
| Associated characteristics |                   |                      |              |
| Postpartum                 | 2 (8.7)           | 4 (5.7)              | 0.635        |
| Catatonic                  | 0 (0.0)           | 2 (2.9)              | 1.000        |
| Melancholic                | 3 (13.0)          | 10 (14.3)            | 1.000        |
| Atypical                   | 4 (17.4)          | 11 (15.7)            | 1.000        |
| Psychotic                  | 5 (21.7)          | 3 (4.3)              | <b>0.021</b> |
| Relieved                   |                   |                      |              |
| Any type                   | 23 (100.0)        | 70 (100.0)           |              |
| Spontaneously              | 8 (34.8)          | 22 (31.4)            | <b>0.022</b> |
| With mood stabilizer       | 2 (8.7)           | 1 (1.4)              |              |
| With antidepressant        | 11 (47.8)         | 47 (67.2)            |              |
| With combined therapy      | 2 (8.7)           | 0 (0.0)              |              |

**Notes:**  $\chi^2$  test–Fisher's exact test–Fisher–Holton–Freeman test. Values in bold indicate statistical significance ( $P<0.05$ ).

**Abbreviation:** BD, bipolar disorder.

**Table 5** MDQ, HSL-32-R, and MIDAS scores in migraineurs with and without comorbid BD

| Scores                  | Migraineurs       |                      | P-value            |
|-------------------------|-------------------|----------------------|--------------------|
|                         | With BD<br>(n=23) | Without<br>BD (n=97) |                    |
| Likelihood of BD, n (%) |                   |                      |                    |
| By MDQ                  | 21 (91.3)         | 2 (2.1)              | $<0.001^a$         |
| By HSL-32-R             | 23 (100.0)        | 68 (70.1)            | 0.003 <sup>a</sup> |
| MIDAS, median (IQR)     | 37.0 (61.0)       | 19.0 (28.0)          | 0.042 <sup>b</sup> |

**Notes:** <sup>a</sup> $\chi^2$  test–Fisher's exact test. <sup>b</sup>Mann–Whitney U test.

**Abbreviations:** MDQ, Mood Disorder Questionnaire; HSL-32-R, Hypomania Checklist-32-Revised; MIDAS, Migraine Disability Assessment Scale; BD, bipolar disorder; IQR, interquartile range.

associated with increased likelihood of having BD among migraineurs (Table 6). Mutually adjusted multivariate logistic regression model revealed that a positive family history of type I BD (odds ratio [OR], 14.42; 95% confidence interval [CI], 2.94–70.73;  $P=0.001$ ) and MIDAS scores  $>30$  (OR, 3.69; 95% CI, 1.12 to 12.19;  $P=0.032$ ) were significant estimators of having bipolar diseases among migraineurs, leading to 14.42 times and 3.69 times increased likelihood of BD, respectively (Table 6).

Albeit not significant based on 5% type 1 error level, parameters including alcohol as a trigger (OR, 2.99; 95% CI, 0.85–10.54;  $P=0.088$ ) and physical abuse in childhood (OR, 2.91; 95% CI, 0.84–10.06;  $P=0.092$ ) may also be considered among the estimators of having bipolar diseases, associated with 2.99 times and 2.91 times increased likelihood of having BD, respectively (Table 6).

## Discussion

Our findings revealed the presence of comorbid BD in 19.2% of migraineurs. No significant difference was noted between migraineurs with and without comorbid BD in terms of sociodemographic, migraine disease, and first-episode characteristics, while migraineurs with comorbid BD than those without comorbid BD had significantly higher MIDAS scores, higher rate for family history of BD, and past history of suicide attempt and physical abuse. Mutually adjusted multivariate logistic regression model revealed that a positive family history of type I BD (OR, 14.42; 95% CI, 2.94–70.73;  $P=0.001$ ) and MIDAS scores  $>30$  (OR, 3.69; 95% CI, 1.12–12.19;  $P=0.032$ ) were significant estimators of having bipolar diseases associated with 14.42 times and 3.69 times higher likelihood of BD among migraineurs, respectively.

Our findings indicate a high prevalence of BD among migraineurs that exceeds the lifetime prevalence of type I and type II BDs estimated to be 0.6% and 0.4%, respectively, in population-based studies.<sup>28</sup> Likewise, comorbid BD was

**Table 6** Univariate and mutually adjusted multivariate logistic regression analyses for estimators of having BD

| Variables                             | Univariate logistic regression <sup>a</sup> |        |       | Multivariate logistic regression <sup>b</sup> |                  |        |       |              |
|---------------------------------------|---|--------|-------|---|------------------|--------|-------|--------------|
|                                       | OR  | 95% CI |       | P-value                                       | OR               | 95% CI |       | P-value      |
|                                       |   | LB     | UB    |   |                  | LB     | UB    |              |
| Caffeine intake                       |   |        |       | <b>0.039</b>                                  |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | Reference        |        |       |              |
| Positive                              | 3.10  | 1.06   | 9.07  |   | 1.30             | 0.30   | 5.61  | 0.726        |
| Migraine with aura                    |   |        |       | 0.098   |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | N/A              |        |       |              |
| Positive                              | 2.35  | 0.85   | 6.48  |   |                  |        |       |              |
| Visual aura                           |   |        |       | 0.076   |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   |                  |        |       |              |
| Positive                              | 2.35  | 0.91   | 6.07  |   |                  |        |       |              |
| Alcohol (migraine trigger)            |   |        |       | <b>0.025</b>                                  |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | Reference        |        |       |              |
| Positive                              | 2.95  | 1.15   | 7.57  |   | 2.99             | 0.85   | 10.54 | 0.088        |
| Osmophobia (migraine accompaniment)   |   |        |       | <b>0.040</b>                                  |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | Reference        |        |       |              |
| Positive                              | 2.89  | 1.05   | 7.96  |   | 2.36             | 0.64   | 8.71  | 0.199        |
| Family history of BD                  |   |        |       | <b>&lt;0.001</b>                              |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | N/A <sup>c</sup> |        |       |              |
| Positive                              | 9.75  | 3.01   | 31.61 |   |                  |        |       |              |
| Family history of type I BD           |   |        |       | <b>&lt;0.001</b>                              |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | Reference        |        |       |              |
| Positive                              | 12.40                                       | 3.32   | 46.34 |   | 14.42            | 2.94   | 70.73 | <b>0.001</b> |
| Previous suicide attempt              |   |        |       | <b>0.001</b>                                  |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | Reference        |        |       |              |
| Positive                              | 8.05  | 2.27   | 28.51 |   | 2.72             | 0.55   | 13.43 | 0.220        |
| Comorbid generalized anxiety disorder |   |        |       | 0.519   |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | N/A              |        |       |              |
| Positive                              | 1.75  | 0.32   | 9.66  |   |                  |        |       |              |
| Comorbid anxiety disorder             |   |        |       | 0.093   |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   |                  |        |       |              |
| Positive                              | 0.45  | 0.18   | 1.14  |   |                  |        |       |              |
| Physical abuse in childhood           |   |        |       | <b>0.022</b>                                  |                  |        |       |              |
| Negative                              | Reference                                   |        |       |   | Reference        |        |       |              |
| Positive                              | 2.98  | 1.17   | 7.58  | 0.109   | 2.91             | 0.84   | 10.06 | 0.092        |
| MIDAS score, numeric                  | 1.01  | 1.00   | 1.02  |   |                  |        |       |              |
| MIDAS score, subgroup                 |   |        |       | <b>0.014</b>                                  |                  |        |       |              |
| ≤30                                   | Reference                                   |        |       |   | Reference        |        |       |              |
| >30                                   | 3.32  | 1.28   | 8.61  |   | 3.69             | 1.12   | 12.19 | <b>0.032</b> |

**Notes:** <sup>a</sup>Variables with  $P$ -value  $\leq 0.10$  for comparison between study groups were evaluated in univariate logistic regression. <sup>b</sup>Variables with statistical significance in univariate logistic regression were included in mutually adjusted multivariate logistic regression model, <sup>c</sup>while family history of BD was omitted due to low OR. N/A, not applicable based on lack of significance in univariate analysis. Values in bold indicate statistical significance ( $P < 0.05$ ).

**Abbreviations:** BD, bipolar disorder; OR, odds ratio; CI, confidence interval; LB, lower boundary of 95% CI; UB, upper boundary of 95% CI; MIDAS, Migraine Disability Assessment Scale.

reported to be the second most prevalent comorbid psychiatric disorder in migraineurs as preceded by major depressive disorder.<sup>14</sup> Other studies addressing the prevalence of BD among migraineurs indicated twofold increase in BD in patients with migraine than in those without migraine,<sup>17</sup> while BD was reported only in 1.2%–1.3% of migraineurs in these studies.<sup>17,18</sup> A family history of BD, type I BD in particular, was more common in migraineurs with comorbid BD than in those without comorbid BD in our cohort. This supports the

reported increase in the risk for having BD from 0.4%–1.6% in the general population to 3%–8% in case of presence of BD in a first-degree relative.<sup>29–31</sup> A family history of mood disorder and migraine in first-degree relatives was also reported to be associated with an increased risk of comorbidity.<sup>32</sup> Besides, parental migraine is suggested to be an independent risk factor for BD in the offspring, even in the absence of parental BD.<sup>33</sup> Given the association of a family history of type I BD with 14.42 times higher likelihood of having BD

in a patients with migraine, our findings emphasize that a positive family history of BD may refer to a stronger risk factor for BD development in the presence of migraine. The presence of a positive family history of type I BD in one-third of migraineurs seems therefore to be associated with a high prevalence of BD in our cohort.

The findings from analysis adjusted for sociodemographics in migraineurs in a past study revealed the association of past-year migraine with increased risk of past-year psychiatric diseases, including agoraphobia without panic disorder (OR, 3.21), dysthymia (OR, 3.17), and BD (OR, 2.78), but not with social phobia, generalized anxiety disorder (GAD), and alcohol or drug abuse/dependence.<sup>4</sup> This seems consistent with the identification of comorbid psychiatric diseases in a majority of migraineurs with the identification of BD in almost 20% of migraineurs in our cohort.

Also, none of the migraineurs with comorbid BD in our cohort had GAD or somatoform disorder, while alcohol use disorder and hypochondriasis were similarly rare and anxiety disorder was similarly common among migraineurs with and without comorbid BD.

Depression and anxiety have been consistently reported to be common psychiatric comorbidities among migraineurs, occurring at higher rates compared with the general population.<sup>32,34,35</sup> Besides, migraine has been suggested to alter clinical course of BD among migraineurs by increasing frequency of depressive episodes and comorbid anxiety disorders.<sup>12,16,36</sup> This seems consistent with high rates for anxiety disorder and first-episode depression in our migraineurs regardless of comorbid BD.

Increased likelihood of index and overall episodes of depression rather than mania in BD patients with migraine than in those without migraine has been suggested to increase the risk of BD patients to receive improper antidepressant monotherapies instead of mood stabilizers.<sup>11</sup> First-episode depression was shown to be relieved by prescription of antidepressants per se in 47.8% and mood stabilizers only in 8.7% of migraineurs with comorbid BD in our cohort. This seems notable given the increased likelihood of pain-killer medication abuse, poor treatment adherence, and poor therapeutic outcome and even an increased risk of suicidality in case of misdiagnosing bipolar characteristics in migraine–BD comorbidity.<sup>11,37–39</sup>

Almost sixfold increase in suicide attempt in migraineurs with comorbid BD than those without comorbid BD in our cohort seems consistent with consideration of BD as a leading cause of premature mortality from suicide<sup>40–43</sup> with ~20–30 times higher suicide risk than the general population with no psychiatric disorder.<sup>44,45</sup> Besides, comorbid migraine has been considered as an important marker of severity of both type I

and type II BDs (20) and to be an independent risk factor for the course of BD,<sup>13</sup> while also shown to be associated with an increased risk of suicidal behavior per se.<sup>16</sup> Hence, our findings indicate careful consideration of migraineurs with comorbid BD in terms of potential risk of suicide attempts.

While association of BD and migraine is suggested to occur only among migraineurs with aura,<sup>46</sup> our findings revealed no significant difference between migraineurs with versus without comorbid BD in terms of presence and type of aura as well as alterations in clinical course attributable to migraine with aura. In addition, our findings revealed no impact of comorbid BD on migraine disease characteristics, including disease duration, frequency, duration and severity of episodes, and prodromal symptoms. Alcohol was a more common triggering factor for migraine in case of comorbid BD, while similarly, low alcohol consumption rates were noted among migraineurs with and without comorbid BD in our cohort. The low rate of alcohol abuse among BD patients was also reported in another study<sup>30</sup> from Turkey and attributed to the overall low alcohol consumption rate in our country, particularly among females.<sup>30,47</sup>

This seems notable given the 2.99 times increased likelihood of having BD among our migraineurs in whom alcohol is a triggering factor, albeit not reached statistical significance in our analysis probably due to already low consumption rates.

Comorbid BD was associated with an increase in MIDAS scores in our cohort, indicating BD to aggravate migraine-associated disability and deterioration in the functionality among migraine patients. Besides, MIDAS scores >30 were associated with 3.69 times increased likelihood of having BD in migraineurs. Accordingly, our findings seem to emphasize the potential of screening for comorbid BD among migraineurs, particularly in those with disability and poor functionality, to implement adequate treatment strategy and limit potential adverse outcome.<sup>12,33,48</sup> Notably, an increase in MIDAS scores and a significant deterioration in the functionality were also reported in a recent study among Turkish migraineurs, in case of comorbid personality disorders.<sup>48</sup>

Our findings support the potential association of migraine–BD comorbidity with adverse health-related outcomes,<sup>12,33</sup> considering not only the migraine-related alteration in course of BD but also BD-related aggravation in migraine-related disability.<sup>12</sup> Hence, our findings emphasize the likely role of earlier detection and proper treatment of each disease in prevention of adverse outcomes associated with migraine–BD comorbidity.<sup>12,33</sup>

A history of childhood physical abuse was more prevalent in migraineurs with comorbid BD than in those without



comorbid BD in our cohort. In addition, albeit not significant a past history of physical abuse in childhood was associated with 2.91 times increased likelihood of having BD in migraineurs. While a twofold rise in migraine prevalence is suggested in patients with a history of childhood abuse than in those without,<sup>49</sup> physical abuse has also been considered a predictive risk factor for mania.<sup>50</sup> Hence, our findings are in agreement with data indicating a significant association of child adversity score with the total number of medical comorbidities in BD patients, including migraine headaches.<sup>51</sup>

Supporting lower specificity and higher sensitivity of HSL-32 compared with MDQ in diagnosing BD,<sup>52,53</sup> our findings indicate HSL-32 and MDQ to reveal the likelihood of comorbid BD in 100.0% and 91.3% of patients, respectively, with confirmed diagnosis, while HSL-32 also revealed positive results in 70.1% of patients without BD. In fact, unipolar depressed patients have been suggested to have clinical features that resemble the type II BD patients in the presence of migraine, possibly indicating that migraine in depressed patients is a bipolar spectrum trait.<sup>54</sup> Notably, 72.1% of migraineurs without comorbid BD in our cohort presented with unipolar depression and HCL-32 revealed possible BD in 70.1% of patients in this group. This seems also notable given the high accuracy of HCL-32 in the detection of hypomanic components and thus “softer” BD cases.<sup>24,55</sup>

Certain limitations to this study should be considered. First, due to the cross-sectional design, establishing any cause and effect relationship is impossible. Second, due to the small sample size and recruiting participants from a single tertiary care center, generalizing our findings to the overall patient population is difficult along with the likelihood of certain regional differences to be ignored. Third, lack of a group without migraine in the study population is another limitation, which otherwise would extend the knowledge achieved in the current study. Nevertheless, despite these certain limitations, given the limited data available on this subject, our findings represent a valuable contribution to the literature.

## Conclusion

Our findings revealed a high prevalence of comorbid BD in migraineurs along with an increased likelihood of having BD in case of a positive family history of type I BD and MIDAS scores >30. Comorbid BD was associated with a higher rate for a family history of BD, more common suicide attempt and childhood physical abuse as well as aggravated migraine-related disability among migraineurs. Migraineurs with and without comorbid BD showed similar sociodemographic and migraine disease characteristics as well as similar high

rates for anxiety, depression, and first-episode depression. Our findings indicate the association of migraine–BD comorbidity with the likelihood of alteration in the clinical course of both diseases along with an increased risk of BD development in patients with a positive family history and severe migraine-related disability. Thus, our findings emphasize enhanced attention and early recognition of migraine–BD comorbidity in the routine clinical practice to minimize and appropriately manage potential adverse health outcomes in the long term. Longitudinal prospective studies addressing the migraine–BD comorbidity in terms of actual prevalence and risk status of each disease and potential adverse impact of comorbidity on the clinical course of each disease per se are needed for elucidating potential mechanisms underlying co-occurrence of migraine and BD and for a better therapeutic outcome.

## Disclosure

The authors report no conflicts of interest in this work.

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