

Preparing for the Future: Analyzing the Long-Term Effects of Traumatic Brain Injury

A. Gleekel and H. Song
Breck School, Minneapolis, MN

Traumatic brain injury (TBI) affects up to 1.7 million Americans annually. At least 2% of patients who suffer from a TBI will live with long-term disability. However, there is little known of the long-term effects of TBIs and their causes. It is essential that research be performed to better characterize the decades long impact of these injuries so that patients and doctors can prepare for the future.

To assess the long-term effects, five tests were used: the Glasgow Coma Scale (GCS), Glasgow Recovery Scale (GRS), Telephone Interview for Cognitive Status - Modified (TICS-M), eye tracking, and blood biomarkers. The GCS and GRS are scales of urgency and recovery, while the TICS-M and eye tracking are assessments of cognitive status. In addition, the effects of hyperbaric oxygen (a common treatment for TBI) on outcome were assessed. After analyzing and collecting data from TBI patients with injuries in the 1980s, we reaffirmed and found:

- The more urgent the TBI, the worse the recovery,
- TICS-M is an invalid assessment to quantify cognitive decline,
- Eye tracking metrics show promise as accurate predictors of cognitive decline,
- And hyperbaric oxygen treatment is an effective treatment option for TBI.

In our study, the GCS scale, eye tracking, and hyperbaric oxygen could be reestablished, while the TICS-M was found to be invalid. It is also the first long-term study of its caliber and magnitude that has been conducted in this area. The results from this unprecedented research will provide invaluable and unique insight into TBI recovery.

Keywords: TBI, hyperbaric oxygen, mortality, recovery, cognitive decline

Abbreviations: Traumatic Brain Injury (TBI), Glasgow Coma Scale (GCS), Glasgow Recovery Scale (GRS), Telephone Interview for Cognitive Status/Modified (TICS-M), Hyperbaric Oxygen (HBO)

Funding and resources were provided by the Brain Injury Research Lab at Hennepin County Medical Center.

This paper received a 2017 Minnesota Academy of Science STEM Communicator Award. The judging process for this award satisfied the function of manuscript review.



http://www.huffingtonpost.com/anat-baniel/brain-injury-awareness_b_2891999.html

INTRODUCTION

Traumatic brain injury (TBI) is the result of an external force that causes physical and structural damage to the brain (1). The source of the external force can range from a sports impact to a minor fall or a car accident, making TBI one of the most common injuries in adults and adolescents. More than half of TBI cases are caused by falls or auto accidents, meaning everybody is susceptible to TBI (2). Annually, approximately 1.7 million Americans suffer from a TBI, leading to about 52,000 deaths; of those who survive, 2% with long-term disabilities (3).

When a patient experiences a severe TBI, a medical professional's primary efforts are focused on saving the patient's life, rather than evaluating the long-term effects. The doctors seldom inform the patients how their life is going to be affected following the injury because their focus is on the initial urgency. This is mainly due to the lack of research dedicated to studying the long-term effects of TBI.

TBIs can have substantial effects on the cognitive, emotional, and behavioral well-being of a patient, yet it is nearly impossible to predict these effects far in advance (4). Cognitive impacts can include difficulty concentrating or difficulty in speaking. Emotionally, patients can become depressed, angry, and irritable. Behaviorally, patients often develop alcoholism and substance abuse issues, further complicating the TBI (5). Studies have shown that substance use increases two to five years after a brain injury, and 10 to 20% of all TBI survivors develop substance abuse problems. Additionally, many post-TBI patients are susceptible to cognitive decline, including a 200 to 400% greater risk of developing dementia (6). It can also adversely affect education, work, relationships, mood, health, and many other aspects of everyday life. The extent of these long-term effects cannot be determined during the injury; however, with further research, TBI patients could seek help following their injury in order to more adequately prepare them to face these potential cognitive, emotional and behavioral challenges.

In order to understand the impact of a TBI on a patient, different tests are used to evaluate the condition of the patient. When a trauma patient is brought into the emergency room, their Glasgow Coma Scale (GCS) is evaluated immediately. This scale is categorized into three subsets: eye opening, motor response, and verbal response (7). After

assessing the patient, the doctor uses a ranking on a scale of 3 to 15 (3 represents no response and 15 is full cognitive capacity). The patients with the lower GCS receive more urgent care. Although this scale reflects the outward response of the patient, it does not diagnose the underlying brain injury nor determine its effects, making it a poor diagnostic tool. The GCS is also poor at determining the long-term outcome for a post-injury patient.

Thankfully, there are some cognitive tools, such as eye tracking and blood-based biomarkers, that can be accurate predictors of the long-term effects of TBI. Eye tracking is a simple tool being developed to evaluate a patient's neurological status (8). This tool can detect elevated intracranial pressure and disruption of eye movement control in the brain. Because of the eye's direct connection to the brain, eye tracking can potentially allow for a more precise diagnosis of the severity of brain injuries. We will also analyze blood to determine the likelihood of developing severe cognitive decline after a TBI. Finding specific biomarkers could assist in rehabilitation and treatments following the injury.

Successful treatment options for TBI are also lacking. In the 1980s, a randomized clinical trial was conducted at Hennepin County Medical Center (HCMC), Minneapolis, MN, assessing the effects of hyperbaric oxygen (HBO) on patients with TBI. A total of 168 patients with a GCS of 9 or below were recruited. Half of the patients were treated with hyperbaric oxygen, and the others were treated with standard of care (10). A different study (with limitations of sample size) reported that HBO treatment improved the patient's GCS score (3).

Our current study uses the cohort of patients from this initial HBO study to assess how brain injury affects long-term recovery (a period of 30 years between initial injury and current day). We also assessed the effects of hyperbaric oxygen on the outcome of TBI. Our goals in this study were to:

- Reaffirm and reestablish the correlation between hyperbaric treatment and mortality,
- Analyze the hyperbaric treatment's effectiveness in decreasing long-term mortality,
- Determine whether the hyperbaric treatment and the GCS scores are viable ways to predict successful patient recovery,
- Investigate the GCS's ability to successfully and accurately predict patient mortality, and

- Compare TBI patients and their age-matched controls in terms of long-term cognitive decline.

MATERIALS AND METHODS

Consent: Consent was originally obtained for the hyperbaric oxygen study by a researcher of Dr. Rockswold. After IRB approval, patients were contacted via telephone for the current study. While reconnecting with the patients, telephone consent was gained by Dr. Molly Hubbard. If the patient decided to come into the lab for further testing, more consent was gained by Dr. Hubbard or one of her medical researchers. Participation in the study was completely voluntary and all subjects and controls were compensated for their time and effort.

Patient Population: Patients were recruited from a cohort that was initially studied by Dr. Gaylan Rockswold in the 1980s. These patients had been randomized to treatment with hyperbaric oxygen or standard of care and were followed for 18 months. This patient population included 168 victims of acute severe head injury with a GCS score of 9 or less (10).

Original records were investigated and entered into a spreadsheet. The Social Security database and a publically available public records searches were used to obtain contact information for surviving patients. If a subject was found to be deceased in the Social Security database, they were not contacted.

Hyperbaric Oxygen Treatment: Hyperbaric oxygen therapy involves breathing pure oxygen in a pressurized room or through a tube where the air pressure is increased to 3 times the normal air pressure (11). The purpose of this approach is to fight bacteria and stimulate the release of growth factors and stem cells. Injured tissue requires more oxygen to survive, so hyperbaric oxygen assists in temporarily restoring normal levels of blood gases and tissue function, promoting healing and combating infection.

In the original study, 84 of the 168 patients were enrolled in the hyperbaric oxygen treatment. These treatments were given in a Sechrist monoplace hyperbaric chamber with compression of 100% oxygen to 1.5 atm absolute, which occurred at a rate of 1 psi/min (10). The patients were kept at depth for 60 minutes and were decompressed at the same rate. The treatments were given every 8 hours for 2

weeks, until the patient was brain dead or could consistently obey simple commands. We used the data from this specific study to analyze the effectiveness of hyperbaric oxygen against standard oxygen.

Glasgow Coma Scale (GCS): As an outcome measure of the severity of the patient's brain injury, the GCS was used, which describes the level of consciousness in patients with traumatic brain injury. The patients in this study were originally given a GCS of 9 or less within 6 to 24 hours after hospital admission (10). A score of 9 on the GCS was the cut off because a score of 9 GCS signals a severe brain injury, and the purpose of Dr. Rockswold's study was to observe the effects of hyperbaric oxygen (HBO) treatment on patients with such TBIs.

Glasgow Recovery Scale (GRS): This scale was used to calculate the recovery of the patients in the hyperbaric oxygen study. A neuropsychologist saw the patients at 1, 3, 6, 12, and 18 months after the original study. During these visits, the patient's GRS scores were taken. The scale is rated from 1 to 5, with 1 defined as good recovery, while 4 represents vegetative survival, and 5 indicates death.

Telephone Interview for Cognitive Status-Modified (TICS-M): The primary outcome measure of cognition for this study is the TICS-M assessment, which is a seven to ten minute assessment of current cognitive functioning (12). There are twelve aspects to the test, which are scored from a range of 0 to 50. The score can be interpreted into four qualitative impairment ranges: unimpaired, ambiguous, mildly impaired, and moderately to severely impaired. For our assessment, we determined the impairment of the patient based on methods from a study by Knopman et al; suggesting that a patient with a score of at most 27 is considered demented, a score of 28 through 31 is mild cognitive impairment, and a score of at least 32 is cognitively normal (13). For the elderly, patients over 85 years of age who have a score of greater than 28 are known to be cognitively normal. Due to HCMC privacy policies and HIPAA, we weren't able to directly interview the patients, but took notes and recorded data while lab personnel conducted the interviews.

Eye Tracking: Eye tracking is a process of following a video with your eyes around the computer screen. The video rotates five times around the screen before the eye tracking is concluded. Afterwards, a

screen will appear with the graphs of the patient’s eye movements for each rotation of the video around the screen (14).

Blood-based Biomarkers: Due to age restrictions, a medical practitioner had to perform a basic phlebotomy on each patient. The blood tubes were sent in early September to Abbott Laboratories for a protein and DNA analysis, and we have yet to receive the results. After receiving a protein and DNA analysis from blood work collected from the studies’ TBI patients and control patients, we plan to analyze five specific biomarkers that we think are directly connected to cognitive decline occurring after brain injury: apolipoprotein e (APOE), brain-derived neurotrophic factor (BDNF), myelin basic protein (MBP), nerve growth factor (NGF), and presenilin 1 and 2 (PS1 and PS2).

Data Analysis: Descriptive statistics for age and gender were calculated. Contingency analysis for mortality split by treatment groups (hyperbaric oxygen and standard care versus standard care alone) was assessed. Kaplan-Meier analysis calculated to find the effect of treatment on survival after TBI. The eye tracking data were tested between treatment groups using two sample Wilcoxon tests. Logistic regression was then performed on groups that were significant. The areas under the receiver operating curves were calculated and reported. All analyses were performed at an alpha of 0.05 using software JMP version 10.0.1.

RESULTS AND DISCUSSION

We reanalyzed the data regarding the GCS scores, GRS scores, and the short-term mortality of the HBO patients in ways that differed from the original study. However, the data for the long-term mortality and cognitive decline of TBI patients was a modern extension of the original study, conducted by Dr. Molly Hubbard, lab personnel, and us. With the data collected from the TICS-M and eye tracking, we performed unique data analysis in order to quantify the viability of these tests to detect cognitive decline in TBI patients.

HBO Short-term Mortality: Figure 1 shows the contingency analysis of the mortality, split by treatment groups. The proportion of the control group patients who died in the study (0.3214) was nearly twice the proportion of dead hyperbaric treatment patients (0.1667). A chi-squared test of

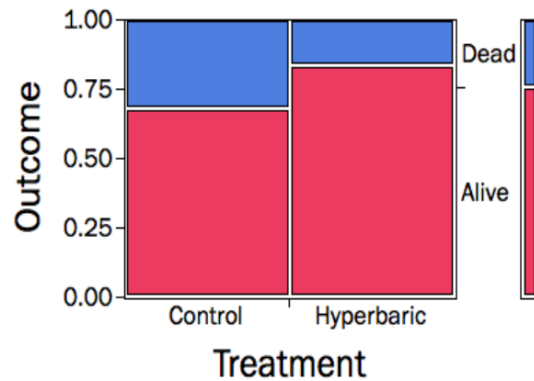


Figure 1. Number of deceased vs. number of living patients from the HBO and control groups. A chi-squared test established a significant difference between the dead and alive patients of the hyperbaric oxygen treatment and the non-hyperbaric treatment (control). Figure by authors.

homogeneity with $\alpha = 0.05$ was conducted to establish a statistically significant difference between the two proportions of treatment groups. The test yielded a p-value of 0.0195, making the difference of treatments statistically significant.

HBO Long-term Mortality: Figure 2 displays the change in the proportions of deaths in each oxygen treatment group in a Kaplan-Meier graph. Apart from the first few days, the change in mortality rate for both treatments declined at a steady pace. However, near 10,000 days (i.e. 27 years) after the injury, there were steeper decreases in the mortality rates. A chi-squared test was conducted on the Kaplan-Meier graphs of the two treatments with $\alpha = 0.05$. From a log rank chi-squared test, the p-value was calculated to be 0.9177, indicating that the difference in the change of mortality proportions between the treatment groups is statistically insignificant.

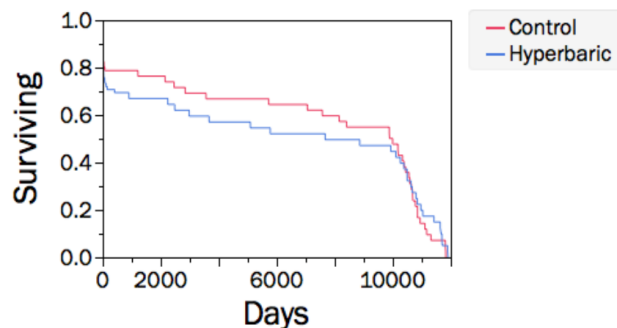


Figure 2. Kaplan-Meier graph for both HBO and control groups. The cumulative survival proportions for each treatment group over time in days is shown in this graph. The survival time was calculated by subtracting their day of TBI from their last known date of survival in the hospital records. Over time, the graph decreased overall from perpetual deaths throughout the 33 years of the study. Figure by authors.

Logistic Fit of Outcome by GCS: Figure 3 shows the logistic fit of outcome by GCS. It plots the curve of the cumulative probability of death for all 168 patients by their GCS scores. A chi-squared test for the different GCS scores conducted with $\alpha = 0.05$ produced a p-value less than 0.0001. The difference in probability of deaths for differing GCS scores was highly statistically significant. Additionally, a Receiver Operating Characteristic graph (Figure 4) was created from the same model and was found with an area under the curve of 0.72314.

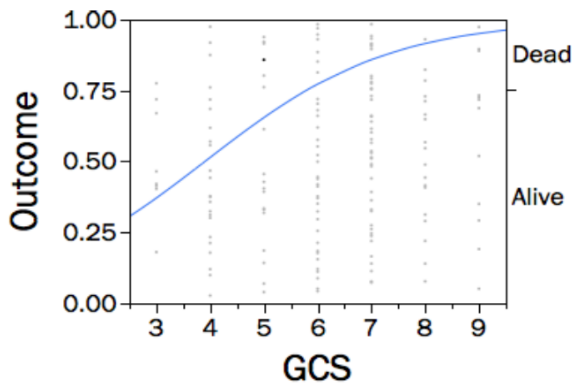


Figure 3. Logistics fit of outcome by GCS. The cumulative probability of death for each GCS score from GCS three to nine. Figure by authors.

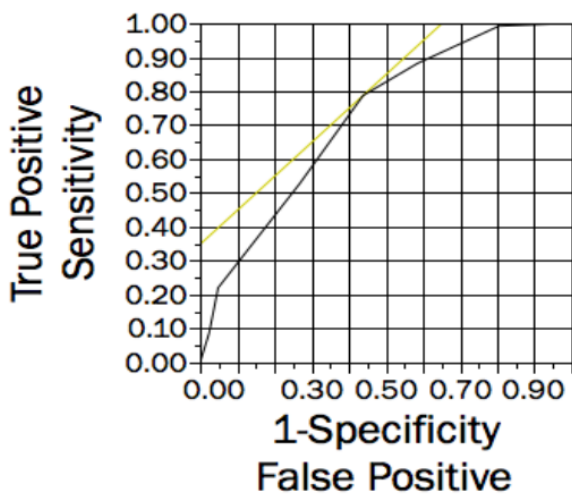


Figure 4: Receiver operating characteristic (ROC) graph. The graph plots the 1-specificity and sensitivity of the model. The area under the curve determines the accuracy of the indicator (GCS Scores) as a predictor for the outcome. Figure by authors.

X	Prob	1-Specificity	Sensitivity	Sens- (1-Spec)	True Pos	True Neg	False Pos	False Neg
.	.	0.0000	0.0000	0.0000	0	41	0	127
9.000000	0.9514	0.0244	0.0866	0.0622	11	40	1	116
8.000000	0.9161	0.0488	0.2205	0.1717	28	39	2	99
7.000000	0.8590	0.2683	0.5276	0.2593	67	30	11	60
6.000000	0.7727	0.4390	0.7874	0.3484 *	100	23	18	27
5.000000	0.6548	0.5854	0.8819	0.2965	112	17	24	15
4.000000	0.5142	0.8049	0.9921	0.1872	126	8	33	1
3.000000	0.3713	1.0000	1.0000	0.0000	127	0	41	0
3.000000	0.3713	1.0000	1.0000	0.0000	127	0	41	0

Table 1. Receiver operating curve (ROC) table. This table shows the different 1-specificities and sensitivities were tested for the indicator (GCS Scores) in the model. It provides the number of true positives and negatives and false positives and negatives each pair of 1-specificity and sensitivity produced. The tables also gives its corresponding probability on the model as well.

Mortality Statistics: Looking at Figure 1, the survival of the hyperbaric treatment patients against the control treatment patients is to be expected because of the results of Dr. Rockswold’s study: 32.14% of the control patients died, while 16.67% of the HBO patients died. Thus, they concluded that the hyperbaric treatment was statistically successful against the control treatment ($p = 0.0195$) in lowering the immediate mortality after TBI.

From the p-value of 0.0195 determined by the chi-squared test of the mortality proportions, a statistically significant difference can be established between the mortality of both treatment groups. Therefore, it can be inferred that the hyperbaric treatment is an effective short-term method of decreasing mortality rates from acute TBI. However, the Kaplan-Meier graph (Fig. 2) and its corresponding chi-squared test ($p = 0.9177$) suggest that there is no long-term difference in mortality for the two groups. Apart from the disparity in mortality rates during the initial duration of the study, there is little sign of discrepancy in the recovery period. Thus, in our limited sample size, there is little to no evidence that suggests that hyperbaric treatment leads to improved survival of TBI patients at 30 years after their initial injury. The lack of significant difference in long-term mortality may be largely due to the age of the patients as they are in their 60s and 70s, approaching a natural time of death.

As a whole, the mortality rate sharply increases from 10,000 days to the present. The marked increase can be attributed to the age of the original patients who participated in the study. Many patients are over the age of 60 today, thus are reaching a natural time of death.

Logistic fit: In order to evaluate the legitimacy and usefulness of the GCS as a predictor of mortality, a logistic fit of survival by GCS score was used. Since GCS is primarily used to evaluate the initial severity of the injury, it was unclear that the scale would be an effective tool to predict the probability of death in brain injury patients. Also, the patients in the study all had GCS scores of < 9, forming a homogeneous group, where outcome can be difficult to predict. However, from our sample group, the log rank chi-squared test yielded a statistically significant p-value ($p < 0.0001$). This low p-value signifies that the categorical model (GCS scores) fit the data incredibly well. The log rank chi-squared test was used instead of the R2 value because it would be inappropriate to be used on a categorical model. Also, as expected, lower GCS scores correlated with higher probabilities of mortality. Because the logistic fit is a cumulative curve, it is clear that the probability of death decreases with each successive GCS score.

The ROC curve (Fig. 4) from the data showed moderate accuracy in the GCS's ability to predict mortality. From the area under the curve, the accuracy of the GCS as a predictor was found to be 72.134%. The curve also provided the ideal cutoff point (1-specificity, sensitivity) of GCS. Since 1-specificity is the false positive rate and sensitivity is the true positive rate, the closer the cutoff point is to (0,1), the better the model. The cutoff point for our data was (0.2126, 0.5610). Although the GCS scores weren't able to detect true positives with an extremely high frequency, they were able to limit the number of false positives significantly.

Glasgow Recovery Scale: Table 2 shows the average rate of recovery at different time increments for the hyperbaric patients and the control patients. Figure 5 is a visual representation 11 of Table 2, showing the difference in the recovery of hyperbaric patients and control patients. Table 3 shows the average rate of recovery for each GCS that appeared at the original injury at different time increments. Figure 6 is a depiction of Table 3, showing the effect of GCS on recovery. Figure 5 is a linear fit of the scatterplot of GRS scores by GCS scores with an R-value of -0.9134, R2 value of 0.8343, and a slope of -0.4222. A student's t test was conducted that produced a p-value less than 0.0001.

Table 2. Average GRS for HBO vs. control.

The average GRS of the hyperbaric oxygen treatment and the normobaric treatment (control) is represented in this table at time increments of 1 month, 3 months, 6 months, 12 months, and 18 months. There were 84 patients in the hyperbaric treatment group, and 83 in the control group. Table by authors.

Time (Months)	HBO	Control
1	3.07	3.31
3	2.7	2.95
6	2.52	2.75
12	2.42	2.71
18	2.17	2.43

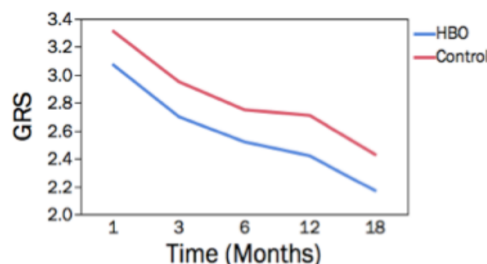


Figure 5. Average GRS for HBO vs. control.

The average GRS of the hyperbaric oxygen treatment and the normobaric treatment (control) is represented in this graph at time increments of 1, 3, 6, 12, and 18 months. The maximum GRS of the hyperbaric group was 3.07, while the max GRS of the control was 3.31. The minimum GRS of the hyperbaric group was 2.17, while the min GRS of the control was 2.43. Figure by authors.

Table 3. Average GRS for levels of GCS.

The average GRS is shown for each GCS (3-9) on admission at time increments of 1 month, 3 months, 6 months, 12 months, and 18 months. There were varying numbers of patients with each GCS: 9 with GCS of 3, 23 with GCS of 4, 18 with GCS of 5, 39 with GCS 6, 48 with GCS 7, 18 with GCS of 8, and 12 with GCS of 9. Table by authors.

Time (Months)	GCS 3	GCS 4	GCS 5	GCS 6	GCS 7	GCS 8	GCS 9
1	4.67	4.04	3.56	3.18	2.92	2.67	2.34
3	4.45	3.74	3.28	2.74	2.52	1.89	2
6	4.34	3.74	3.23	2.41	2.17	1.95	1.58
12	4.45	3.61	3.12	2.31	2.04	2	1.67
18	4.12	3.22	2.89	2	1.75	1.73	1.67

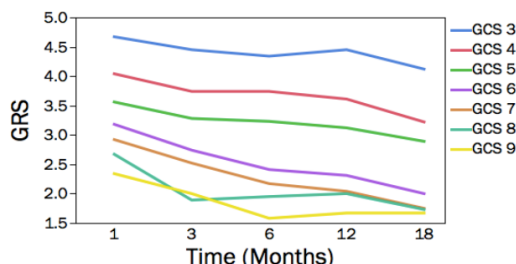


Figure 6. Average GRS for levels of GCS.
The average GRS is shown for each GCS (3-9) on admission at time increments of 1, 3, 6, 12, and 18 months. Figure by authors.

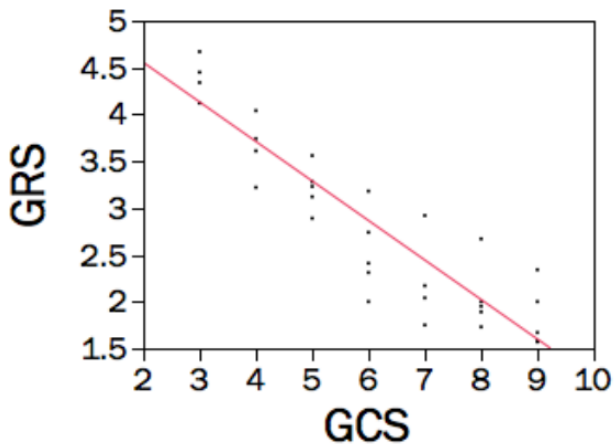


Figure 7. Linear fit of GRS by GCS.
Patients' GCS scores were plotted against their corresponding GRS scores. A linear fit was then conducted on the scatterplot. Figure by authors.

Recovery and Treatment: Figure 5 shows the difference in GRS of both treatment groups. As expected, over time, the HBO treatment group had a lower GRS, thus improved outcomes, at 1, 3, 6, 12, and 18 months. The maximum GRS of the HBO group was 3.07, while the maximum GRS of the control group was 3.31. The minimum GRS of the HBO group was 2.17, while the minimum GRS of the control group was 2.43.

Recovery and GCS: Figure 6 shows the difference in GRS of each GCS on admission (3- 9 GCS). As hypothesized, the lower the GCS, the higher the GRS. The only difference is in the 3 month follow-up: the average GRS of GCS 8 is 1.89, while the average GRS of GCS 9 is 2. It was hypothesized that each average GRS is greater at the lower GCS than the higher. It is expected that there are differences that disprove the hypothesis, but each GRS besides the 3 month follow-up at GCS 8 and 9 yield true to the hypothesis.

From the scatterplot and its linear fit, an R-value of -0.9134 and R² value of 0.8343 were produced. The moderately high R² value (R² = 0.8343) and the

strong R-value (R = -0.9134) from the linear fit of patients' GCS scores vs. patients' GRS scores indicated that a negative linear relationship between GCS scores and GRS scores was appropriate. The slope of the linear fit (m = -0.4222), showed that for every single GCS score increase, approximately a half score decrease in GRS score can be expected. Additionally, an extremely low p-value (p < 0.0001) suggested that the difference in GRS scores for each GCS score was statistically significant.

Cognitive Decline: Figure 8 displays the distribution of TICS-M scores for each group membership. For the long-term aspect of the study, the patients who had sustained traumatic brain injuries approximately 35 years ago and their age-matched controls were given different cognitive assessments, including the TICS-M. A two-sample Wilcoxon test performed on the two groups with $\alpha = 0.05$ produced a p-value of 0.1787. From the eye tracking data, two sample Wilcoxon tests with $\alpha = 0.05$ were conducted on each metric to determine statistically significant difference between the results of the two groups. Fourteen metrics in particular, produced p-values lower than the alpha level (Figure 9). Further statistical analyses were conducted to determine the effective of the metrics. The Receiving Operating Characteristic (ROC) curves then were created and the four largest areas under the curves were 0.72801, 0.72106, 0.71412, and 0.70023 (Figs. 10, 11, 12, and 13).

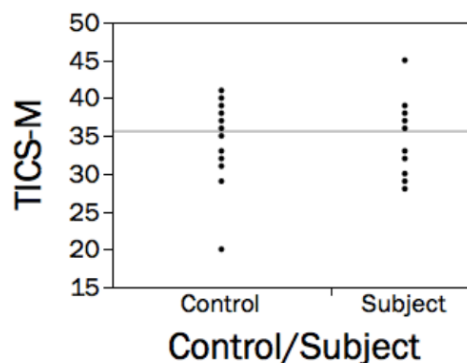
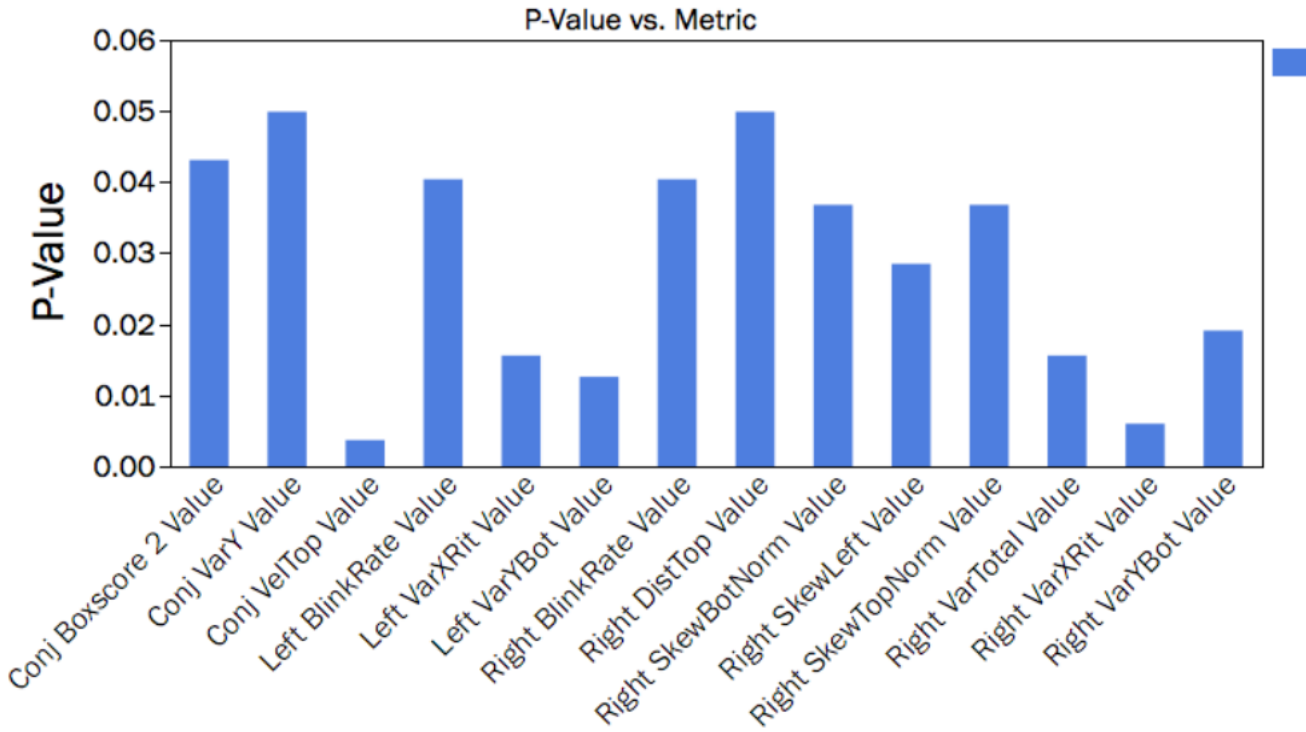
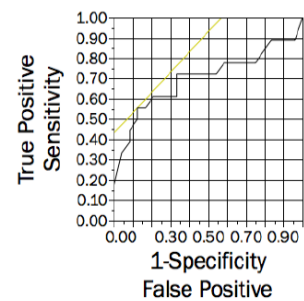
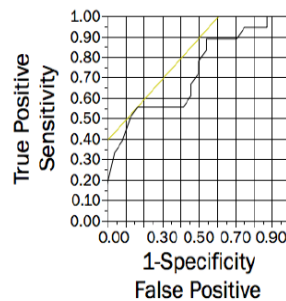
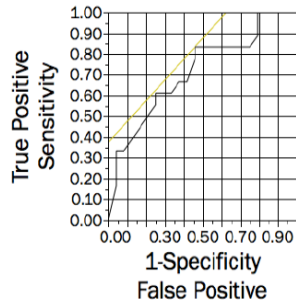
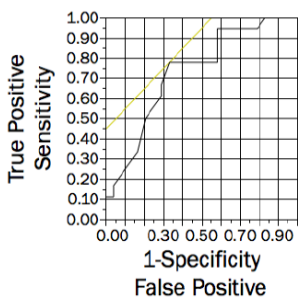


Figure 8. Distribution of TICS-M scores by injury history. Figure by authors.



METRIC

Figure 9. Histogram of p-values by eye tracking metric. Figure by authors.



Figures 10, 11, 12, and 13. Receiving operating characteristic graphs of left eye X variance, right eye X variance, right eye bottom skewed norm values, and right eye top skewed norm values.

Cognitive Test (TICS-M/Eye Tracking): Due to the high p-value of 0.1787 obtained from the two sample Wilcoxon test, there was no evidence to suggest that there was a statistically significant difference among the distribution of TICS-M scores between the two groups. From this result, it can be concluded that the TICS-M is not an effective predictor of long-term cognitive decline. This may be due to the limited sample size, or from other factors leading to cognitive decline in the control cohort.

However, certain metrics from the eye tracking data showed promise as useful cognitive tools. Fourteen metrics produced significant p-values, indicating that there were statistically significant differences between the results of the groups for those metrics. Additional statistical analyses were conducted in the form of ROC curves to test the accuracy of each metric. P-values alone were insufficient to determine the effect grouping had on the metric results. Then out of the fourteen significant metrics, only four displayed potential as effective predictors of cognitive decline with their area under the curve values. The areas 0.72801, 0.72106, 0.71412, and 0.70023, indicated that the four metrics were capable of predicting with approximately 73%, 72%, 71%, and 70% accuracy, respectively. The four metrics, left varXrit, right varXrit, right skewTopNorm, and right skewBotNorm, each measured a different component of a subject's eye tracking assessment; left and right varXrit measured the decrease in variance of each eye as it moved vertically and right skewTopNorm and right skewBotNorm calculated the statistical skewness of side to side right eye movement when the video was located at the top and bottom of the screen. The accuracy of these three metrics may be attributed to the neural pathways that were disrupted due to TBI, which inhibits one's ability to move their eyes around to follow and focus on the moving video.

Blood Based Biomarkers: When we receive the blood data, we plan to perform many of the same statistical protocols used for the eye tracking metrics. Two sample Wilcoxon tests will be conducted on the different biomarkers to establish a significant difference between the TBI patient cohort and their controls with p-values. The biomarkers with significant p-values will then be evaluated with ROC curves to determine their accuracy in predicting long-term cognitive decline.

CONCLUSIONS

Through the process of analyzing the effectiveness of hyperbaric treatment, the reliability of the Glasgow Coma Scale, the rate of recovery after a traumatic brain injury, and the cognitive status thirty years after a brain injury, we reaffirmed and confirmed many conclusions:

- Hyperbaric oxygen is a viable treatment option for TBI patients,
- A higher GCS score predicts a worse recovery,
- And the TICS-M test and eye tracking show little discrepancy between TBI patients and non-TBI patients.

In evaluating the effectiveness of hyperbaric oxygen, there was evidence supporting our hypothesis that hyperbaric oxygen treatment would be more effective on the treatment of TBI than standard oxygen treatment. In our test group, almost twice the number of the patients died while in standard treatment compared to hyperbaric treatment. Further studies are being pursued to better understand how HBO can be utilized in a TBI population.

However, regarding the hyperbaric treatment's long-term effects in this study, there was little to no evidence to suggest that the type of treatment the patient received had any effect on his or her long-term outcome ($p = 0.9177$). The result came at a surprise, considering how clear the disparity of the outcomes between treatments had been. In the Kaplan-Meier graph analysis, there was some uncertainty in the data, as some patients' outcomes could not be confirmed. The patient's last follow-up date was used instead as the date of information. This uncertainty in the data induced some potential fluctuations in the results, but they proved to not hold great statistical leverage given the high p-value ($p = 0.9177$).

Although the GCS does not diagnose a brain injury or determine the future effects of the injury, in this study the hypothesis that the lower the GCS, the worse the outcome yielded true. This was confirmed by the logistic fit performed on the outcome by the GCS score. As a potential predictor, the GCS had moderate ability to predict patient outcome with high accuracy, as evidenced by the ROC curve. 17

The hypothesis remained the same for the GRS: the lower the GCS, the higher the GRS. The strong negative correlation ($R = -0.9134$) and the negative

slope ($m = -0.4222$) supported the hypothesis regarding the negative direct relationship between GCS scores and GRS scores. In addition, the GCS showed potential as an effective predictor of patient recovery, as indicated by the low p-value ($p < 0.0001$). We recognize that this is derived from a small sample size of 168, but in our sample group, the hypothesis on rate of recovery remained true for both GCS and hyperbaric oxygen treatment.

Overall, the TICS-M test showed little to no potential as a possible predictor of long-term cognitive decline. With the high p-value of 0.1787, our hypothesis was not supported. The eye tracking showed some promise as an effective cognitive tool, however. Four of its metrics, left varXrit, right varXrit, right skewTopNorm, and right skewBotNorm, had both significant p-values and high accuracy rates of prediction, supporting our hypothesis. Because the eye tracking software is relatively new, further studies with larger sample sizes are needed to cross-validate the reported findings.

Limitations: Due to the long period of follow-up, many patients passed away and cognition data was not obtainable. This further limited the sample size in this study to the time period between the initial injury and the present, as well as the difficulty in contacting subjects who have moved away. Our limited sample size introduced an element of uncertainty in the statistical analyses; therefore, further research with a larger sample size is needed to verify our findings.

Future Work: Further work will include blood draws, additional eye movement tracking, and cognitive status evaluation of the patients willing to follow-up. With the patients' blood samples and eye movement data, more precise ways of recognizing cognitive decline can be found from certain proteins and other blood-based biomarkers. Since these assessment tools are more heavily based on quantitative results rather than patient performance, we believe that they will prove to be more accurate predictors of cognitive decline with further research.

The long-term aspect of the study will provide deeper insight to the development of cognitive decline and dementia over time after a severe TBI. Considering the lack of a long-term TBI study of this scale and caliber to date, the results we have gathered so far and those that will be gathered as the study progresses should reveal new information we haven't seen previously. Information on the long-term effects

of a traumatic brain injury is limited, so this study will provide more information on the status of a brain injury survivor after a period of 30 years.

With a deeper understanding of the long-term evolution of traumatic brain injuries, patients and doctors alike will be able to learn of early onsets of cognitive decline and dementia post initial trauma, which in turn, will aid preparations for appropriate treatments. Because the long-term effects of serious traumatic brain injuries permeate through a patient's daily life and significantly affects their family, it is crucial that more effective predictors are developed in order to sufficiently plan for the patients' future well-being.

ACKNOWLEDGEMENTS

Over the course of the past year, we have learned so much about traumatic brain injuries, and hopefully made progress towards advancing the field. None of this would have been possible without the support, encouragement, and guidance we received. We appreciate all of the assistance we received from the following individuals: Dr. Molly Hubbard served as our mentor, assisting us in data collection. Dr. Uzma Samadani graciously allowed us access to her lab and its resources. Mr. Drake Burri, a research assistant, acclimated us to the lab and taught us the equipment methods. Dr. Abdullah Bin Zahid and Dr. David Balser provided us with statistical insight. Finally, Mrs. Princesa Hansen and our classmates gave us invaluable advice on our paper and presentation.

REFERENCES

1. Vincent A, Roebuck-Spencer T, Cernich A. Cognitive changes and dementia risk after traumatic brain injury: implications for aging military personnel. *ScienceDirect*. 2014; 10(3): 174-187.
2. Centers for Disease Control and Prevention. Brainline.org. <http://www.brainline.org/content/2008/07/facts-about-traumatic-brain-injury.html>. Published 2009, accessed September 4, 2016.
3. Bennett M, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Library. Published December 12, 2012.
4. Novack T and Bushnik T. MSKCT. <http://www.msktc.org/tbi/factsheets/Understanding-TBI/Brain-Injury-Impact-On-Individuals-Functioning>. Published 2002, accessed September 12, 2016.
5. Ohio Valley Center for Brain Injury Prevention and Rehabilitation. [brainline.org](http://www.brainline.org). http://www.brainline.org/content/2009/03/substance-abuse-and-traumatic-braininjury_pageall.html. Published 2009, accessed September 12, 2016.
6. Shively S, Scher A, Perl D, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: what is the pathology. *JAMA Neurology*. 2012; 69(10):1245-1251.
7. Christensen B. Medscape. <http://emedicine.medscape.com/article/2172603-overview>. Published December 5, 2014, accessed August 2, 2016.
8. Shively S, Scher A, Perl D, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: what is the pathology. *JAMA Neurology*. 2012; 69(10):1245-1251.
9. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE. Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. *Journal of neurosurgery*. 1992; 76(6):929-34.
10. Mayo Clinic Staff. Mayo Clinic. <http://www.mayoclinic.org/tests-procedures/hyperbaric-oxygen-therapy/basics/definition/prc-20019167>. Published November 25, 2014, accessed August 2, 2016.
11. Thomas H. Patient. <http://patient.info/doctor/glasgow-coma-scale-gcs>. Published December 28, 2016, accessed August 2, 2016.
12. Brandt J, Folstein M. PAR Creating Connections Changing Lives. <http://www4.parinc.com/Products/Product.aspx?ProductID=TICS>. Published 2012, accessed June 2, 2012.
13. Knopman D, Roberts R, Geda Y, Pankratz S, Christianson T, Petersen R, Rocca W. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology*. 2010; 34:34-42.
14. Brain Injury Research Lab. "Eye Tracking Manual Version 2.0". Lab handbook. HCMC. Minneapolis, MN. July 11, 2016. Lab manual.