Research Article

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# Impact of a new migraine-specific comorbidity index on prognosis: A methodology study

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## Abstract

**Objective:** To develop and validate a comorbidity index to estimate the prognosis of migraine, defined as the severity of headache measured longitudinally in a heterogeneous population.

**Methods:** The study data were collected from a computer-based Turkish Headache Database with 15-year's follow-up data. The primary outcome was defined as the severity of headache [visual analog scale (VAS)] obtained from baseline to the 7th visit. The procedure was multistage: First, latent subgroups were determined using group-based trajectory modeling (GBTM) because the change in outcomes over time were different for each patient. Second, group-based trajectory modeling analysis was applied with the purpose of understanding how to evaluate comorbidities. Lastly, according to the results obtained from the GBTM analysis and physicians viewpoints, a migraine-specific comorbidity index was developed and validated.

**Results:** Out of all weighting methods to evaluate comorbidities, the three-group model and quadratic form of all groups fitted the data best. After deciding the number of groups and functional form, the information criteria and minimum group percentage of the weighting methods were compared. The best method was the posterior probabilities obtained from latent class analysis (LCA) taken as weights. At the same time, age was effective in the separation of the second and third groups from the first group for severity (p=0.047, p=0.007). Sex difference had no effect on the prognosis of migraine (p=0.99, p=0.16).

**Conclusion:** According to these results, an index formula was developed to evaluate the effect of covariates on migraine severity prognosis. A migraine-specific comorbidity index called the Migraine Comorbidity Index (MCI) was created by applying the formula.

**Keywords:** Migraine, group-based trajectory modeling, co-morbidity index, prognosis.

## INTRODUCTION

Chronic diseases and morbidities are the most common and costly health problems. Diseases such as cardiovascular, chronic respiratory, diabetes, and mental health disorders are highly influential on mortality and morbidity as comorbidities of many existing diseases. Comorbidities affect the diagnosis, treatment, and prognosis of a disease significantly and cause great economic and social burden. Especially in randomized controlled and prognostic studies examining the efficacy of treatment, comorbid conditions of individuals should be considered to avoid confounding bias. It has been emphasized that the inefficiency of the classification and analysis of comorbid diseases might cause many difficulties in medical statistics (1-3). Accordingly, many prospective studies are planned with the exception of patients with comorbidities. However, exclusion of these patients may cause a lack of evidence in disease burden, inadequate sample size, and also hide the effect of comorbidities on the efficacy of treatment. On the other hand, there is no gold standard method for evaluating comorbidities (4). In the literature, clinical-based comorbidity indices are developed to measure the impact of comorbidities (5). The best-known clinical-based comorbidity index is the Charlson Comorbidity Index (CCI) developed by Mary Charlson in 1987 (6, 7). Unfortunately, coexisting diseases may not be the same for every index disease, which has to be taken into account while measur-

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ing comorbidities. For this reason, developing a disease-specific comorbidity index is the best solution (8).

Migraine is a good example for index diseases with multiple comorbidities (9, 10). The primary outcome of a migraine treatment is the severity of headache, as measured using a visual analog scale (VAS). Previous studies considering comorbidities are essential during accurate treatment of severe migraine headaches (11).

Common comorbidity indices are generally used to predict mortality in many disease groups (e.g., cancer, kidney diseases, stroke and liver diseases). However, comorbidities are important factors for mortality and for morbidity associated with chronic health problems such as migraine. In addition, chronic diseases require long-term follow-up. The response to treatment varies for each patient because of different baseline severities of headache and prognosis. Hence, migraine databases have both longitudinal and heteregoneous structure. Approaches for modelling heterogeneous longitudinal data have been proposed in recent years. Group-based trajectory modeling (GBTM) is the most effective method of analyzing heterogeneous populations. In this approach, prognosis is estimated by classifying patients into homogeneous subgroups (12-14).

The aim of this methodologic study was to develop and validate a comorbidity index for patients with migraine using computer-based follow-up data. The proposed index will be useful for physicians when planning treatment for patients and estimating accurate prognoses.

## Materials

### Sources of Data

The study data were based on follow-up data in a 15-year computer-based Turkish Headache Database. The study was approved by the clinical research ethics committees of Mersin University on 11/26/2015 (Meeting number/Decision number: 22/355). Informed consent was not required because the dataset consists of de-identified secondary data. Two hundred twenty-five (11.2%) patients were diagnosed as having migraine with aura, 1271 (63.2%) had migraine without aura, and 516 (25.6%) patients had chronic migraine according to the International Classification of Headache Disorders (ICHD-3) criteria (15).

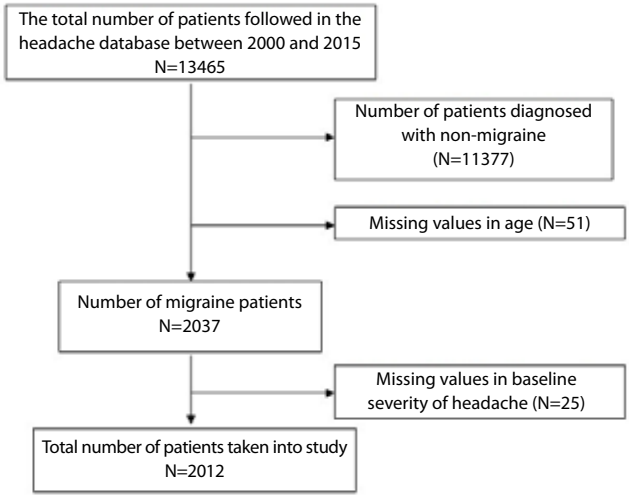
We used variables of sex, age, comorbidities of migraine (epilepsy, allergy, atherosclerosis, hypertension, diabetes mellitus, coronary artery disease, anxiety and depression) and longitudinal data of severity (VAS), duration (hour) and frequency (day/month) of headache (headache days not migraine days) from the database. A flow chart of the sample is given in Figure 1.

Even though patients were followed during 18 visits with 3-6–month intervals, there was a significant decrease in the number of patients after the 6$^{th}$ visit. We used baseline and six values of primary outcomes because the decrease in the sample size could have a worse effect on the validity of the results, and the prognosis in the first six visits was clinically important for phycisians.

### Determining Comorbidities

In this study, there were psychiatric (depression and anxiety) and organic comorbidities (epilepsy, allergy, atherosclerosis, hypertension, diabetes mellitus, coronary artery disease), which were determined with headache specialists. Psychiatric comorbidities were assessed using the Diagnostic and Statistical Manual of Mental Disorders - 4$^{th}$ Edition (DSM-IV) diagnostic criteria.

**Figure 1.** Flow chart of the sample




## METHODS

### Modeling Comorbidities

Initially, comorbidities were modeled according to the presence or absence of comorbidities or the total number of comorbidities in order to demonstrate their effect on prognosis. However, these approaches had some weaknesses because the comorbidities did not have equal effects on outcomes. The predominant feature of the CCI was weighting of comorbidities. Weighting methods in the literature used comorbidity frequencies, hazard ratios obtained from Cox regression, and adjusted odds ratios obtained from logistic regression analysis (14, 16-21). Current comorbidity indices are associated with mortality. Hovewer, in our study, the primary outcome was the severity of headache, not mortality. For this reason, we aimed to estimate the effect of comorbidities on the prognosis and determine an appropriate weighting method for longitudinally measured outcomes. We proposed four methods for weighting comorbidities. The first method used observed frequencies of comorbidities in the study sample as

weights. In the second, the weights were obtained by multiplying frequencies of comorbidities and individual comorbidity burden, which was calculated by dividing the number of comorbidities in each patient into the total number of comorbidities. Differently, the third and fourth methods were based on Latent Class Analysis (LCA) with and without considering the relationship between comorbidities.

Latent Class Analysis (LCA) was an iterative method to identify the unobserved class membership among the subjects by using categorical observed variables. First, marginal and joint probabilities of the combinations of binary responses (yes or no) given to different comorbidities were calculated. Then posterior probabilities were calculated and individuals were classified to latent classes according to their posterior probabilities (22).

### Modeling Prognosis and Comorbidities Together

When the current developed comorbidity indices were examined, large data sets were studied, but the homogeneity of the population was not considered (12, 13). Modeling the effect of comorbidities on prognosis should be examined in homogeneous subgroups because the responses to migraine treatment for each patient were different. Hence, individuals that showed similar changes over time were grouped by using GBTM analysis and the groups were called 'trajectories.' The distribution of the data was examined and censored normal distribution was used because the outcome was right-skewed scale type data, which tends to cluster at the scale maximum (23). In the GBTM analysis, the first important decision was to decide the optimal number of trajectories. The second important decision was the degree of the model. It was then necessary to compare the models to find the most appropriate model to data by changing the number of groups (one to three) and parameter degree (linear, quadratic, and cubic). Model fit statistics such as Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and group memberhips were used to determine the best model. The models with the lowest information criteria and more than 5% group memberships were the best compared with the other models (12, 24, 25).

**Table 1. Demographic and clinical variables**

| | | Count | % |
|---|---|---|---|
| Smoking | User | 669 | 33.3 |
| | Non user | 1317 | 65.6 |
| | Give up | 23 | 1.1 |
| Alcohol | User | 326 | 16.2 |
| | Non user | 1679 | 83.67 |
| | Give up | 2 | 0.1 |
| Migraine causes | Emotional stress | 1574 | 78.5 |
| | Physical activity | 1186 | 59.6 |
| | Menstrual cycle | 742 | 37.3 |
| | Seasonal relationship | 389 | 19.7 |
| Types of migraine | Migraine without aura | 1271 | 63.2 |
| | Migraine with aura | 225 | 11.2 |
| | Chronic migraine | 516 | 25.6 |
| Comorbidities of migraine | Epilepsy | 13 | 0.6 |
| | Allergy | 201 | 9.9 |
| | Atherosclerosis | 5 | 0.2 |
| | Hypertension | 461 | 22.9 |
| | Diabetes mellitus | 343 | 17.0 |
| | Coronary artery disease | 319 | 15.8 |
| | Anxiety | 333 | 16.5 |
| | Depression | 757 | 37.6 |

### Dealing with Missing Data

In this study, missing dependent variables were assumed as missing at random. GBTM analysis was appropriate for this kind of missing mechanism. In other words, even dependent variables with at least one observation were included. However, if there was a missing observation in risk factors (covariates), these individuals were excluded from the study (23). The sample size for this study was sufficient because a sample size of at least 300-500 was recommended for GBTM (13).

### Software

Latent Class Analysis (LCA) was applied using the software (Latent Gold 5.1; Statistical Innovations, Belmont, USA) (26, 27) and GBTM analysis was applied using TRAJ plugin in software (STATA MP/11; StataCorp LLC, Texas, USA).

## RESULTS

The mean age of the patients was 37.27±12.11 years. The majority (86.9%) of the patients were women. The demographic and clinical variables of the patients are summarized in Table 1.

A summary of the statistics of severity, duration, and frequency of headache is given in Table 2.

We had clinical information about age and sex as risk factors for migraine. In addition, our previous study showed that age was effective when the second and third groups of severity were seperated from the first (p=0.047, p=0.007). It was found that sex had no effect on the prognosis of migraine (p=0.99, p=0.16). Therefore, age was included in all the models obtained from the different methods (11).

Of all the weighting methods, a three-group model and quadratic form of all groups fitted the data best. The final model included age, baseline duration and frequency of headache, and posterior probabilities from LCA considering the relation-

**Table 2. Summary statistics for severity (VAS), duration (hour), and frequency (day/month) of headache at baseline and the following 6 visits**

| Visit | n | Severity (VAS) | Duration (hour) | Frequency (day/month) |
|---|---|---|---|---|
| Baseline | 2012 | 9.79±9.25 | 26.38±26.06 | 8.04±1.67 |
| Visit 1 | 554 | 7.75±8.18 | 18.39±21.61 | 6.92±2.30 |
| Visit 2 | 320 | 6.78±7.42 | 16.51±19.31 | 6.00±2.54 |
| Visit 3 | 175 | 6.30±7.86 | 14.01±18.06 | 5.39±2.68 |
| Visit 4 | 101 | 6.95±8.18 | 15.10±19.62 | 5.80±2.45 |
| Visit 5 | 65 | 5.63±7.59 | 11.87±16.62 | 5.34±2.79 |
| Visit 6 | 35 | 6.54±8.54 | 14.13±20.92 | 5.63±2.38 |

The variables were presented as mean±standard deviation. VAS: visual analog scale

**Table 3. Migraine comorbidity index**

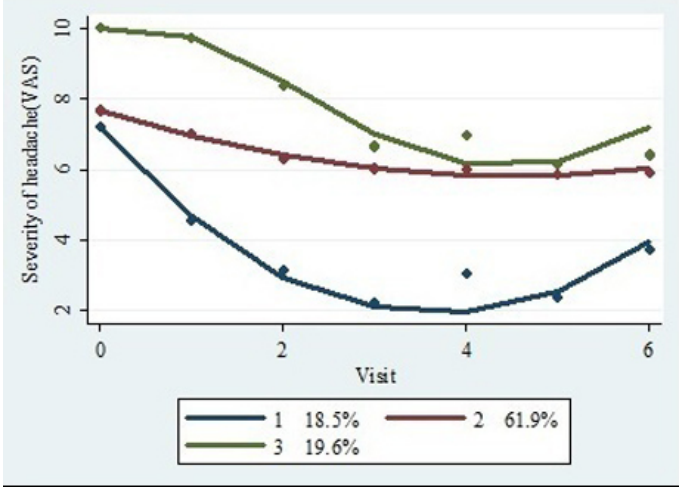
| | | Score |
|---|---|---|
| Age | 0-17 | 1 |
| | 18-65 | 2 |
| | 66-79 | 3 |
| | 80-99 | 4 |
| Baseline duration of headache (hours) | 0-16 | 1 |
| | 17-41 | 2 |
| | 42-62 | 3 |
| | 63+ | 4 |
| Baseline frequency of headache (day/month) | 0-15 | 1 |
| | 16-26 | 2 |
| | 27+ | 3 |
| Comorbidities | Seen(1) | Absent(0) |
| Epilepsy | ☐ | ☐ |
| Allergy | ☐ | ☐ |
| Atherosclerosis | ☐ | ☐ |
| Hypertension | ☐ | ☐ |
| Diabetes mellitus | ☐ | ☐ |
| Coronary artery disease | ☐ | ☐ |
| Anxious | ☐ | ☐ |
| Depression | ☐ | ☐ |
| Posterior probability of individual | | |
| Total score | Age score *Posterior probability *(Frequency of headache score + Duration of headache score) | |

ships between the comorbidities. The model performance criteria for the final model were AIC=12562.36, BIC=12674.43, and the minimum group membership was 19.6%. The prognosis estimation for this model is illustrated in Figure 2.

An index formula was developed and the effect of covariates on migraine severity prognosis was evaluated. To apply this formula, a comorbidity index for migraine called the Migraine

**Figure 2.** Trajectories of the severity of headache (VAS)

VAS: visual analog scale




Comorbidity Index (MCI) was created, which is given in Table 3. This index could be applied to all age groups (children, adolescents, and adults) where the score ranges of baseline frequency and duration of headache were determined according to the previous study and histogram charts (28). At the same time, age-adjusted CCI was taken as an example to score age, and age groups were determined according to the groups designated by the World Health Organization (29). The index formula is given in Equation 1.

Migraine comorbidity index score= Age score* Posterior probability*(Baseline duration of headache score + baseline frequency of headache score) (1).

Migraine comorbidity index scores had a right-skewed distribution within a range of 0-28, the mean and standard deviation were obtained as 5.07±2.19.

### Validity of Migraine Comorbidity Index

For testing validity, the effect of the proposed index on the estimation of prognosis was evaluated using GBTM and models including only age and both age and MCI score were

compared through goodness of fit criteria (AIC and BIC). For the first model, AIC and BIC were calculated as 12758.58 and 12825.86, respectively. When the MCI index score was included in the model, AIC and BIC values were calculated lower than the first model (AIC=12607.04 and BIC=12685.38). Moreover, the means of baseline severity of headache between subgroups were compared using analysis of variance (ANOVA), and we tried to evaluate the validation of the final model in patient classification. There was a statistically significant difference between the three groups ($p<0.001$). The means (± standard deviation) of headache severity for the subgroups were 6.76±1.98, 7.38±1.30, and 10.0±0.0, respectively.

## DISCUSSION

Prospective studies are planned to estimate the efficacy of treatment and prognosis considering comorbid conditions. To evaluate the effect of comorbidities, various clinical comorbidity indices were previously recommended. For chronic health problems such as migraine, for which long-term follow-up data are required, repeated measurements of the same patient at different times are necessary to analyze changes in pain. In addition, trajectory models were frequently used in the longitudinal studies considering the intra-individual difference and heterogeneity due to the different baseline severity headache of each individual.

A person-centered approach was required for studies searching comorbidity effect because severity of comorbidities and demographic properties of patients were different and these differences affect outcome. The weakest property of well-known indices to date (e.g., Elixhauser Comorbidity Index, CCI, Cumulative Illness Rating Scale) is that failure to consider population hetereogeneity (30, 31). Hence, GBTM was the most appropriate statistical method for model evaluation.

After population heterogeneity was taken into consideration, four methods were tested by using the literature to investigate how comorbidities should be handled. It was observed that posterior probabilities calculated by latent class analysis considering the relationship between comorbidities was the best method. At the same time, age, baseline frequency and baseline duration of headache were considered together with comorbidities according to results. Temporal change of frequency and duration of headache has been tried to be analyzed but the high correlation between primary outcome and these variables led to a multicollinearity problem. The validation of a disease-specific comorbidity index must be examined in order to be applicable (4, 32, 33). Optimal goodness of fit statistics were obtained when MCI score was included in the model. Moreover, the means of baseline severity of headache between trajectory groups were compared and a statistically significant difference was detected. According to these results, the developed index was valid for use.

There are several limitations to our study. First, the severity of comorbidities could not be considered in this study. Secondly, missing values for covariates or outcomes, wrong data entry, and the dramatic decrease in sample size in the follow-up were limitations. However, the most important limitation was that revisit intervals were not the same for each patient (longer or shorter) and it was difficult to control this situation. Fortunately, the GBTM was robust to non-linearity change between visits and missing values (13). In addition, because of the similarity with real-life data, a hospital-based headache database was used in this study like in previous comorbidity studies (34).



To conclude, age and comorbidities are important factors influencing treatment selection, outcomes, and prognosis in patients with migraine. There are severel examples regarding the diffuculties of diagnosis and treatment of migraine because of its comorbidities (35). For example, both migraine and depression can cause behavioral changes related to pain. Beta blockers have less therapeutic effect on migraine patients with depression. For this reason, comorbidities of migraine must be considered by physicians.

For statistical efficacy, there are four important reasons for taking comorbidities into account. These are increasing the internal validity of studies by considering the confounder effect of comorbidities, examining the effect on outcome variables, estimating disease prognosis, and accumulating many comorbid diseases under a valid and comprehensive variable.

The MCI proposed in this study might be the first in the world medical literature and should be adapted to other long-term diseases. Thus, modelling treatment efficacy with less information loss may be possible by including the patients with comorbidities. Furthermore, it can be used as a part of a quality assessment scale in the life insurance sector and will present a new perspective in the evaluation of patients with chronic migraine.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Mersin University on 11/26/2015 (Meeting number/Decision number: 22/355).

**Informed Consent:** Informed consent was not required because the dataset consists of de-identified secondary data.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – D.D.Y., B.T., A.Ö., D.U.; Design – D.D.Y., B.T., S.Y.; Data Collection and/or Processing – D.U., A.Ö.; Analysis and/or Interpretation – D.D.Y., B.T., S.Y.; Literature Search – D.D.Y., B.T.; Writing Manuscript – D.D.Y., B.T.; Critical Review – D.D.Y., B.T., D.U., A.Ö., S.Y.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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