**LONGITUDINAL CHARACTERIZATION OF HEADACHE AFTER TBI AND POTENTIAL IMMUNOLOGICAL TARGET**

by

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BA in Neuroscience, Northwestern University, 2017

Submitted to the Graduate Faculty of

Epidemiology

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2018

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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**ABSTRACT**

Headaches are a common adverse outcome after a traumatic brain injury (TBI) that can persist through the first year post-injury. Inflammation has been implicated in the pathophysiology of migraines and persists chronically after a TBI. Through the process of trans-signaling, the binding of interleukin(IL)-6 to its soluble receptor can lead to widespread inflammation. This process is restricted by the presence of soluble g-protein130 (sgp130). Previous studies have not examined the relationships between the IL-6 family soluble receptors and headaches in TBI patients. The aim of this study was to identify headache phenotypes and how these phenotypes are associated with other TBI outcomes. We also hypothesized that the relative levels of IL-6 family soluble receptors underlies post-traumatic headache pathophysiology.

We used monthly questionnaires to categorize headaches and to create temporal headache trajectory profiles in a prospective cohort of adults with TBI (n=79). We examined the relationship between trajectory profiles and quarterly ratios of sgp130 levels to levels of the sIL-6R (sgp130:sIL6-R), and other secondary outcomes including stress hormone, quality of life, anxiety, depression, fatigue, and disability.

There were three distinct headache profiles: low, resolve, and chronic trajectory groups. We compared ratios in the symptomatic trajectory groups, and determined a cut-point for an individual to be considered at risk. Those in the resolve trajectory group had higher sgp130:sIL-6R ratios compared to those in the chronic trajectory group across all time points (p<0.05 for all comparisons). In the adjusted model, a one standard deviation increase in quarter 1 sgp130:sIL-6R protects against chronic headaches by 75.9% (p=0.006). Those in the chronic trajectory group experienced elevated levels of stress hormone, lower quality of life, and higher anxiety, depression, fatigue and disability.

Those in the chronic trajectory group had less inhibition of the widespread inflammation caused by IL-6 binding to sIL-6R and worse co-occurring impairments. Future studies should test the effect of a sgp130:sIL-6R targeted immunotherapy to mitigate the detrimental and long-lasting effects of PTH after TBI.

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# Introduction

## TRAUMATIC BRAIN INJURY EPIDEMIOLOGY AND IMPACT

Traumatic brain injuries (TBIs) are an underrated public health problem in the United States today. Moderate to severe TBIs are commonly caused by motor vehicle accidents and falls. Military personnel exposed to explosions can acquire a TBI via blast injuries. Symptom onset is commonly immediately after injury, including dizziness and loss of consciousness. Later-onset of symptoms is also common and can include headache, loss of balance, tinnitus, depression, anxiety, and problems with cognition. These symptoms often persist for years post-injury and can even occur with mild TBIs, also known as concussion.1

Approximately 1.7 million civilians require medical attention after a TBI every year, with a resultant 53,000 deaths and 275,000 non-fatal hospitalizations.2 An additional 20,000 TBIs per year occur in the US military population.3 Of those who were hospitalized, an estimated 43% of individuals live with a disability after one year.4 The disabilities that are acquired after a TBI put individuals at higher risk for poor health outcomes including chronic diseases, unemployment, additional medical complications, and increased healthcare costs. The economic burden of TBI is calculated as healthcare costs and expenses associated with ongoing care; it is estimated to be approximately $400 billion per year.5

Civilian populations at increased risk for a mild TBI include the homeless, prisoners, and refugees. The incidence of mild TBI in these groups is associated with disinhibited behaviors, alcohol, and subsequent head injuries. The life expectancy of those who sustain a TBI is significantly lessened when compared to other forms of injury.6 Moderate to severe TBIs in particular are associated with mood and cognitive impairments that impact quality of life and return to work after injury. One of the most common neurobehavioral complications post-injury is post-traumatic depression (PTD). Compared to the 6% annual rate of depression in the general population, individuals who sustain a moderate to severe TBI have a 53% annual rate, and are at increased risk for recurring depressive episodes. In both populations, depressive symptoms are associated with additional cognitive impairments that could be due to underlying neuropathologies.5 Understanding the underlying biology and consequential public health significance of this condition in the moderate to severe TBI population can inform rehabilitation efforts to improve impairments in mobility, cognition, independent living, and performance on activities of daily living.

Currently, the management of disability after TBI is difficult due to the heterogeneous nature of injury. Unlike most public health problems, the predicted recovery and long-term impairments for an individual are diverse. The variability that results in functional, cognitive, emotional, and behavioral outcomes can be due to pre- and post-injury environmental factors, pre-injury personal biology, and injury-induced pathology. Thus, current research focuses on the development of biomarker-guided clinical decision algorithms in order to generate appropriate screening and prevention tools for undesirable complications and persistent post-injury disabilities.5

## HEADACHES AFTER TBI

Post-traumatic headache (PTH) is a secondary headache disorder that can result after a TBI.7,8 Detrimental long-term effects of headaches have been demonstrated in TBI,7,9–13 US Army soldiers deployed in support of Operation Iraqi Freedom14, and in populations with chronic migraine.15,16 Headaches after TBI do not occur in isolation, and individuals with TBI often have multiple co-occurring impairments, including anxiety and depression,17 seizures,10 cognitive issues,7,12 other neuropsychiatric symptoms,18 and sleep disorders such as insomnia and sleep apnea.8,11,19–21 It is also well-documented that headaches negatively impact quality of life,14,15 satisfaction with life,20 and physical and social function.12

Past studies have also gathered limited data on longitudinal patterns of headaches and relationships with other common and potentially treatable TBI impairments. In the general population, migraines and headaches are themselves a public health problem. Women are disproportionately affected; in 2015, the prevalence in women was 20.7% but the prevalence in men was 9.7%. Additionally, headache or pain in the head was the fifth leading cause of visits to the emergency department in 2015.22 Headaches have many comorbid conditions. Physical and emotional symptoms of depression have been associated with headaches in the general population. This association is worsened with the co-occurrence of an anxiety mood disorder.23 In individuals with Generalized Anxiety Disorder, an accurate diagnosis and treatment of headache disorder can improve clinical outcomes.24 Independent of depression and anxiety, individuals with primary headache disorders have an overall reduced quality of life.25 Primary headache disorders have been suggested to be a maladaptive response to stress,26 and are more common in individuals who have Chronic Fatigue Syndrome.27

Previous studies have reported wide incidence rates of headache after a TBI, ranging from 13% to 90%.10,17,28 The disparity in incidence rates could be due to varying definitions of headache, differences in TBI severities, and data collection methods and time points. The prevalence of headaches is reported to remain above 40% throughout the first year after injury.9,13,29

Past studies have focused on calculating incidence and identifying distinct types of headaches after a TBI with follow-up at 3, 6, and 12 months.9,13,29 The most commonly identified headache type is migraine, followed by tension-type headaches.13,29,30 Impact on daily life has also been assessed at 3, 6, and 12 months, and disability is concomitant with headaches at these time points.13 Characteristics of pain and other symptoms associated with headaches, such as vision changes, pain type, location, duration, or severity have not yet been assessed longitudinally in a TBI population. Likewise, the onset and subsequent trajectory of headaches after TBI have not yet been assessed. The influencing factors and biological mechanisms by which some individuals develop headaches after TBI are unknown.

## PATHOPHYSIOLOGY OF TBI AND HEADACHES

The pathophysiological mechanisms of headaches after TBI are poorly understood, but inflammation represents a common pathway implicated in both headaches and TBI, presentingthe potential for targeted treatment. An inflammatory response is rapidly elicited in response to a brain injury that can have both beneficial and deleterious effects. The brain mounts a local innate immune response and peripheral leukocytes are recruited acutely to injury sites resulting in cellular and tissue damage and the release of endogenous factors that activate pathways that ultimately result in the release of inflammatory markers, including the pro-inflammatory cytokine interleukin (IL)-6.4,31 Acute (first 2 weeks post-TBI) IL-6 upregulation is associated with tissue regeneration and prevention of neuron apoptosis.32 This regeneration and preclusion of further cellular death is essential for recovery after TBI. However, sustained upregulation of IL-6 into the sub-acute phase (2weeks-3months post-injury) contributes to adverse outcomes in animal model of brain inflammation33 and persistently elevated levels are well-documented after TBI in humans.34,35 The pro-inflammatory effects of IL-6 are a crucial component of the acute innate response after injury, but high levels of IL-6 past the first two weeks post-injury are associated with unfavorable outcomes.31 The role of IL-6 in the chronic phase (post-1 month) after TBI is less understood. In one prospective cohort study, serum cytokine load, which includes IL-6, was found to be elevated over 3 months after a TBI. An elevated cytokine load was associated with unfavorable global outcomes at 6 and 12 months.36

IL-6 is involved in classical signaling and trans-signaling, the latter of which is responsible for harmful downstream effects. In trans-signaling, IL-6 binds to its soluble receptor (sIL-6R), which is readily detected at sites of inflammation. The activity of this complex is blocked by the soluble form of glycoprotein130 (sgp130).37 Following trauma, sIL-6R is released from neutrophils, but sgp130 antagonizes the IL-6 trans-signaling. The ratio of sgp130 to sIL-6R could therefore provide an indication of how much trans-signaling activity is being impeded. Thus, this ratio provides an estimate of how much IL-6 is prevented from crossing the blood brain barrier. In the context of headache, patients with cluster headaches had serum levels of IL-2 receptors that were elevated relative to controls with no cluster headaches; however, IL-6, sIL-6R, and sgp130 levels did not differ between headache groups.38 Prior studies have failed to examine the relationships between these two IL-6 family soluble receptors and headaches in TBI patients, and none of the acute changes that occur post-injury have been associated with headache in a way that could inform therapeutic decision-making.

## CURRENT STUDY

Headaches after TBI represent one of the most prevalent impairments impacting quality of life for patients with TBI.9,13 Though anti-inflammatory treatments have been proven beneficial in acute migraine treatment39 and in alleviating pain and moderating headache severity in the general population,40,41 these treatments are not currently effective for headaches or migraines after TBI.7,28,42 This suggests that the TBI alters the pathophysiology of headache and thus necessitates different treatment strategies. Nevertheless, non-steroidal anti-inflammatory drugs are widely prescribed as a treatment for headaches after TBI. The ineffectiveness of using migraine or headache treatments in the TBI population suggests the need for clinical studies to evaluate specific inflammatory mechanisms implicated with headaches after TBI.39

To this end, the objective of the present study was to characterize headache phenotypes over time and to describe associations of these phenotypes with other co-occurring post-TBI conditions. As inflammation is implicated both in headaches and in TBI, the present study tests the hypothesis that relative levels of the inflammatory biomarkers sgp130 and sIL-6R underlie the pathophysiology of chronic headache over time after TBI.

# MATERIALS AND METHODS

## PARTICIPANTS

Participants were recruited as a part of a prospective cohort study. All procedures were approved by the University of Pittsburgh’s Institutional Review Board. Informed consent was obtained. Participants were approached for enrollment in an acute care hospital, rehab hospital, or outpatient clinic. Patients were included if they had a non-penetrating closed head injury verified with TBI-related ICD-9 diagnosis code and/or sufficient medical documentation of medical or functional complications on day of injury, including positive anatomic neuroimaging findings or focal neurologic signs. Patients were excluded if they (i) were older than 79 years; (ii) had a penetrating head injury; (iii) had an untreated endocrine disorder; (iv) had an autoimmune disorder; (v) had a history of significant neurological or neurodegenerative disease; (vi) had documented history of previous TBI or stroke; or (vii) were a prisoner. Demographic, serum samples, headache and other outcome data were collected monthly across the first year. There were n=79 individuals with data from a headache questionnaire at two or more of the monthly time points. N=2 of those individuals refused blood for various reasons. As a reference group for inflammatory marker concentrations, 18 healthy adult controls with no prior history of TBI provided a single serum sample.

## DEMOGRAPHIC INFORMATION

Demographic and clinical variables collected from medical chart review included: age, BMI, sex, Glasgow Coma Score (GCS), race, mechanism of injury, pre-injury history of anxiety, pre-injury history of depression, pre-injury history of alcoholism, pre-injury history of headache, smoking status, and illicit drug use status. Smoking and illicit drug use statuses was dichotomized into two groups: never users and ever users.

## BIOMARKER COLLECTION

Serum samples (n= 77 subjects, n= 240 samples) were collected monthly by trained research coordinators. Samples were centrifuged, aliquoted, and stored at -80 °C until pulled for batch analysis.

Inflammatory markers were measured using a Luminex™ bead array assay (Millipore, Billerica, Massachusetts). The markers included in this study (IL-6, sgp130, and sIL-6R) were part of larger assays containing several markers. Signal detection uses a microsphere tagged with fluorescent-labelled markers to analyze protein binding. The minimum detectable concentrations for IL-6, sgp130, and sIL-6R were 0.11pg/mL, 6pg/mL and 9pg/mL, respectively. The observed inter- and intra-assay coefficients of variation (CV) for the assay containing IL-6 were <5% and <20%, respectively. For the assay containing sgp130 and sIL-6R, the inter- and intra-assay CV were <10% and <15%, respectively. Due to missing data at some monthly time points, serum sgp130 and sIL-6R averages were calculated over three month increments and the ratio of these mean values was used for analysis.

Serum cortisol levels were measured using a commercial ELISA kit43 according to manufacturers’ instruction. Samples were run for each of the monthly time points using the ELISA technique. To avoid matrix effects with this assay, serum samples were diluted 1:36. Although the it was developed and validated for saliva, a pilot experiment using serum cortisol showed an excellent profile of linearity with serial dilution, and recovery (90-110%) for standards with a range of dilution 1:20 to 1:40. Among the 96 wells in each plate, 10 wells were used in duplicate to evaluate intra-plate reliability, and an additional 6 wells were used to evaluate inter-plate reliability. Otherwise, all samples were evaluated in singlet to conserve sample volume. Throughout all plates, the observed intra- and inter-plate CV were <5% and <6%, respectively.

## PRIMARY OUTCOME VARIABLES

The primary outcome of interest was headache status over the first year post-injury. A monthly headache questionnaire was administered, and headache status (yes/no) was identified. Information on vision changes and face or arm skin sensations with onset of headache were also obtained as a part of the headache questionnaire. Headache location, pain types, duration, severity, and frequency measures were other measures included in the questionnaire.

## SECONDARY OUTCOME VARIABLES

Previous studies have used serum cortisol levels as an indicator of stress after trauma. Trauma-induced physical stress can incite increased cortisol levels in plasma, which can be attributed to increased cortisol secretion rates. Thus, serum cortisol levels were determined monthly as an indicator of stress. Due to missing data at some monthly time points and in order to match the quarterly time frame of the predictor (sgp130:sIL-6R), quarterly averages of these levels were used for analysis. This quarterly average approach was used for all secondary outcome variables with monthly data.

At 6 and 12 month visits, questions were asked regarding a person’s return to normal functioning using a Percent Back to Normal Questionnaire.44 Participants were asked to rate their functioning relative to prior their injuries. Patients self-reported a percentage back to normal (i) overall; (ii) in physical function; (iii) in cognitive function; and (iv) emotionally, where “normal” was defined as function pre-injury.

The Generalized Anxiety Disorder (GAD-7) questionnaire45 was used to assess anxiety at each monthly visit. GAD-7 evaluates seven statements regarding anxiety with the following responses and corresponding scores: “not at all” (0), “several days” (1), “more than half the days” (2), and “nearly every day” (3). These responses were summed, and quarterly averages of the scores were used for analysis. The range of scores for this test is 0-21.

Post-traumatic depression (PTD) was assessed using the Patient Health Questionnaire (PHQ-9).46 PHQ-9 scores the 9 DSM-IV criteria from “not at all” (0) to “nearly every day” (3). PHQ-9 scores were collected monthly, and a PTD status was assigned based on the endorsement of ≥5 symptoms, with at least one being one of the cardinal depression symptoms, depressed mood or anhedonia. This definition of PTD has shown strong validity in TBI populations.47 A quarterly PTD variable was created for analysis. If a person had PTD in any of the corresponding 3 months, the PTD for that quarter was “yes”. If a person did not have PTD in each of the corresponding 3 months, the PTD for that quarter was “no”.

Fatigue was assessed using two questionnaires: PROMIS-Fatigue (PROMIS)48 and Fatigue Severity Scale (FSS).49 The PROMIS questionnaire evaluates eight fatigue variables on a 1-5 frequency Likert scale, ranging from “never” to “always” or “not at all” to “very much”, depending on the question. Thus, the range of these scores is 8-40. The FSS questionnaire consists of nine statements regarding fatigue, and the patient self-reports agreement with each on a 1-7 Likert scale, which are summed for a total score. Thus, the range of values for this score is 9-63. Lower numbers of both fatigue measures indicate disagreement with a statement, and higher numbers indicates agreement with the statement. Both questionnaires were administered monthly, and quarterly averages of each were used for analysis.

## STATISTICAL ANALYSIS

Statistical analyses were performed using SAS™ Version 9.4. Group-based trajectory analysis was used to identify subgroups of the population with different temporal patterns of headache status across the first year. Trajectory groups were generated using the PROC TRAJ SAS Macro and fit using a Bernoulli distribution. trajectory was used to identify meaningful clinical subgroups, mapping the developmental course of headaches status in this TBI population. The model with the lowest Bayesian Information Criterion was used to ascertain the number of groups and each group’s polynomial order. The fit of the model was confirmed by evaluating at the posterior probability for each group.

Due to missing data at some monthly time points, serum sgp130 and sIL-6R averages were calculated over three month increments and the ratio of these mean values was used for analysis. The quarterly ratios of sgp130 and sIL-6R (sgp130:sIL-6R) were tested for bivariate associations with covariates. Means were computed to describe continuous demographic and clinical covariates, and Pearson correlations were determined. Frequency measures were used for categorical covariates, and Spearman correlations were determined. Headache trajectory groups were also tested for bivariate associations with sgp130:sIL-6R and covariates. Means were computed to describe continuous variables and nonparametric Mann Whitney U tests were conducted. For categorical variables, frequency measures were used and Chi-Square tests or Fisher’s Exact tests were conducted appropriately. The quarterly mean differences in sgp130:sIL-6R between trajectory groups were tested using the Kruskal-Wallis Test.

Multivariable logistic regression was used to assess relationships between sgp130:sIL-6R and trajectory groups, while controlling for relevant covariates. To enhance the interpretability of the effect size, quarter 1 sgp130:sIL-6R values were standardized to represent differences in the probability of the outcome for each one standard deviation change in the ratio. To adjust for covariates, age, sex, GCS, pre-injury history of alcoholism, and pre-injury history of headaches were assessed in addition to sgp130:sIL-6R in the final logistic regression model. Age was included in the model to control for confounding. Previous studies have demonstrated associations between sex differences in immune responses after TBI,50 between GCS and inflammation profiles,51 and between pre-injury substance abuse and post-injury outcomes.52 There are also established relationships between the development of headaches after TBI and both sex and pre-injury history of headaches.9 Thus, an a priori decision was made to control for several other covariates in the model including sex, GCS, pre-injury history of alcoholism, and pre-injury history of headaches.

To determine if headache trajectory group was associated with secondary outcome variables, nonparametric Mann Whitney U tests were conducted for continuous variables and Chi-Square tests were conducted for categorical variables. The significance level was set at α=0.05.

# RESULTS

## DESCRIPTION OF THE COHORT

Table 1. Demographic characterization of the cohort and associations of demographic and clinical variables with sgp130:sIL-6R.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total sample (n=79)** | **Association with sgp130:sIL-6R** | **p-value** |
| **Age, mean (SD)** | 40.18 (2.13) | -0.047 | 0.707 |
| **BMI, mean (SD)** | 29.91 (1.62) | -0.048 | 0.816 |
| **Gender, n (%; male)** | 57 (72.2%) | -0.062 | 0.877 |
| **GCS, mean (SD)** | 8.31 (0.62) | 0.118 | 0.347 |
| **Race, n (%)** |  |  |  |
| **African American** | 2 (3.0%) | -0.713 | 0.511 |
| **White (referent)** | 63 (95.5%) | - | - |
| **Other** | 1 (1.5%) | -1.597 | 0.296 |
| **Mechanism of Injury, n (%)** |  |  |  |
| **Motor Vehicle (referent)** | 33 (55.9%) | - | - |
| **Falls** | 22 (37.3%) | 0.466 | 0.275 |
| **Other** | 4 (6.8%) | -0.255 | 0.786 |
| **History of Anxiety, n (%)** | 20 (26.3%) | -0.03 | 0.942 |
| **History of Depression, n (%)** | 23 (30.3%) | -0.019 | 0.963 |
| **History of Alcoholism, n (%)** | 3 (8.6%) | -0.153 | 0.766 |
| **History of Headaches, n (%)** | 19 (25.3%) | 0.082 | 0.839 |
| **Ever smoke, n (%)** | 57 (79.2%) | 0.35 | 0.46 |
| **Ever illicit drug use, n (%)** | 33 (47.1%) | -0.825 | **0.027** |

**Demographic characterization of the cohort and associations of demographic and clinical variables with sgp130:sIL-6R. Bolded p-values indicate statistical significant differences (p<0.05) for Chi-Square associations between sgp130:sIL-6R and categorical variables and for Pearson correlations between sgp130:sIL-6R and continuous variables. BMI: Body Mass Index. GCS: Glasgow Coma Scale**.

Table 1 outlines demographic and clinical variables for the TBI cohort. The mean age of thecohort was 40.18, compared to a mean age of 29.85 in the non-injured control group. This cohort is predominantly male (72.2%), compared to a 43.75% male non-injured control group. Both the cohort and the non-injured control group were predominantly white individuals (95.5% and 71.88%, respectively). The most common mechanism of injury was a motor vehicle accident, followed by falls. Table 1 also outlines associations of the demographic and clinical variables with sgp130:sIL-6R. The only statistically significant association was a strong, negative correlation between illicit drug use status and sgp130:sIL-6R (p=0.027).

## trajectory groups



Figure 1. Percent of individuals who endorsed headache at a given month by trajectory group.

**Individuals must have completed the headache questionnaire to be considered in the denominator.**

In our cohort, three trajectory group profiles (*low, resolve,* and *chronic*) were identified for headache status over time for the first year post-injury. Monthly headache status (percentage of those who endorsed headache) for each trajectory group are graphed in Figure 1. The average group posterior probability was 0.845 for the *low* trajectory group, 0.890 for the *resolve* trajectory group, and 0.891 for the *chronic* trajectory group.

The maximum prevalence of headache endorsement among individuals in the *low* trajectory group (n=21) was 9.09% (n=1) in month 1. No individuals in the low trajectory group endorsed headaches at any other month, except 8.33% (n=2) in month 11. The *resolve* trajectory group (n=23) consists of individuals who endorse having headaches in the first several months, but the percentage of those who endorse headaches in the *resolve* trajectory groups declines linearly after month 2. The *chronic* trajectory group (n=35) follows a cubic trajectory consisting of individuals who have headaches that persist through 12 months post-injury. The percentage of those who endorsed headaches was always above 55% in the *chronic* trajectory group.

## the effect of tbi on sgp130:sil6-R



Figure 2. Mean quarterly sgp130:sIL6R levels for individuals after a TBI (n=77).

**Error bars indicate standard error of the mean. Control sgp130:sIL6R values are provided for n=18.**

We hypothesized that individuals with a TBI would have lower sgp130:sIL-6R levels than non-injury controls. Thus, a one-sided p-value was used. The effect of TBI on sgp130:sIL-6R is graphed in Figure 2. Individuals with a TBI (n=77) have lower levels of sgp30:sIL-6R in all four quarters post-injury compared to controls with no injury (n=18). This difference is statistically significant in quarters 1, 3, and 4 (p=0.039, 0.032, and 0.031, respectively).

## determining the sgp130:sIl-6R cut-point

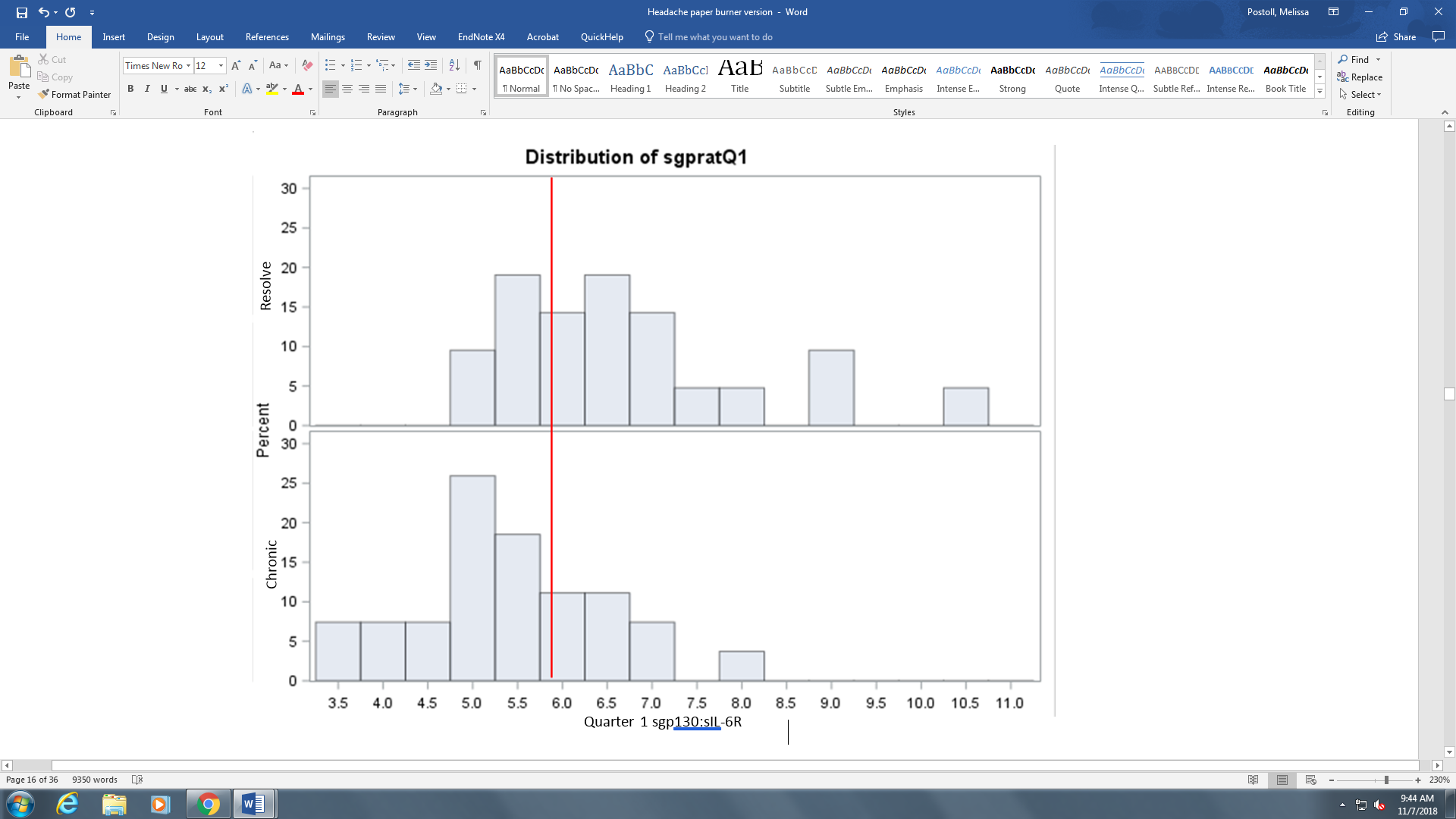


Figure 3. Distribution of sgp130:sIL-6R in the resolve and chronic trajectory groups.

**The red line indicates sgp130:sIL-6R=5.9, the determined cut-point.**

To use sgp130:sIL-6R as a diagnostic predictor of symptomatic trajectory group membership (*resolve* and *chronic*), the ratio was dichotomized into high and low sgp130:sIL6R ratios. A cut-point of 5.9 was determined by examining the distribution of sgp130:sIL-6R by symptomatic trajectory groups as seen in Figure 3. Quarter 1 sgp130:sIL-6R was used because the trajectory between the *resolve* and *chronic* trajectory groups diverges after month 3. The distribution of the *low* trajectory group was not considered for determining the cut-point since nearly all these individuals do not exhibit headache throughout the time course. The sensitivity and specificity to predict headache trajectory group (*resolve* vs *chronic*) were 74.1% and 61.9%, respectively.

Table 2. Demographic characterization of the cohort by trajectory group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Low (n=21)** | **Resolve (n=23)** | **Chronic (n=35)** | **pvalue** |
| **Age, mean (SD)** | 49.14 (4.61) | 37.61 (3.47) | 36.49 (2.99) | **0.047** |
| **BMI, mean (SD)** | 27.11 (1.8) | 30.87 (3.0) | 31.24 (3.1) | 0.577 |
| **Gender, n (%; male)** | 17 (81.0) | 15 (65.2) | 25 (71.4) | 0.504 |
| **GCS, mean (SD)** | 9.62 (1.2) | 7.43 (1.1) | 8.09 (1.0) | 0.338 |
| **Race, n (%)** |  |  |  | 0.169 |
| **African American** | 0 | 0 | 2 (7.4) |  |
| **White** | 16 (94.1) | 22 (100) | 25 (92.6) |  |
| **Other** | 1 (5.9) | 0 | 0 |  |
| **Mechanism of Injury, n (%)** |  |  |  | 0.934 |
| **Motor Vehicle** | 8 (50) | 12 (63.2) | 13 (54.2) |  |
| **Falls** | 7 (43.8) | 6 (31.4) | 9 (37.5) |  |
| **Other** | 1 (6.2) | 1 (5.3) | 2 (8.3) |  |
| **History of Anxiety, n (%)** | 4 (21.1) | 6 (27.3) | 10 (28.6) | 0.892 |
| **History of Depression, n (%)** | 4 (21.1) | 8 (36.4) | 11 (31.4) | 0.558 |
| **History of Alcoholism, n (%)** | 0 | 0 | 3 (21.4) | 0.099 |
| **History of Headaches, n (%)** | 4 (20) | 5 (21.7) | 12 (34.3) | 0.489 |
| **Ever smoke, n (%)** | 9 (81.8) | 6 (60) | 9 (60) | 0.497 |
| **Ever illicit drug use, n (%)** | 7 (43.8) | 10 (52.6) | 17 (58.6) | 0.622 |

**Bolded p-values indicate statistical significant differences (p<0.05) between trajectory groups. BMI: Body Mass Index. GCS: Glasgow Coma Scale**.

Table 2 outlines demographic and clinical variables by trajectory group. The mean age of the *low* trajectory group was higher than the *resolve* and *chronic* trajectory groups (p=0.047). Individuals in the *chronic* trajectory group had a greater pre-injury history of alcoholism (p=0.099), but this difference was not statistically significant.

## biomarker relationships to headache trajectory group

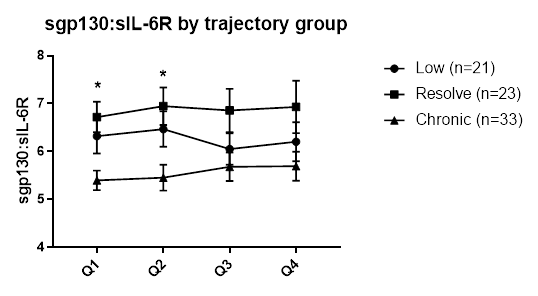


Figure 4. Mean quarterly sgp130:sIL6R levels for the low (n=21), resolve (n=23), and chronic (n=33) headache trajectory groups.

**Error bars indicate standard error of the mean. There was a significant difference in ratio levels between groups in quarters 1 (p=0.005) and 2 (p=0.013).**



Figure 5. Mean quarterly sgp130:sIL6R levels for the resolve (n=23) and chronic (n=33) headache trajectory groups.

**Error bars indicate standard error of the mean. Control sgp130:sIL6R values are provided for those with no injury (n=18). There was a significant difference in ratio levels between groups in quarters 1 (p=0.001), 2 (p=0.007), and 4 (p=0.020).**

The average levels of IL-6 did not differ by trajectory group in any quarter (data not shown, p≥0.214 for all quarters). The sgp130:sIL-6R quarterly averages stratified by trajectory group are graphed in Figure 4. Individuals in the *chronic* trajectory group had significantly lower sgp130:sIL-6R ratios than among individuals in the *low* and *resolve* trajectory groups in quarters 1 and 2 (p=0.005 and 0.013, respectively). The sgp130:sIL-6R quarterly averages of the trajectory groups with headache symptoms in quarter 1 (the *resolve* and *chronic* trajectory groups) are graphed in Figure 5. Individuals in the *resolve* trajectorygroup had similar sgp130:sIL-6R ratios to non-injury controls at all quarterly time points (p>0.05 all comparisons). In contrast, individuals in the *chronic* trajectory group had significantly lower sgp130:sIL-6R ratios at all quarterly time points (p<0.05 all comparisons).

Table 3. Univariate and Multivariate models for Q1 sgp130:sIL6R.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Logistic Regression Model for *Chronic* vs. *Resolve* Headache Trajectory Groups** | | | | | |
|  | Univariate | |  | Multivariate | |
|  | OR (95% CI) | pvalue |  | OR (95% CI) | pvalue |
| Q1 sgp130:sIL6R | 0.262 [0.104, 0.660] | **0.005** |  | 0.241 [0.087,0.669] | **0.006** |
| Age |  |  |  | 0.951 [0.896,1.010] | 0.103 |
| Sex |  |  |  | 2.881 [0.417,19.876] | 0.283 |
| GCS |  |  |  | 1.003 [0.758,1.327] | 0.986 |
| Pre-injury history of alcoholism |  |  |  | 0.502 [0.034,7.420] | 0.616 |
| Pre-injury history of headaches |  |  |  | 7.868 [0.600,103.270] | 0.116 |

**The multivariate model was adjusted for age, sex, GCS, pre-injury history of alcoholism, and pre-injury history of headaches. Bolded p-values indicate statistical significance (p<0.05). GCS: Glasgow Coma Scale**.

In order to compare the trajectory groups that are symptomatic in the first quarter, a binary logistic regression model was run with the *resolve* and *chronic* trajectory groups only (Table 3). The probability of chronic trajectory group was modelled relative to resolve trajectory. Quarter 1 sgp130:sIL-6R was assessed as a continuous independent variable in the initial logistic regression model for headache trajectory group. In the unadjusted model, a one standard deviation increase in quarter 1 sgp130:sIL-6R protects against *chronic* headache trajectory membership compared to *resolve* by 73.8% [OR=0.262; 95% CI: 0.104-0.660; p=0.005]. After controlling for age, sex, GCS, pre-injury history of alcoholism, and pre-injury history of headaches, a one standard deviation increase in quarter 1 sgp130:sIL-6R protects against *chronic* headache trajectory membership compared to *resolve* by 75.9% [OR=0.241; 95% CI: 0.087-0.669; p=0.006].

## characterization of headache

Between individuals in the *resolve* and *chronic* trajectory groups, there were no differences in vision changes (19% and 28%, respectively, p=0.526), nor in skin sensations (27% and 34%, respectively, p=0.579) prior to onset and after onset of headache. The most frequently reported headache locations among individuals in the *resolve* trajectory group were the front, and the left and right temples, reported an average of 7.96%, 6.82%, and 6.82% of the months, respectively. The most frequently reported headache locations among individuals in the *chronic* trajectory group were the back, front, and the right temple, reported an average of 19.79%, 19.08%, and 14.90% of the months, respectively. The most frequently reported pain types associated with headaches among individuals in the *resolve* trajectory group were pressure (16.29%), constant (12.88%), throbbing (11.37%), and tightness (10.32% of the months). The most frequently reported pain types associated with headaches among individuals in the *chronic* trajectory group were pressure (34.76%), constant (28.03%), pounding (24.51%), and throbbing (23.53% of the months).



Figure 6. Headache characteristics for resolve and chronic trajectory groups

**(a) Quarterly mean number of headache days in a month by resolve (n=23) and chronic (n=35) headache trajectory groups.** **Error bars indicate standard error of the mean. The mean number of headache days in the chronic trajectory group was above 15 in quarters 1, 3, and 4. (b) Quarterly mean severity of monthly headaches in the resolve (n=23) and chronic (n=35) headache trajectory groups. Error bars indicate standard error of the mean. A severity of 1.0 indicates mild severity, 2.0 indicates moderate severity, and 3.0 indicates severe severity.**

The numbers of headache days reported by individuals each month were averaged by quarter and these averages are graphed in Figure 6a, stratified by trajectory group. The mean number of headache days per month reported by individuals in the *chronic* group was 22 days in quarter 1, 14.4 days in quarter 2, 21.8 days in quarter 3, and 16.4 days in quarter 4. The severity of headaches was reported by individuals to be mild (1), moderate (2), or severe (3). These monthly severity reports were averaged by quarter and these averages are graphed in Figure 6b, stratified by trajectory group. There were no significant differences in reported severity between individuals in the *resolve* and *chronic* trajectory groups, but the mean severity for those in the *chronic* trajectory group always trended higher than the mean severity for individuals in the *resolve* trajectory group.

## associations between headache trajectory group and secondary outcomes

### Percent back to normal

Table 4. Quality of life by trajectory group

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Low (n=21)** | **Resolve (n=23)** | **Chronic (n=35)** | **pvalue** |
| **Total 6mo** | 88.59 (3.2) | 76.21 (6.5) | 72.28 (5.0) | 0.063 |
| **Total 12mo** | 88.24 (3.3) | 84.58 (3.5) | 78.10 (3.3) | 0.113 |
| **Physical 6mo** | 87.65 (4.3) | 65.93 (8.4) | 72.60 (5.2) | **0.023** |
| **Physical 12mo** | 89.41 (4.1) | 87.53 (3.6) | 74.66 (4.8) | **0.016** |
| **Emotional 6mo** | 88.12 (4.8) | 77.86 (9.1) | 77.60 (4.9) | 0.324 |
| **Emotional 12mo** | 89.94 (3.5) | 92.26 (3.3) | 82.25 (3.5) | 0.075 |
| **Cognitive 6mo** | 83.82 (6.1) | 82.50 (7.0) | 71.00 (5.8) | 0.093 |
| **Cognitive 12mo** | 90.06 (3.4) | 87.89 (3.9) | 80.59 (3.8) | 0.127 |

**Quality of Life was measured by self-reported percent back to pre-injury normal functioning and stratified by trajectory group.** **Mean (stderr) of total, physical, emotional, and cognitive percentages back to normal were reported at 6 and 12 months. Statistically significant differences between trajectory groups are indicated by bolded p-values (p<0.05).**

Mean percent back to normal was reported at 6 and 12-month visits, and the results are shown in Table 4. The average total percent back to normal was not significantly different between the three headache trajectory groups at either 6 months (p=0.063) or at 12 months (p=0.113), but individuals in the *resolve* trajectory group trended lower than individuals in the *low* trajectory group at both 6 months (76.2% vs. 88.6%) and at 12 months (84.6% vs. 88.2%). Those in the *chronic* trajectory group trended lower than individuals in the *low* and *resolve* trajectory groups at both 6 months (72.3%) and 12 months (78.1%). The average reported physical percent back to normal at 6 months were significantly lower for individuals in the *resolve* and *chronic* trajectory groups (65.9% vs. 72.6%) than those in the *low* trajectory group (87.7%; p=0.023). By 12 months, individuals in the *resolve* trajectory group reported average a physical percent back to normal that was similar to the physical percent back to normal reported by those in the *low* trajectory group (87.5% vs. 89.4%). The percentage reported by those in the *resolve* trajectory group remained significantly lower (74.7%, p=0.016). A similar temporal pattern was also seen in the average reported emotional percent back to normal. At 6 months, emotional percent back to normal showed no trends in differences among groups. At 12 months, individuals in the *low* trajectory group reported 89.9% back to normal emotionally, individuals in the *resolve* trajectory group reported 92.3%, and those in the *chronic* trajectory group reported 82.3% (p=0.075). Similar trends were also seen in the average cognitive percent back to normal, but the differences were not significant at either 6 months (*low*: 83.8%; *resolve*: 82.5%; *chronic*; 71.0%, p=0.093) or 12 months (*low*: 90.1%; *resolve*: 87.9%; *chronic*; 80.6%, p=0.127).

### Anxiety, PTD, and fatigue

Table 5. Quarterly anxiety, PTD, PROMIS, and FSS by trajectory group

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Quarter** | **Low (n=21)** | **Resolve (n=23)** | **Chronic (n=35)** | **pvalue** |
| **Table 5a: GAD-7** | 1 | 1.74 (0.8) | 4.88 (1.4) | 4.27 (1.2) | 0.105 |
|  | 2 | 2.19 (0.9) | 2.85 (0.8) | 3.67 (0.7) | 0.249 |
|  | 3 | 1.90 (0.9) | 3.36 (0.9) | 4.61 (0.8) | **0.021** |
|  | 4 | 1.60 (0.8) | 2.96 (0.8) | 3.72 (0.6) | **0.031** |
| **Table 5b: PTD (n,%)** | 1 | 4 (26.7) | 7 (43.8) | 7 (29.2) | 0.617 |
|  | 2 | 3 (17.7) | 6 (28.6) | 12 (44.4) | 0.160 |
|  | 3 | 3 (20) | 5 (25) | 11 (39.3) | 0.410 |
|  | 4 | 1 (5.9) | 4 (19.1) | 11 (37.9) | **0.040** |
| **Table 5c: PROMIS** | 1 | 11.89 (1.6) | 18.65 (1.5) | 16.05 (1.3) | **0.002** |
|  | 2 | 12.52 (1.4) | 14.53 (1.2) | 16.26 (1.3) | 0.066 |
|  | 3 | 12.47 (1.7) | 14.53 (1.7) | 15.87 (1.4) | 0.071 |
|  | 4 | 11.41 (1.1) | 12.94 (1.2) | 14.83 (1.2) | 0.068 |
| **Table 5d: FSS** | 1 | 16.43 (3.3) | 27.73 (2.5) | 24.67 (2.9) | **0.004** |
|  | 2 | 17.81 (2.8) | 22.10 (2.7) | 24.35 (3.0) | 0.303 |
|  | 3 | 16.99 (3.5) | 22.39 (3.9) | 23.74 (2.9) | 0.135 |
|  | 4 | 14.94 (2.7) | 19.27 (3.0) | 22.44 (2.5) | 0.070 |

**(a) Quarterly anxiety, measured as mean monthly GAD-7 scores, stratified by trajectory group. (b) Quarterly PTD measured via PHQ-9 questionnaires, stratified by trajectory group. (c) Quarterly PROMIS questionnaire scores, stratified by trajectory group. (d) Quarterly FSS questionnaire scores, stratified by trajectory group. NOTE: Mean (stderr) reported, unless otherwise specified. Statistically significant differences between trajectory groups are indicated by bolded p-values (p<0.05).**

Mean GAD-7 scores are provided in Table 5a, stratified by headache trajectory group. Scores for individuals in the *resolve* trajectory group decreased over time, and the difference between groups was significant in quarter 3 (*low*: 1.90; *resolve*: 3.36; *chronic*: 4.61, p=0.021). This trend continued into quarter 4, in which individuals in the *low* and *resolve* trajectory groups scored significantly lower than those in the *chronic* group (*low*: 1.60; *resolve*: 2.96; *chronic*: 3.72, p=0.031).

The number and percentage of individuals with PTD each quarter are provided in Table 5b, stratified by headache trajectory group. There was a significant difference between trajectory groups in quarter 4, in which there were significantly more individuals with PTD in the *chronic* trajectory group (n=11, 37.9%) compared to the *low* (n=1, 5.9%) and *resolve* groups (n=4, 19.1%; p=0.040). Notably, the percentage of individuals with PTD in *low* and *resolve* trajectory groups roughly decreased over the four quarters, whereas the percentage of individuals with PTD in the *chronic* trajectory group roughly increased from quarter 1 (n=7, 29.2%) to 2 (n=12, 44.4%), and then remained high in quarters 3 (n=11, 39.3%) and 4 (n=11, 37.9%).

PROMIS scores were averaged quarterly and the mean scores are provided in Table 5c, stratified by headache trajectory group. There was a significant difference in PROMIS scores between trajectory groups in quarter 1 scores (p=0.002). Individuals in the *low* trajectory group had the lowest mean PROMIS score compared to individuals in the *resolve* and *chronic* trajectory groups in the first quarter (11.89 vs. 18.65 and 16.05), the second quarter (12.52 vs. 14.53 and 16.26; p=0.066), the third quarter (12.47 vs. 14.53 and 15.87; p=0.071) and the fourth quarter (11.41 vs. 12.94 and 14.83; p=0.068). Mean FSS scores are provided in Table 5d, stratified by headache trajectory group. There was a significant difference in FSS scores between trajectory groups in quarter 1 scores (p=0.004); individuals in the *low* trajectory group had the lowest mean FSS score compared to individuals in the *resolve* and *chronic* trajectory groups (16.43 vs. 27.73 and 24.67). A similar pattern between groups existed the fourth quarter (14.94 vs. 19.27 and 22.44; p=0.070).

### Cortisol

There was a statistically significant difference between trajectory groups in Quarter 3 (p=0.049), in which individuals in the *chronic*trajectory group had higher average levels of cortisol (167.2 ng/mL) than did those in the *low*and *resolve*trajectory groups (142.2 and 143.3 ng/mL). This pattern was also seen in quarter 2 (152.8 vs. 140.8 and 131.6 ng/mL) ; p=0.127), but the difference between groups was not statistically significant.

# discussion

Headache after TBI is an important public health issue, as it is one of the most common impairments after TBI and is the most common secondary headache disorder.44 Yet few studies have identified temporal profiles of headaches and biological correlates. Previous literature examines post-traumatic headache longitudinally, but only in 3 month intervals or more.9,13,29 The present study used group-based trajectory analysis with monthly time points to uncover three clinically relevant and meaningful headache profiles. We identified an inflammatory marker, sgp130:sIL-6R, that is a potentially highly relevant prognostic marker for chronic headache trajectory after TBI.

The International Classification of Headache Disorders-3 (ICHD-3) acknowledges that there are no specific features known to distinguish the types of headaches attributed to trauma or injury to the head or neck, and does not distinguish between type, such as migraine or tension-type headaches, despite differences in triggers, symptoms, and treatments.53 Currently, the ICHD-3 diagnoses acute post-traumatic headache if the headaches occur within the first three months and persistent post-traumatic headache if they continue to occur. In our study, the *resolve* and *chronic* trajectory groups experience differences in types of headaches, besides the acute versus persistent distinctions. For example, those in the *resolve* trajectory group experienced headaches most commonly in the right and left temples, whereas those in the *chronic* trajectory group experienced them most commonly in the back and front of the head. Further, those in the *resolve* trajectory group frequently reported tightness while those in the *chronic* trajectory group did not. Those in the *chronic* trajectory group frequently reported pounding sensations, whereas those in the *resolve* trajectory group did not. Although differences in the reported severity of headaches does not differ statistically between groups, the reported severity in the *chronic* trajectory groups trends above *resolve* trajectory throughout the first year. In general, the headaches of those in the *chronic* trajectory group not only persist longer, but are also more frequent, more migraine-like, and may also be more severe with respect to pain. These nuanced differences between individuals with chronic versus resolving headaches may be important to include in future ICHD classification systems.

Chronic daily headache (CDH) is defined as a 3-month history of headaches occurring for at least 15 days per month.54 In our study, we observed that the number of days with headache in a month experienced by individuals in the *chronic* trajectory group almost always averages above this 15 days per month mark. Treating CDH in general populations is incredibly complex and difficult.54,55 Current practice recommends lifestyle changes such as moderating caffeine intake, increasing physical activity, improving sleep hygiene and diet.55 Furthermore, no randomized clinical trials have been conducted to date on treatments for headaches after TBI.

A novel component of our study was the investigation into biological correlates of headache trajectory. Previous studies have suggested that IL-6 itself could serve as a biomarker of inflammatory burden after a TBI, and intrinsic brain mechanisms such as inflammation due to innate and adaptive immune responses impact outcomes after TBI.31 No human studies have considered the ratio between sIL-6R and sgp130 and its clinical implications for headaches, despite a need to better understand post-traumatic headaches.39 The present study assesses these relationships longitudinally after injury in a moderate to severe TBI population and evaluates the associations of the sgp130:sIL-6R ratio with outcomes.

In classical IL-6 signaling, IL-6 binds to its alpha receptor (IL-6R), which is not involved in signal transduction and is not expressed on all cells in the body. When the IL-6/IL-6R complex associates with the widely-expressed G-protein130, signal transduction is possible. Downstream effects of classic IL-6 signaling are primarily beneficial. However, IL-6 can also bind a soluble form of the IL-6 receptor (sIL-6R) and initiate a process known as trans-signaling in which the IL-6/sIL-6R complex activates the ubiquitously expressed membrane-bound gp130.56 Trans-signaling is responsible for the detrimental effects of IL-6, as it increases the half-life and bioavailability of IL-6 and can lead to chronic inflammation.57 In serum, the IL-6/sIL-6R complex is limited by the presence of the soluble form of G-protein130 (sgp130), which blocks IL-6/sIL-6R trans-signaling. Sgp130 has no effect on signal transmission via the classical IL-6 signaling processes.56 Therefore, in post-TBI inflammation, sgp130 may be a therapeutic target for the prevention of adverse effects of trans-signaling by blocking chronic IL-6 effects that are mediated via sIL-6R.

Individuals with TBI in our study had significantly lower levels of sgp130:sIL-6R but similar levels of IL-6 across headache trajectory groups. Importantly, the quarter 1 sgp130:sIL-6R levels of those in the *chronic* trajectory group were lower than the quarter 1 sgp130:sIL-6R of those in the *low* trajectory group, and significantly lower still than the quarter 1 sgp130:sIL-6R levels of those in the *resolve* trajectory group. Those in the *resolve* trajectory group have quarter 1 sgp130:sIL-6R similar to levels in the non-injury controls. Thus, it is possible that an increase in sgp130 relative to sIL-6R in this *resolve* trajectory group of individuals with a TBI acts to prevent the deleterious effects of trans-signaling, which is associated with poor global outcomes through twelve months post-injury.36 As the effect of sgp130 is inhibitory to the potent effects of sIL-6R on the activity of IL-6, sgp130 is a potential novel immunotherapy target for headaches and its associated post-injury outcomes.

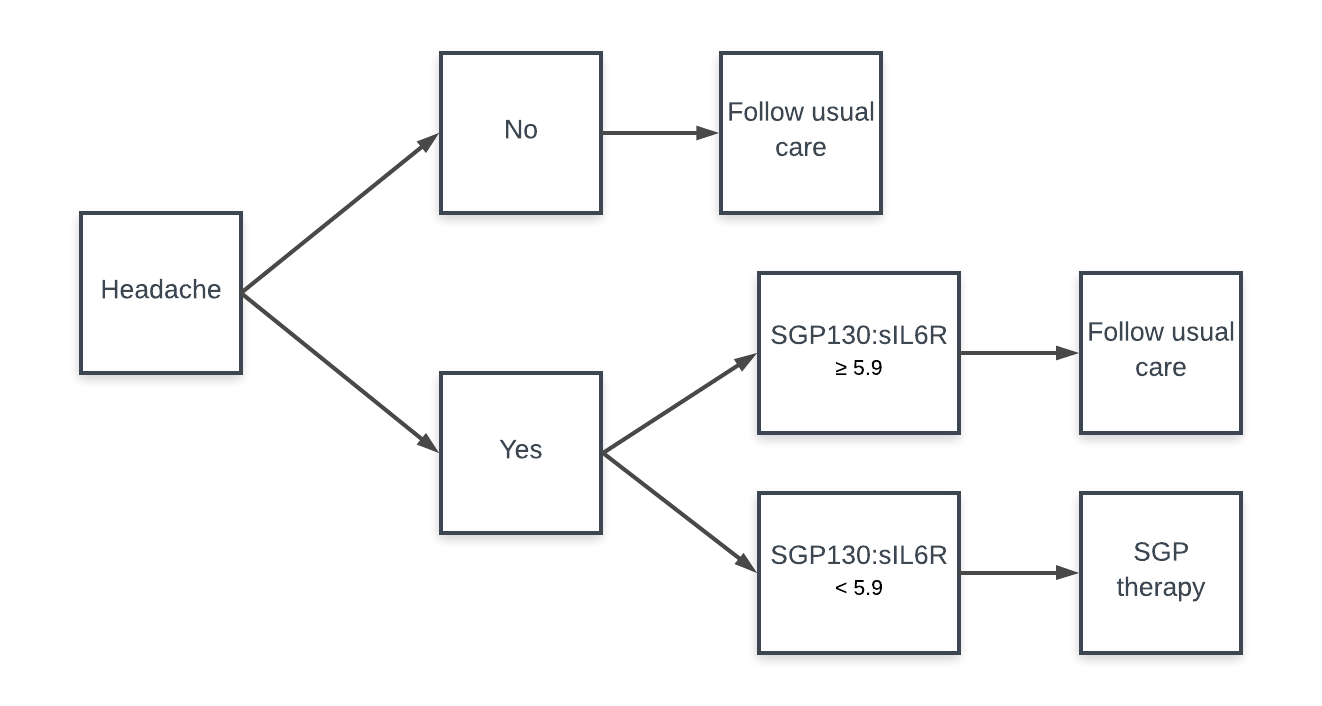


Figure 7. Clinical decision tree to model the suggested care for a patient given the sgp130:sIL-6R cut-point of 5.9.

This research has clinical and translational implications. For example, we propose a potential clinical decision tree in Figure 7 based on the results of this study. If an individual does not report a headache in the first quarter, we suggest that this individual would likely follow a trajectory similar to that of a member of the *low* trajectory group and could therefore follow usual care. An individual that reports a headache in the first quarter and has a sgp130:sIL-6R ratio equal to or above 5.9, we suggest that this individual might resemble a member of the *resolve* trajectory group and that their headaches will taper off in subsequent months. Finally, an individual that reports a headache in the first quarter and has a sgp130:sIL-6R ratio below 5.9, we suggest that this individual would likely resemble a member of the *chronic* trajectory group and could therefore qualify for immunotherapy treatment. However, this decision tree is theoretical, and these suggestions need to be tested.

Those with migraines and chronic headache are twice as likely to have comorbidities such as depression, anxiety, chronic pain, and are at higher risk for cardiovascular and respiratory events.58 The low sgp130:sIL-6R ratio and the presence of headaches in first three months after TBI are associated with several unfavorable outcomes. Specifically, the present study found that an individual’s membership in the *chronic* trajectory group was associated with poorer outcomes after TBI. These individuals had worse reported percent back to normal measures, especially in the physical function area. Those with headaches in the first quarter (both the *resolve* and *chronic* trajectory groups) had worse fatigue scores in those first three months, as measured by both the FSS and PROMIS questionnaires. Then in the third quarter, those in the *chronic* trajectory group had higher cortisol levels, elevated levels of which exacerbate inflammation and are associated with more unfavorable outcomes and worse Glasgow Outcome Scores.59 In the third quarter, those in the *chronic* trajectory group also had higher anxiety, which continued into the fourth quarter after injury, at which time the *chronic* trajectory group also exhibited higher frequencies of post-traumatic depression. Previous studies have found that persistent IL-6 elevation can lead the individual with a TBI to experience worse outcomes.31 The results of the present study suggest that these unfavorable outcomes for the individuals in the *chronic* trajectory group may have been due to the chronic lack of inhibition of IL-6 by low levels of sgp130 relative to sIL-6R during the first three months post-injury.

There are limitations of this study to consider. The inclusion criteria of this study limit the severity of injury to moderate or severe TBIs. Thus, the results of this study may not generalize to mild TBIs. At some timepoints, individuals may have had missing data for various reasons. Additionally, the cohort of the present study is of a TBI population in Pittsburgh that largely consists of white men, and therefore may not be generalized to women, other races, or populations in other regions. Also, the average age of the individuals in our study was 40.1 years. Therefore, these results need to be verified among older populations and potentially in children. Another important limitation of this study was that the control group was not selected based on matches in demographic features such as age or gender. Differences in the control group and the TBI group in this study could be driven by these demographic differences. However, we did not find that sgp130:sIL-6R levels were associated with either age or gender.

Previous studies have shown that TBI outcomes are associated with genetic variation.60–63 It is possible that genetic variations are associated with differences in pain responses after injury for these headache profiles. Future studies should examine how sgp130:sIL-6R may have a role in the moderation of this pain, and they should also examine how headache outcomes are associated with other types of chronic pain. Additionally, headaches have long been associated with seizures; they are typical episodic neurological disorders and have some shared genetic mutations, such as the neuronal voltage-gated sodium channel SCN1A.64,65 Studying these associations longitudinally in a TBI population could elicit important relationships between these two post-injury outcomes. Finally, work should be done in animal models to determine what produces sgp130 and its mechanisms. These animal studies should also endeavor to determine if treating animals with sgp130 results in any changes in the animal headache phenotype.

This study has added to the moderate to severe TBI literature by providing a comprehensive, longitudinal characterization of headaches after TBI, and its comorbid impairments. The identification of a biological correlate of headaches after TBI is an important and novel contribution to the field, as it has implications for the treatment and rehabilitation of individuals with TBI. Understanding the underlying biology and recognizing the consequential public health significance of this condition in the moderate to severe TBI population can inform rehabilitation efforts to improve impairments that result from both TBI and from consequential headaches. Because of the heterogeneous nature of injury, the recovery processes and long-term deficiencies for this population are also diverse. Developing a biomarker clinical decision algorithms, such as the one presented with sgp130:sIL-6R in this study, could generate appropriate screening and prevention tools for undesirable complications and persistent post-injury disabilities.

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