Intracranial Pressure Patterns Over Time

in Traumatic Brain Injury Patients

by

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CERTIFICATE OF APPROVAL

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Abstract

One of the challenges clinicians face in caring for patients with a severe or moderate traumatic brain injury (TBI) is the issue of when, and how aggressively, to treat increased intracranial pressure, or ICP. It is well studied and recognized that increased ICP is strongly associated with poor neurological and functional outcome in this patient group, however, most of the treatments and medications used to control elevated ICP can also be harmful or fatal for the patients.

Most studies in the current literature have explored increased ICP solely as a dichotomous variable (either present or absent, usually with the value of 20 mmHg or 30 mmHg used as the cutoff point),even though there is usually a tremendous amount of information on a patient's ICP values over a given time. For instance, the dataset used in this analysis initially contained over 100,000 datapoints, even though this study had a relatively small sample size. This amount of data collection is not uncommon in head injury studies. By using ICP and other measurements such as blood pressure as dichotomous or categorical variables, a great deal of data which could potentially elucidate important relationships are never used. Thus a tremendous amount of data, and the resources utilized to collect it, are wasted.

This study utilized the data from a cohort of patients admitted to the Oregon Health & Science University Intensive Care Unit with a diagnosis of TBI between March of 1999 and March of 2002. Measurements of the ICP, the treatments

used to control elevated ICP (as recorded by the therapy intensity level, or TIL), systolic and diastolic blood pressure, the Glasgow Coma Scale (GCS) score, and pupillary reaction were recorded hourly for the first 72 hours after injury, or until the ICP monitor was removed, whichever was longer. The hourly recorded ICP, TIL, along with the times recorded were entered into SPSS v11.5. Cluster membership was assigned according to the K-Means Method of clustering, which was used to group individuals with similar profiles over time together. In each case, 3 different clusters were formed, each with distinct cerebral perfusion pressure (CPP), ICP, and TIL patterns over time. Each cluster was examined, and provided an accurate representation of the individual members of each cluster. Cluster membership, along with the patient's age, the best motor GCS score (mGCS) in the first 24 hours and pupillary reactivity (known predictors of outcome in this patient population) were then entered into a multiple regression model, with the one-month Disability Rating Scale score as the dependent variable. Although the cluster membership was not significantly associated with outcome in this study, there did appear to be a trend for patients in the high TIL cluster to have a better outcome than those in the lower TIL cluster. One possible explanation for the lack of significant findings is that the sample size of this study was not large enough to detect a significant difference. Further research using this promising analytical technique is recommended.

Introduction

Traumatic brain injury (TBI) is a significant health problem affecting millions of people in the United States. Each year approximately 80,000 Americans survive a hospitalization for traumatic brain injury but are discharged with TBI-related disabilities, such as decreased cognition and decreased motor function. In addition, an estimated 5.3 million Americans are living today with a TBI-related disability (Thurman, et. al, 1999). This translates into an estimated $75-100 billion per year (as estimated in 1985) in lost productivity and medical expenses (*Injury in America: A Continuing Public Health Problem*, 1985).

When a person has an initial impact to the brain, as happens in an automobile collision, that initial injury to the brain is known as primary brain injury. Certain physiological changes then happen, due to cellular chemical changes and swelling in the brain tissue. The damage that can occur due to these changes is known as secondary brain injury. In order to maximize patient neurological outcome, attention must be focused on minimizing the impact of secondary brain injury. This secondary brain injury is commonly associated with either the mechanical compression or distortion of brain tissue due to increased pressure, or a decrease of oxygenated blood flow to the brain tissues, causing cerebral ischemia (Iacono, 2000; Marik, Chen, Varon, Fromm, & Sternbach, 1999; Struchen, Hannay, Contant, & Robertson, 2001). Cerebral ischemia, in turn, causes increased neuronal injury and increased cerebral edema, which further

increases the intracranial pressure (ICP) and can lead to irreversible neurological damage and even death. In 1995 the Brain Trauma Foundation and the American Association of Neurological Surgeons (AANS) developed and published the *Guidelines for the Management of Severe Head Injury*. The *Guidelines* were endorsed by the AANS and the World Health Organization, and were the first scientific, evidence-based document that evaluated various practices and interventions in the treatment and care of patients with a TBI. This document recommended the prevention of secondary brain injury associated with intracranial hypertension, systemic hypotension, hypoxia, and cerebral edema in order to improve the outcome of patients who suffered a TBI(*Guidelines for the Management of Severe Head Injury.*, 1995).

Many observational and ecologic studies have been done that demonstrate the strong association of intracranial hypertension (as measured by increased ICP) with increased morbidity and mortality from TBI (Becker, et. al, 1977; Marmarou, et.al., 1991; Miller, et.al., 1977). Although there has not been a randomized, controlled trial confirming the effects of increased ICP, due to ethical considerations this will almost certainly not occur (it would be unethical to allow patients to undergo increased ICP to study the effects of this when there are so many observational studies that have found it to be associated with poor and fatal outcome). Since the publication of the *Guidelines* (*Guidelines for the Management of Severe Head Injury.*, 1995), monitoring of patient ICP has become a standard of care in the treatment of patients with severe and moderate

TBI. The ICP is typically monitored by placing one of several different devices into a hole that has been bored through the skull, and then threading the device either into the brain tissue, the space surrounding the brain, or one of the spaces (ventricles) in the brain. ICP monitoring involves risks both in the placement of the monitor, but also in the increasing chance of infection in the brain. The longer the ICP is left in place, the higher the chance that an infection will occur. Therefore, one of the goals in ICP monitoring is to remove the device as soon as possible.

In more recent years, there has been increasing controversy regarding the significance of using the cerebral perfusion pressure (CPP) rather than the ICP to direct TBI management (Bulger et al., 2002). The CPP is calculated by subtracting the ICP measurement from the mean arterial pressure (MAP). The MAP is a calculated value, determined by adding twice the diastolic blood pressure to the systolic blood pressure, and then dividing that sum by three (the MAP is a measurement commonly used in all Intensive Care Units). Bulger notes that the CPP is argued to be a more accurate reflection of the cerebral blood flow than the ICP, and some studies have found an association between the maintenance of adequate CPP and improved neurological outcome (Changaris, McGraw, & Richardson, 1987; Robertson, Contant, & Narayan, 1992; Rosner, Rosner, & Johnson, 1995). However, more recent studies have found that intracranial hypertension is more closely associated with outcome than the maintenance of CPP (Juul, Morris, & Marshall, 2000; Robertson, Valadaka, &

Hannay, 1999). To date, there does not appear to be a definitive answer as to which measurement should be used to direct TBI patient management.

Almost all of the studies that have examined the relationship between ICP or CPP and outcome in this population of patients have examined ICP and CPP as discrete variables (either presence or absence of increased ICP, usually with a cutoff of ICP of 20 mmHg, which was given as a guideline in the *Guidelines for the Management of Severe Head Injury,* or a decrease in the CPP below either 50 or 70 mmHg). Very few studies have evaluated the outcome of patients based on the number of episodes of elevated ICP or decreased CPP, the duration of time spent at an elevated ICP level or decreased CPP, or the total proportion of time spent at elevated ICP levels or decreased CPP levels. Two studies have been identified in the literature that did examine these factors. One study by Struchen (Struchen et al., 2001), determined that continuous measures of ICP, mean arterial pressure (MAP), cerebral perfusion pressure (CPP), and another physiologic measurement were significantly related to outcome in patients with severe TBI. These authors found that duration of increased ICP or decreased CPP accounted for a significant percentage of the variance in outcome in the Disability Rating Scale (DRS) at 1, 3 and 6 months post-injury. The DRS is a commonly used tool to measure functional outcome in this population, and will be discussed further in the Methods section. Another study by Clifton (Clifton, et al., 2002) explored various different thresholds for ICP, MAP and CPP as well as possible frequency effects of these measures on the

functional outcome of patients with severe TBI. The authors of this study found threshold effects of both elevated ICP and decreased CPP, although the 95% confidence intervals for each of these included 1. Neither of these studies, however, examined the relationships between the values, the number and duration of occurrences, time from injury, level of treatment for the ICP or CPP and outcome. No studies were found in the literature that examined the potential effects of the occurrences of increased ICP at different time periods post injury.

Recently, several studies have used a therapy intensity level (TIL) to measure the level of intensity of the therapy that is given to patients to treat their increased ICP or hypotension (Clifton, et al., 2002; Narayan & Michel, 2002). The therapies that were recorded for this study and this group of subjects were the presence of:

- sedation (usually with intravenous [IV] morpine or fentanyl)
- mild hyperventilation (defined as a pCO2 of 30 – 35 mmHg)
- paralytics (usually vecuronium)
- mannitol (an osmotic diuretic)
- hypertensive agent (usually with dopamine or neoepinepherine given as a constant IV infusion)
- ventricular drainage
- aggressive hyperventilation (defined as a pCO2 of 25 – 29 mmHg)
- induction of a chemical coma (with Diprivan via constant IV infusion) and

- decompressive craniectomy.

Each of the above therapies was assigned a numerical value from 1 to 6, based on the aggressiveness of the therapy (for instance, sedation was given a value of 1, while decompressive craniectomy was assigned a value of 6). The therapies used in each hour were recorded, and the sum of the numbers were assigned as the score for each hour.

The use of a TIL is not meant to be a surrogate for severity of brain injury, or a separate predictor of outcome, but it is recognized that there is an interaction between the level of the ICP and the type of treatment a patient receives, and that the primary function of the TIL is to assist in the interpretation of the ICP (Narayan & Michel, 2002).

Historically, many studies have used the Glasgow Outcome Scale (GOS) to measure neurological outcome following a TBI (Struchen et. al, 2001). The GOS is a very quick, brief measure that rates TBI patients on a 5-point scale, ranging from dead (1) to good recovery (5). The Disability Rating Scale (DRS) is another scale frequently used to measure the outcome in this patient population. The DRS is a 30-point scale that assesses patient function in four main areas, and was designed to assess TBI patient disability in a range from coma through community re-entry. In a recent study by Struchen (Struchen et. al, 2001), both the DRS and GOS were used to predict outcome in TBI patients, using a variety of physiologic variables. The authors found that when they performed the analysis using the GOS, which is a fairly generalized or gross measure, they

were unable to detect potentially important differences in TBI outcome, such as differences in patients' functional ability. When performing the same analysis using the DRS as the outcome variable, they were able to discover an improvement in the prediction of patient outcome using the selected independent variables and DRS that was not seen when using the same independent variables with GOS as the outcome variable. The authors theorized that the use of the DRS provided increased sensitivity to changes in the patients that were not available when using the GOS.

It is well known that many of the treatments for increased ICP and decreased CPP can have significant, and even fatal, side effects. These side effects can range from mild hypotension, dehydration and mild systemic vasoconstriction to life-threatening pneumonias and systemic sepsis. The clinician is often put in the difficult position of trying to determine if the patient is more at risk of increased morbidity and or mortality from the treatments used to bring down the ICP or raise the CPP, or the increased ICP itself. The clinician is challenged to achieve the difficult and delicate balance between minimizing the secondary insult to the brain and minimizing potentially life-threatening side effects of the treatments used to decrease intracranial hypertension.

Specific Aims:

The three specific aims for this project were:

1. To utilize the K-Means method of clustering to develop a waveform pattern that represented the magnitude of the intracranial pressure (ICP), cerebral perfusion pressure (CPP) and the level of treatment intensity (as measured by the TIL) over time, as measured in hours post injury, and then to group these individual patterns into like clusters.
2. To evaluate these clusters to determine if they present a reasonably accurate representation of the members of each cluster.
3. To examine any association between the clusters and the disability status at one month post injury.

In this study, through the use of the multi-dimensional patterns (consisting of ICP or CPP, and the TIL over the time from injury), it was hypothesized that there might be an improvement in the ability to predict outcome in TBI patients. In evaluating different patterns and outcomes, it was hypothesized that it would be possible to distinguish differences in outcome between "early" and "late" elevations in ICP (or drop in the CPP). If it were determined, for example, that an early elevation in ICP was predictive of poor outcome, but that a later rise in the ICP was not predictive of poor outcome, these findings might assist the clinician in deciding to be less aggressive in the treatment of the late increased ICP than is currently recommended. This could potentially impact the care given to TBI patients, and allow clinicians to maximize neurological outcome while at the

same time minimizing the potential risks from the side effects of the therapeutic options.

Methods

Overview of the Design

This project was a retrospective cohort study, utilizing the previously existing database compiled for the Oregon Traumatic Brain Injury Model Systems Project (OTBIMS), a study that followed patients who were admitted to the Intensive Care Unit (ICU) at Oregon Health & Sciences University (OHSU) with a severe or moderate TBI during a three-year period, March 1999 to March 2002. Information collected on each patient included an hourly recording of the neurological status of the patient by using the Glasgow Coma Score (GCS), pupillary size and reactivity, systolic and diastolic blood pressure, temperature, heart rate, oxygen saturation, ICP, and therapies used to treat increased ICP (the TIL, or therapy intensity level). This information was collected for the first 72 hours after injury or until the ICP monitor was removed, whichever was longer. Each patient was evaluated at multiple times over the three years of the OTBIMS study (up through two years post injury) using several different disability function instruments, including the Disability Rating Scale (DRS). The key evaluation period to be used in this study is the one-month post-injury time point. Because this thesis project was examining the effects of physiologic variables (such as the ICP), it was felt to be important to minimize other strong non-physiological variables, such as family support. The one month time period was felt to be the least sensitive to non-physiological influences, such as presence or absence of supportive family, an any rehabilitation and therapy utilized by the patient. The standardized method of collection of these measurements provide an accurate

and reliable database for the evaluation of ICP and CPP management, and the potential impact on disability at the one month follow-up.

Study Subjects

All patients aged 17 and older who were admitted between March of 1999 and March of 2002 to OHSU's ICU through the Trauma System were screened for potential admission into the OTBIMS study. Inclusion criteria included a diagnosis of TBI and a best Glasgow Coma Score (GCS) of 12 or less in the first 24 hours after injury (indicative of a severe or moderate TBI). Patients with non-traumatic brain injury, such as that caused by asphyxiation or drowning and those patients who died in the Emergency department or shortly after admission to the ICU were not included in the potential patient population, as this study was designed to examine the functional outcomes in survivors of brain injuries with a traumatic etiology. Also excluded were illegal aliens and known felons. The 105 patients who gave (or whose families gave on their behalf) informed consent for enrollment were each assigned a unique identification number, based on the number for the study center and the order in which the patients were enrolled. After enrollment, the patients were randomly assigned to either receive the services of a "Community Resource Advocate" (CRA) (whose job it was to facilitate post-acute coordination of services and serve as a resource for the TBI survivor and their families) or not. All study personnel (with the exception of the person randomizing and the CRAs) were blinded to the treatment group of all patients. The intervention was not anticipated to interfere with or bias the

outcomes of this project, as the intervention did not begin until after the one-month evaluation for most patients. In addition, it was anticipated that the primary anticipated benefit of this intervention would not be in the first month after injury, when institutional coordination and information was readily available, but rather several months or years after the acute hospitalization and rehabilitation (if present) discharge have occurred. Both the OTBIMS study and this research study were reviewed and approved by the OHSU Institutional Review Board.

Measurements

The independent variables included in this study were the systolic and diastolic blood pressure (used only to calculate the cerebral perfusion pressure, or CPP), the ICP, and the TIL, or therapy intensity level. This information was recorded on a flow sheet by the nurses in the Intensive Care Unit each hour, and collected by this researcher or one of the other team members for the first 72 hours after injury or until the ICP monitor was removed, whichever was longer. The mean arterial pressure and ICP were then used to calculate the cerebral perfusion pressure (CPP). Parallel analyses which included either the ICP or the CPP were run seperately, in order to determine if one variable provided superior predictive capability over the other.

These data were collected at frequent time points for each individual, which resulted in a large dataset with hundreds of datapoints per subject. In addition to the preceding variables, the best Glasgow Coma Scale (GCS) in the first 24 hours (without presence of medications), patient age, and pupillary reaction

(presence or absence of bilaterally reactive pupils) were also collected, so that they could be controled for in analysis, as they are associated with patient outcome.

The Disability Rating Scale (DRS) is a well-validated outcome scale that has been used in measuring the neurological outcome of patients for the past 20 years (Rappaport, Hall, & Hopkins, 1982). The scores range from a low of 0, which is indicative of normal function, to a high of 30, indicative of a vegetative state. The dependent variable used in this study was the DRS score obtained at one-month post-injury. Table 1 presents a summary of all measurements obtained on each individual in this study.

Table 1 Table and Description of All Measurements Used in This Study

Measurement Name	*Type*	*Definition*	*Frequency or Time Interval Measured*
DRS	Dependent	Ordinal: patient cumulative scale score	At one month post injury
ICP	Independent *	Discrete: measured in mmHg	Hourly
CPP	Independent *	Discrete: calculated as mean arterial pressure - ICP	Hourly
TIL	Independent *	Ordinal: Sum of interventions used for the hour measured	Hourly
Best GCS	Independent (confounding)	Ordinal: best GCS in the first 24 hours	At admission
Age	Independent (confounding)	Continuous: patient age at injury	At admission
Pupillary reaction	Independent (confounding)	Dichotomous: Presence or absence of non-reactive pupil	Occurrence at any time

*These measurements, collected hourly, were the measurements that the K-Means Clustering Analyses were performed on.

Data Management and Statistical Methods

Quality Control and Data Management

The quality of the data resulting from the OTBIMS study was excellent. Data was taken from the source documentation and entered directly into the computer, to eliminate transcription error. Stringent quality assurance measures were utilized during the entire collection of the data, with approximately 10% of the subject data re-abstracted and re-entered into the computer, and then compared with the initial entry. An error rate of less than 5% was seen. All study personnel were required to take a training module and pass an examination prior to performing the DRS evaluation, and inter-rater and intra-rater reliability checks were performed every 6 months to ensure the accuracy and reliability of the evaluations. The standardized method of collection of these measurements provide an accurate and reliable database for the evaluation of ICP and CPP management, and the potential impact on disability.

The data for this study were received in six different Microsoft Access2000 data files. The sets which consisted of the TIL and the ICP, the systolic and diastolic blood pressures and the hourly record of pupillary activity were received separated into two groups (subject numbers from 1 to 50 in one set, and 51 to 105 in another), for a total of four datasets containing this information. Another dataset contained the one-month DRS scores, and the final dataset contained the age (in years, at injury) and the best motor score of the GCS in the first 24

hours. Each dataset was exported into Excel2000 and imported and merged into SPSS v11.5.

The set of files containing the hourly TIL information for subjects 1 to 50 and 51 to 105 were merged by subject ID, which was the unique identifier common to all data files. The same procedure was performed on the datasets containing the two separate subject group information on the ICP and other measurements.

The next step in the process was to calculate the CPP. To do this, an intermediary variable, the MAP or mean arterial pressure was created. The MAP was calculated for each hour of data, using the common formula (systolic blood pressure) + 2(diastolic blood pressure)/3.Once this variable was created, the CPP variable was calculated, using the formula of CPP = MAP – ICP. The above manipulations resulted in four final data files, one each for the TIL, the ICP, the CPP and the DRS. Each of these files contained all of the hourly records for each subject for that variable.

All files were examined for completeness, using the "frequencies" function. A comparison between the TIL, CPP and DRS files was done. Of the original 105 subjects, eight subjects did not have an ICP monitor placed while in ICU, which meant that they did not have either the required ICP or TIL records, and thus were eliminated. One subject had an entirely blank record (reason not known), and was deleted. Three subjects died prior to reaching the one-month evaluation period, and nine subjects were missing their DRS scores (reason not known). This resulted in a total of 84 subjects.

Data Preprocessing (Smoothing)

A SAS v8.0 program was written and performed on a limited dataset to take a first look at the case series. This transformation in SAS was necessary, as the data in SPSS were created with the variables in columns, and repeated cases (for however many hours were necessary) in rows (see Table 2, below, for an example).

Table 2 Example of Original SPSS Format

	ICP	CPP	TIL
Subject 1 hour 1	18	70	4
Subject 1 hour 2	19	69	4
Subject 1 hour 3	16	75	2
Subject 1 hour 4	21	64	5

Further graphing and averaging of the cases could not be done with the data in this format. A few of the cases were thus transformed and re-imported back into SPSS. These data were then arranged with each single case in a row, and multiple variables by hour (for instance, icp_1, icp_2...) in the columns (see Table 3 for example).

Table 3 Example of Data after SAS Transformation

	ICP 1	ICP 2	ICP 3	ICP 4	CPP 1	CPP 2	CPP 3	CPP 4	TIL 1	TIL 2	TIL 3	TIL 4
Subject 1	18	19	16	21	70	69	75	64	4	4	2	5
Subject 2	21	23	25	24	68	66	60	62	5	5	6	6
Subject 3	15	12	10	11	75	78	80	78	3	2	1	1

This limited data was then graphed, and it was noted that the resultant curves contained a great deal of variability. It was decided to reduce the variability of these data by smoothing. The SPSS smoothing function, known as T4253H Smoothing, is a compound data smoother used in creating time series data (SPSS, 1999). The smoothing function required the data to be in the original format (with single variables in the columns and multiple cases in the rows), in order to be performed. The three datasets (ICP, CPP and TIL) all had this smoothing function performed on the data.

Once the data in each dataset were smoothed, each file was exported into a portable SPSS file, then imported into SAS, and all of the data were reconfigured as previously described. These SAS files were then exported into text files, and re-imported back into SPSS. The aforementioned steps were performed separately on each of the three (ICP, CPP and TIL) files.

A frequency analysis was performed on the ICP file to make an initial determination of the amount of data available. From this, it was apparent that only 50% of the cases had more than 50 hours of data recorded. Because the sample size of this group was already small, it was decided to examine the available data to determine what contiguous time period would allow for the greatest number of subject data to be analyzed. It appeared that the time period between hours 8 and 44 would allow the most subjects to be included.

Missing Value Imputation

The ICP records were sporadically missing information over the course of the hours recorded, and the records started at different hours for different subjects—in fact, one subject did not have ICP monitoring begin until hour number 59 after injury. Therefore, some of this missing data needed to be estimated (imputed). It was decided to delete from the records the hours prior to commencement of ICP monitoring for each subject, as these data could not reasonably be imputed. The remaining missing datapoints were replaced by the mean of the two datapoints on either side of the missing value. For instance, if during hours 10, 11 and 12 a patient had ICPs recorded as 16, a missing value and 20, then the missing value was imputed to be 18. This method of imputing was done on both the ICP and CPP datasets. The 84 subjects were not missing any of the TIL datapoints, and therefore did not need any values imputed.

Because it was desirable to retain as much of the sample as possible, it was decided to impute the missing hours (which were missing due to either a 'late' startup of ICP monitoring or an 'early' termination of monitoring, with the maximum number of eight hours imputed) for an additional 19 subjects to include them in this analysis. To most accurately impute the values missing from the beginning of the series, it was decided that the percentage change between the first two values in a series would be used to create these new values. First, the percent difference between the first two values was determined, and then that percent was applied to the first datapoint in the series, creating the new first

datapoint (working 'backwards'). The same percent change was then applied to this new value, and so on, filling in the missing datapoints in the beginning of the series. This method was decided upon because it was noted that the initial values in the series were dynamic, frequently with an increasing or decreasing slope. It was determined that using the percent change in the initial values would most accurately reflect the actual, but unknown, data.

In looking at the final hours of the series, it was noted that these values appeared to be much more stable, which made sense clinically (the monitoring was typically discontinued when the readings had stabilized and no longer required treatment). Therefore, in imputing the missing datapoints in the last eight hours, the final datapoint was simply repeated for as many hours as were missing (up to eight). This method brought the total sample size for the analysis up to 72 subjects who had complete, contiguous data between hours 8 and 44. A K-means cluster analysis was then done on each file using K = 3 (three clusters).

Clustering Methods

Due to missing data, only 53 of the 84 subjects were initially evaluated in the K-Means Clustering Procedure. There are three basic steps used with the K-means clustering. First, the number of clusters desired is determined, and from the entire dataset a mean for each cluster is determined. Secondly, each record is assigned to the cluster whose centroid is the nearest (computed using

Euclidean distance). The centroid of the cluster is then recalculated using the newest addition, and reassignments potentially occur if the recalculated centroid changes the nearest cluster for any previously assigned member. These steps are repeated until all records are assigned, and no reassignments occur (Wichern & Johnson, 2002).

Two, three and four clusters were selected for analysis in order to determine the optimal number. Once the cluster analysis had been run, those results were then entered into the one-way ANOVA analysis to obtain descriptive statistics and test for differences between the clusters. From this table, the resulting data were graphed. The rows and columns were manipulated to produce the cluster membership with the 95% confidence interval in the rows, and the mean hourly data for that cluster in the columns.

This procedure was then repeated for the two remaining files, the CPP and the TIL.

Once the cluster analysis utilizing three clusters and the increased sample size of 72 was completed for each of the three groups (ICP, CPP and TIL), a "spaghetti plot" was drawn of the members of each cluster. These graphs showed the line graphs of each individual subject, one on top of the other, in order to visually inspect the cohesiveness of each of the three clusters. This was repeated until all three groups had individual cluster "spaghetti plots" drawn for each group.

To complete the data management procedures required before any further analyses could be done, the rest of the data needed to be aggregated, and the final merge performed. All files were first screened so that they all contained the same subjects as the cluster membership files. The ICP and CPP were aggregated in one file which contained the maximum ICP and minimum CPP in the time period of interest (hours 8 through 44) for each subject. Another file that was required contained the hourly records of the Glasgow Coma Scale (GCS) scores for each patient. This file was aggregated into the maximum motor GCS score in the first 24 hours (clinically, the most predictive piece of the GCS score). The final aggregated file contained the worst (highest score) pupillary reaction in the time period of interest (hours 8 through 44) for each subject. All of the above separate files were sequentially merged with a file containing the subject age at injury. This master file was then merged with each of the files containing cluster membership and the final file with the DRS score at one month (the dependant variable). This process resulted in a final, master file containing all required elements.

Associations Between Clusters and Disability Status

A number of different analyses were performed to examine any association between cluster membership and disability status (as measured by the DRS at one month post injury). When evaluating the crosstabs analysis of TIL cluster membership, it was noted that the subjects in Clusters 2 and 3 had very similar outcome scores, and thus it was decided to combine clusters 2 and 3, and

evaluate the TIL cluster as a dichotomous variable (with Cluster 1 representing a "low" level of therapy, and Clusters 2 and 3 representing a "high" level of therapy).

The association between ICP Cluster membership and outcome was stratified by the dichotomous TIL cluster membership, in order to control for potential differences that might have occurred between groups, based on the level of therapy.

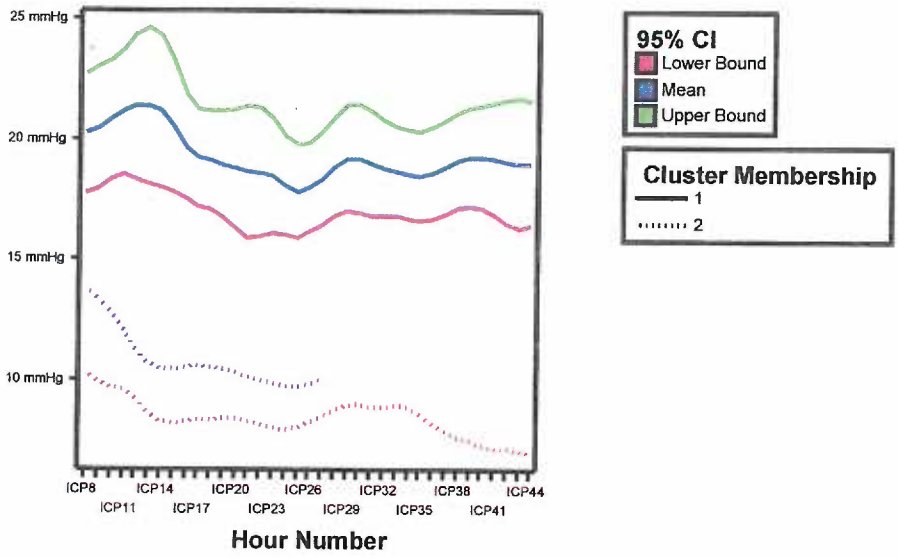
Chi Square tests of independence were performed using cluster membership and the one month post injury DRS scores. In addition, a number of separate simple logistic regression models were examined, using the known predictors of outcome in the model, along with cluster membership and cluster membership grouped into dichotomous variables.

In all analyses, the outcome (the DRS score at one month post injury) was dichotomized into "good" outcome, (with a DRS score of 6 or less) or a "poor" outcome (a DRS score of over 6). This cutpoint was felt to be clinically significant.

Results

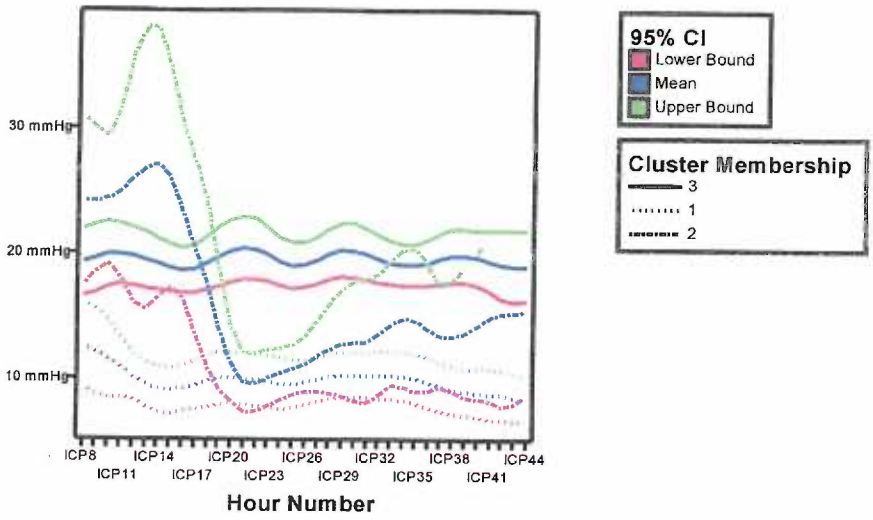
Figures 1 –3 illustrate the results for the first aim of this study, to develop a waveform pattern for each subject that represented the magnitude of the ICP, CPP and TIL over time, as measured in hours post injury. Some similar results were noted for the ICP, CPP and TIL. When the K-Means procedure was limited to 2 clusters, the resulting cluster profiles had fairly narrow confidence intervals (shown for ICP in Figure 1).

Figure 1 ICP Course, Analysis Using 2 Clusters (all subjects)



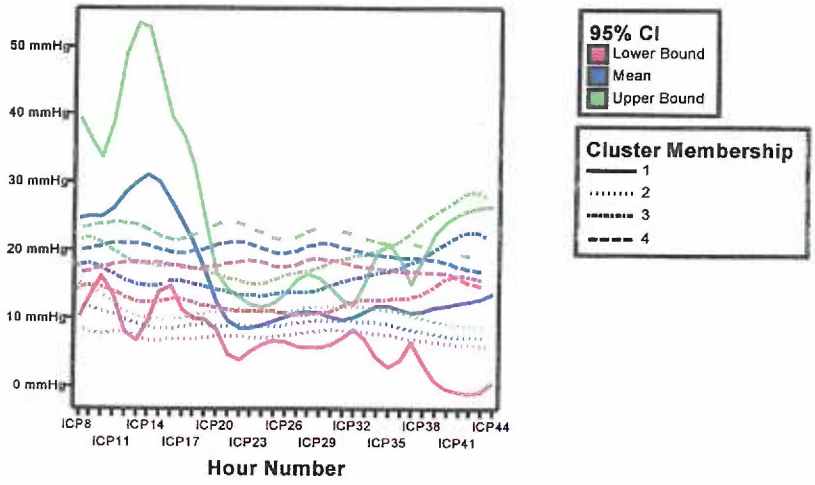
When the clusters were increased to three, three clearly different, clinically significant patterns were observed, all with fairly narrow confidence intervals (shown for ICP in Figure 2).

Figure 2 ICP Course, Analysis Using 3 Clusters (all subjects)



When subjects were classified into 4 clusters, they did not provide any further information. In addition, a fourth cluster had considerable variability, due to small sample sizes (shown for ICP in Figure 3).

Figure 3 ICP Course, Analysis Using 4 Clusters (all subjects)

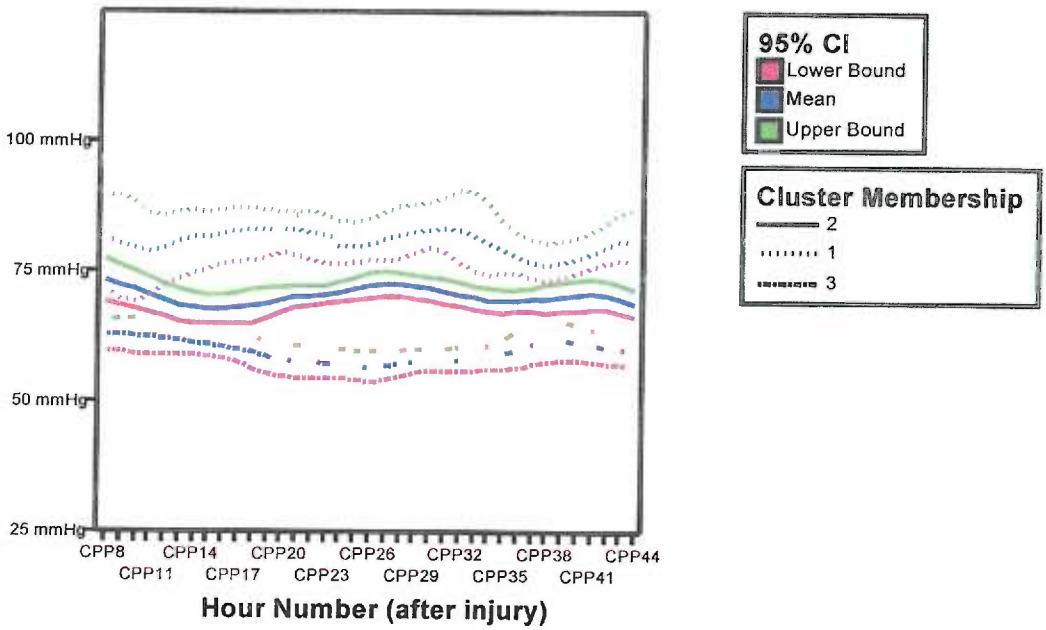


Three clusters appeared to provide the greatest differentiation in pattern with the least variability (minimized confidence intervals). It should be noted that of the three groups (ICP, CPP and TIL) the CPP clustering comprised the least distinct clustering with the greatest variability.

For the ICP values (Figure 2), Cluster 1 consisted of constant, low values. Cluster 2 members had fairly constant, elevated values, and Cluster 3 members appeared to have elevated initial values, that dropped to a fairly normal range in the first 24 hours after injury.

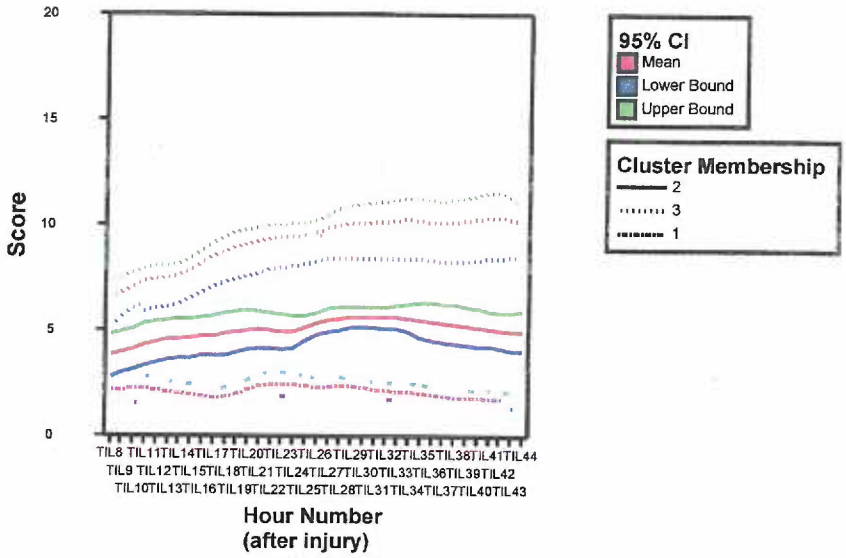
For the CPP values (Figure 4), Cluster 1 members had stable, high values. Cluster 2 members displayed slightly decreased but stable CPP values, and Cluster 3 members demonstrated the lowest (yet still fairly constant) values.

Figure 4 CPP in 3 Clusters



In examining the TIL clusters (Figure 5), it can be seen that Cluster 1 members displayed a constant, low level of therapy. Cluster 2 started out with fairly low levels that gradually increased, and Cluster 3 demonstrated the highest initial levels and increased from there.

Figure 5 TIL in 3 Clusters



The second aim of this study was to assess the different clusters to determine if they presented a reasonably accurate representation of the members of each cluster (Figures 6 - 14 display the graphs of the individual cluster memberships for the ICP, CPP and TIL clusters). Tables 4 - 6 (below) display the demographic characteristics for each cluster. In the ICP clusters (Table 4), it is interesting to note that Cluster 3 has the highest percentage of any event of a fixed pupil, along with the highest percentage of any event of CPP less than 50 mmHg (due to the fact that ICP is used to calculate CPP). Both of these factors are considered to be ominous indicators of poor functional outcome. Another factor of possible

interest is that Cluster 1 has the highest mean age, over 40, which is known to be a strong predictor of poor outcome.

Figure 6 ICP Cluster 1 Membership

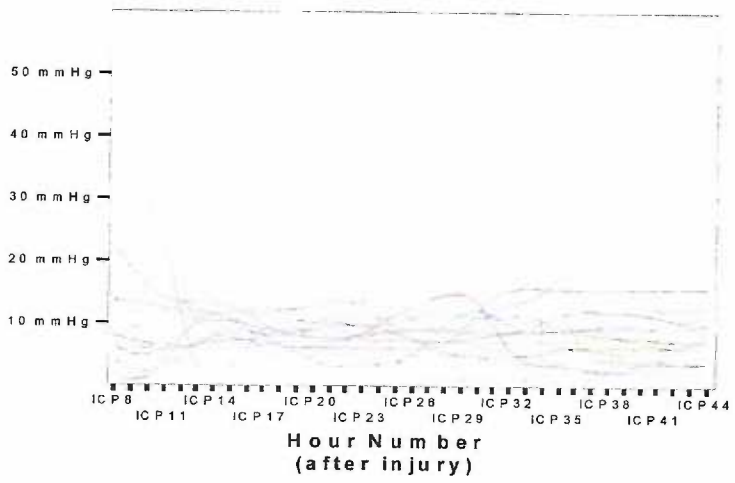


Figure 7 ICP Cluster 2 Membership

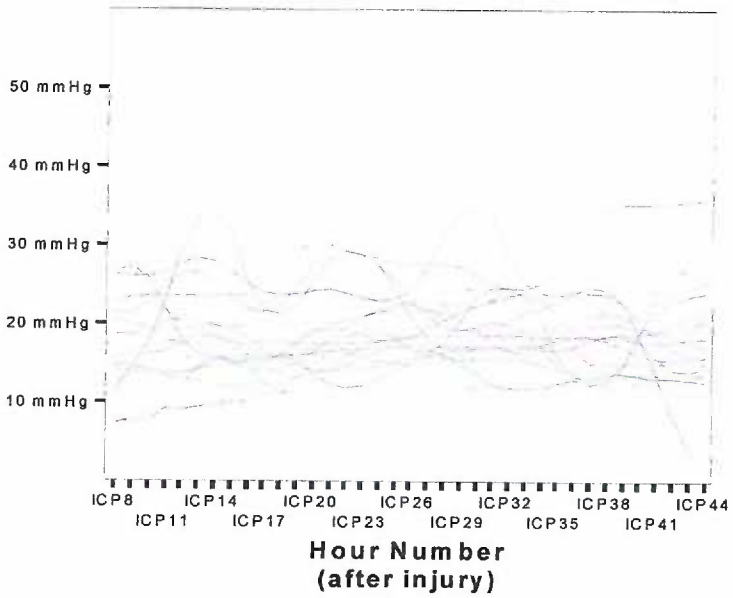


Figure 8 ICP Cluster 3 Membership

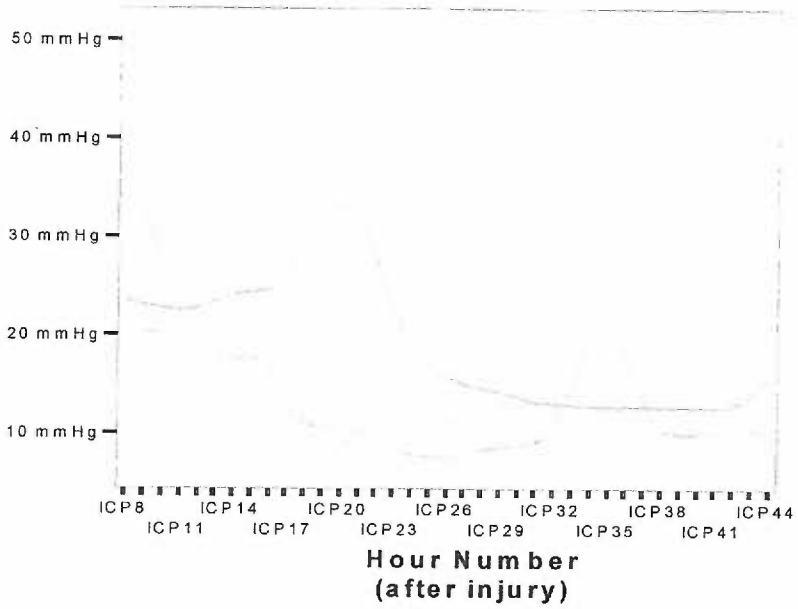


Table 4 Demographics of the ICP Clusters

Demographics	ICP Cluster 1 N = 28	ICP Cluster 2 N = 34	ICP Cluster 3 N = 10
Mean Age (+/- SD)	43.75 (19.27)	31.76 (14.21)	34.20 (13.11)
Age Range	17 - 67	17 - 73	18 - 55
% with any event of Fixed Pupil	14.3%	17.6%	30%
% with mGCS of 6	32.1%	20.6%	30%
% with any event of CPP < 50 mmHg	28.6%	73.5%	90%

It can be seen in Table 5 that the most notable difference between the three CPP clusters is that the third cluster has the highest percentage of any event of ICP greater than 30 mmHg (again, due to the dependence of CPP on ICP).

Figure 9 CPP Cluster 1 Membership

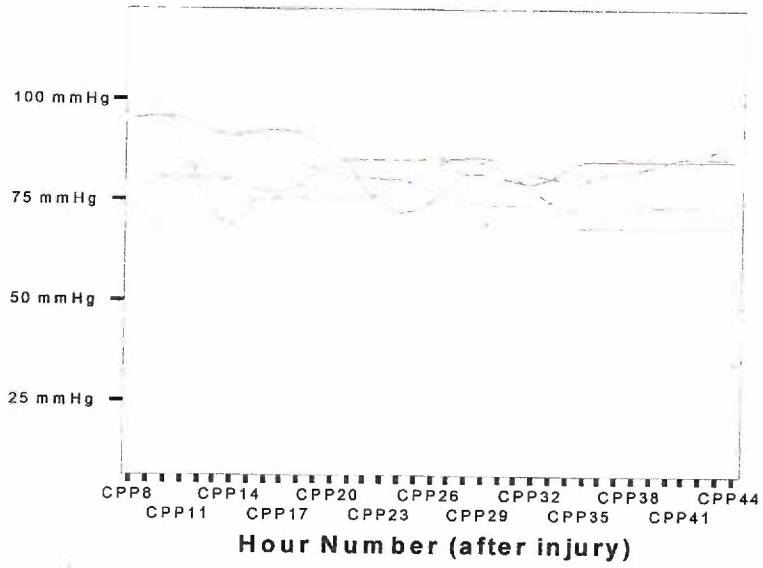


Figure 10 CPP Cluster 2 Membership

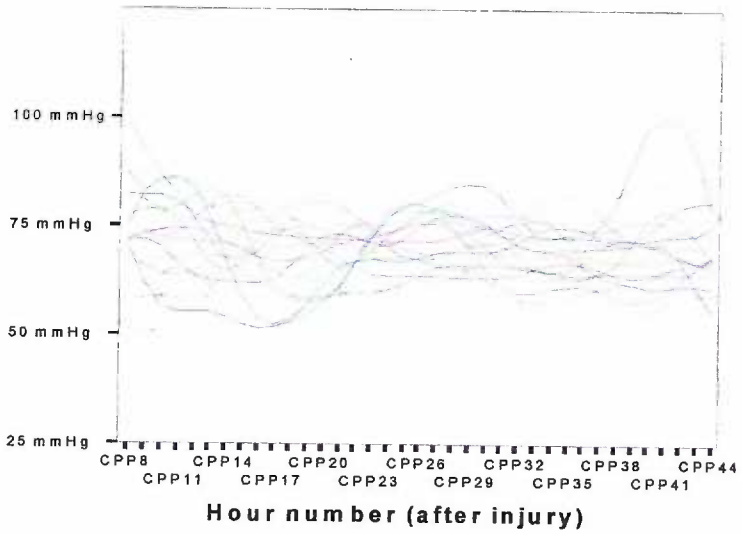


Figure 11 CPP Cluster 3 Membership

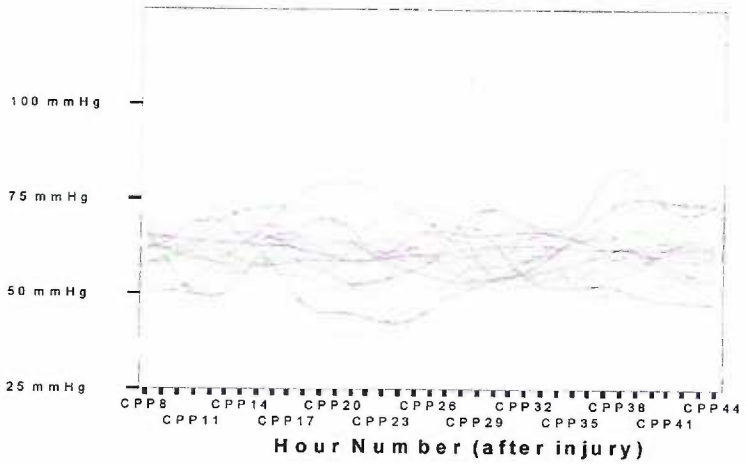


Table 5 Demographics of the CPP Clusters

Demographics	CPP Cluster 1 N = 11	CPP Cluster 2 N = 32	CPP Cluster 3 N = 28
Mean Age (+/- SD)	36.55 (13.14)	39.34 (19.93)	32.79 (13.40)
Age Range	17 - 77	17 - 77	17 - 64
% with any event of Fixed Pupil	9.1%	25%	14.3%
% with mGCS of 6	27.3%	21.9%	32.1%
% with any event of ICP > 30 mmHg	27.3%	31.3%	60.7%

In Table 6 it can be observed that TIL clusters 2 and 3 have very similar characteristics. The most notable difference between all clusters is the presence of any event of an ICP greater than 30 mmHg is much higher in clusters 2 and 3 than cluster 1.

Figure 12 TIL Cluster 1 Membership

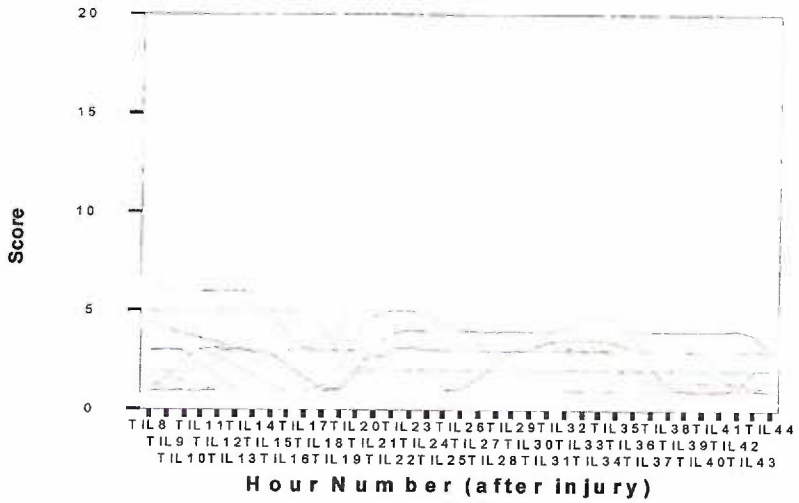


Figure 13 TIL Cluster 2 Membership

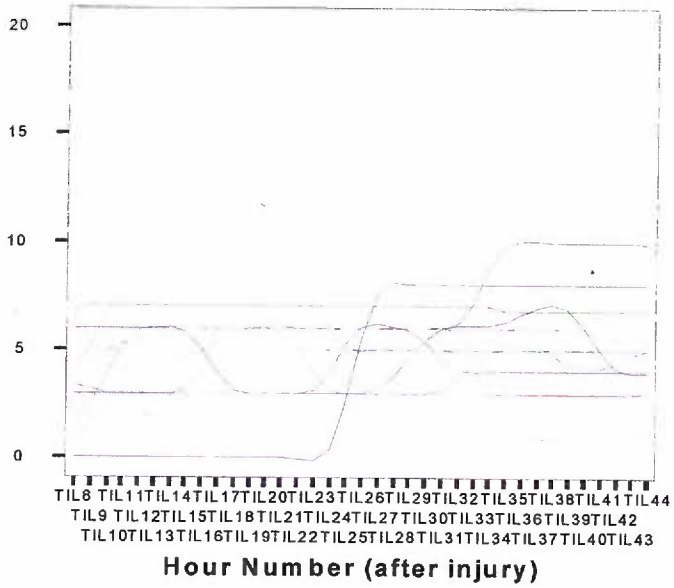


Figure 14 TIL Cluster 3 Membership

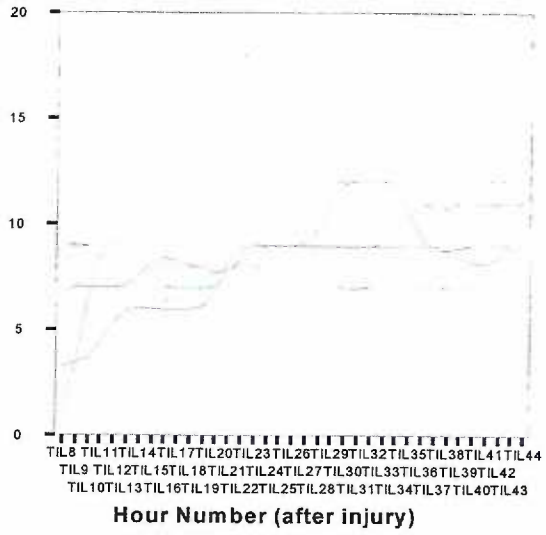


Table 6 Demographics of the TIL Clusters

Demographics	TIL Cluster 1 N = 36	TIL Cluster 2 N = 20	TIL Cluster 3 N = 16
Mean Age (+/- SD)	36.69 (18.42)	37.00 (17.32)	36.63 (14.01)
Age Range	17 - 77	17 - 77	18 - 64
% with any event of Fixed Pupil	16.7%	15.0%	25.0%
% with mGCS of 6	30.6%	25.0%	18.8%
% with any of ICP > 30 mmHg for duration of time measured	22.2%	65.0%	56.3%
% with any of CPP < 50 mmHg for duration of time measured	50.0%	75.0%	56.3%

Table 7 illustrates the demographics of TIL Cluster 1 versus the combined Clusters 2 and 3, with the same findings as discussed previously.

Table 7 Demographics of the Combined TIL Clusters (1 vs. 2 and 3)

Demographics	TIL Cluster 1 N = 36	TIL Cluster 2 (clusters 2 and 3 combined) N = 36
Mean Age (σ)	36.69 (18.42)	36.83 (15.72)
Age Range	17 - 77	17 - 77
% with any event of Fixed Pupil	16.7%	19.4%
% with mGCS of 6	30.6%	22.2%
% with any event of ICP > 30 mmHg	22.2%	61.1%
% with any event of CPP < 50 mmHg	50.0%	66.7%

In the ICP clusters, it is noted that the three different clusters are representative of three different clinical experiences. Historically, an ICP value of 20 mmHg has been typically considered to be a treatment "threshold" (an ICP of 10 mmHg or less is considered to be normal). Cluster 1 (Figure 6) contains 28 subjects, and represents those with an essentially normal ICP over the course of the 36 hours included in this time window. Cluster 2 (Figure 7) contains 34 subjects and represents those who had a constantly elevated ICP (with a mean of approximately 18 mmHg) over the entire course of their experience. The third

cluster, Cluster 3 (Figure 8), represents 10 subjects who had an early initial spike in their ICP, which resolves in the first 24 hours after injury. The subjects in Cluster 3 could reasonably be considered to be at higher risk for a worse neurological outcome than those subjects in Cluster 1, as their ICP was typically over the threshold of 20 mmHg for approximately 8 hours.

The groups clustered by CPP were not as distinctly differentiated as the ICP clusters were. The first CPP cluster of 11 subjects (Figure 9) described the "best" clinical course, according to current thought. The CPP for all members stayed over the accepted threshold of 70 mmHg for the entire period examined, except one brief initial drop experienced by one subject. The 32 subjects in the second cluster (Figure 10) experienced a slightly worse clinical course, with their average CPP hovering around 65 mmHg, and dipping below 60 mmHg fairly often. The 28 subjects in third cluster (Figure 11) had a slightly worse clinical course, as their average CPP hovering around 60 mmHg, with many dipping below 50 mmHg over the course of the 36 hours. In the absence of any other factors, the subjects in the third group might be expected to experience a worse functional outcome.

The TIL clusters also represented three different clinical experiences. The first cluster (Figure 12) describes a group of 36 subjects who generally were not treated very aggressively. These subjects all had fairly consistent, minimal treatment (although there were a couple of patients with brief increases in the

intensity of therapy). The second cluster of 20 subjects (Figure 13) generally had a fairly steady, moderate level of treatments for their increased ICPs. The third cluster of 16 subjects (Figure 14) had an increasingly aggressive course of treatment.

The third aim of this study was to assess the defined clusters' assocation with patient outcome while controlling for confounders.

None of the identified cluster memberships were significantly associated with the dichotomized DRS outcome (Table 8, below).

Table 8 Association Between Cluster Membership and Outcome

Cluster	% Subjects with Good Outcome*	% Subjects with Poor Outcome**
ICP Cluster 1	29	71
ICP Cluster 2	26	74
ICP Cluster 3	40	60
CPP Cluster 1	36	64
CPP Cluster 2	25	75
CPP Cluster 3	32	68
TIL Cluster 1	39	61
TIL Cluster 2	20	80
TIL Cluster 3	19	81

*Good outcome is defined as a one month DRS score of 6 or less
**Poor outcome is defined as a one month DRS score of 7 or greater

Both the ICP cluster membership ($p = .707$) and the CPP cluster membership ($p = .721$) in the crosstabs analysis were not significantly associated with the outcome (Table 9 below). When the TIL cluster membership was placed in the crosstabs, the results came closer to approaching a level of significance ($p = .192$), and subjects in clusters 2 and 3 had very similar outcomes.

Table 9 Association between Cluster Membership and DRS at 1 Month

Variable Name	χ^2	P value *	Odds Ratio (OR) **	95% CI for OR
Cluster Membership of ICP (3 clusters)	.69	.71	(Cluster 1 is referent) (2 vs. 1) 1.67 (3 vs. 1) 1.85	 0.37, 7.53 0.42, 8.11
Cluster Membership of CPP (3 clusters)	.65	.72	(Cluster 1 is referent) (2 vs. 1) 1.71 (3 vs. 1) 1.21	 0.40, 7.42 0.28, 5.21
Cluster Membership of TIL (3 clusters)	3.30	.19	(Cluster 1 is referent) (2 vs. 1) 2.54 (3 vs. 1) 2.76	 0.71, 9.19 0.67, 11.44
Dichotomized ICP clusters (clusters 2 and 3 vs. 1)	.01	1.00	.954	.34, 2.71
Dichotomized CPP clusters (clusters 2 and 3 vs. 1)	.29	.72	1.45	.37, 5.60
Dichotomized TIL clusters (cluster 1 vs. 2 and 3)	3.29	.12	2.636	.91, 7.63

* p-value from two-sided Fisher's Exact Test
** Odds Ratio comparing the odds of a good outcome, defined as a DRS score of 6 or less

The three clusters were examined to determine if the same subjects were grouped together across the three types of clusters examined. It was expected that ICP and CPP Cluster Membership would be significantly correlated, that is, that many of the same subjects were in each group, as the ICP is used to calculate the CPP. Indeed, this was demonstrated, with the two groups of clusters showing significant association ($p < .001$). ICP and CPP each were not significantly correlated with the TIL ($p = .301$ and $p = .841$, respectively).

Some findings of interest were noted when examining the association between ICP Cluster membership and outcome, stratified by the dichotomous TIL Cluster membership (Table 10). In the lowest TIL group (those subjects who received less intensive treatment), there did not seem to be a significant relationship between the ICP cluster membership and the DRS outcome at 1 month (χ^2 = .887, p = .642). However, the highest TIL cluster has a higher percentage overall of patients with a "good" outcome on the DRS, and there does appear to be a trend towards significance of the ICP cluster membership (χ^2 = 3.536, p = .171). There does appear to be a trend towards improved outcome with more intensive levels of treatment (despite ICP course), although the results were not significant.

Table 10 Association between ICP Cluster Membership and Outcome, Stratified by TIL Cluster Membership

		% with "Good" Outcome	**% with "Poor" Outcome**
Lowest TIL Cluster (1)	ICP Cluster 1	25%	75%
	ICP Cluster 2	12.5%	87.5%
	ICP Cluster 3	25%	75%
Total % (n = 36)		19%	80%
Highest TIL Cluster (Clusters 2 and 3)	ICP Cluster 1	31%	69%
	ICP Cluster 2	39%	61%
	ICP Cluster 3	100% (n = 2)	0%
Total % (n = 36)		39%	61%

Similar results were seen when examining the CPP cluster membership and the DRS outcome at 1 month, when stratified by dichotomous TIL cluster (Table 11). In the lowest TIL group, $\chi^2 = .089$, $p = .957$, and in the highest TIL group, $\chi^2 = 1.034$, $p = .596$. There does appear to be a trend towards improved outcome with more intensive levels of treatment (despite CPP course), although the results were not significant.

Table 11 Association between CPP Cluster Membership and Outcome, Stratified by TIL Cluster Membership

		% with Good Outcome*	% with Poor Outcome**
Lowest TIL Cluster (1)	CPP Cluster 1	25%	75%
	CPP Cluster 2	19%	81%
	CPP Cluster 3	19%	81%
Total % (n = 36)		19%	81%
Highest TIL Cluster (Clusters 2 and 3)	CPP Cluster 1	43%	57%
	CPP Cluster 2	31%	69%
	CPP Cluster 3	50%	50%
Total % (n=36)		40%	60%

*Good outcome is defined as a one month DRS score of 6 or less
**Poor outcome is defined as a one month DRS score of 7 or greater

Age under 40 (OR 3.78, 95% CI 1.12, 12.80; p = .034) and having the presence of a best motor GCS score of 6 in the first 24 hours after injury (OR 4.24, 95% CI 1.39, 12.99; p = .017) were the only significant predictors of good outcome found in this study (Table 12).

Table 12 Association Between Known Predictors of Outcomeand DRS at 1 month

Variable Name	χ^2	P value *	Odds Ratio (OR) **	95% CI for OR
Maximum motor GCS	6.88	.017		
mGCS < 6			1.00	
mGCS =6			4.24	1.39, 12.99
Age	4.91	.034		
			3.78	1.12, 12.80
< 40 years			1.00	
40 years or over				
Left Pupillary reaction	1.62	.317		
Never Fixed			2.75	.55, 13.68
Ever Fixed			1.00	
Maximum ICP (any event)				
0 – 20 mmHg	.005	1.00	.96	.31, 2.95
>20 mmHg			1.00	
0 – 30 mmHg			1.64	.57, 4.75
> 30 mmHg	0.847	.436	1.00	

* p-value from two-sided Fisher's Exact Test
** Odds Ratio comparing the odds of a good outcome, defined as a DRS score of 6 or less

The results of the simple logistic regression models with the DRS as the dependent variable can be seen in Table 13. It is noted again, as in the previous analysis, that the only variables that are significantly associated with the outcome at the .05 level are age and the mGCS score (best motor GCS score in the first 24 hours after injury).

Table 13 Results of Simple Logistic Regression Models with DRS (Good vs. Poor) as the Dependent Variable

Variable	β	se(β)	OR	95% CI (OR)	- 2 Log Likelihood	p*
Constant	.887	.259				
Age	1.329	.622	3.78	1.12, 12.79	81.671	.033
mGCS	1.445	.571	4.24	1.39, 12.99	80.42	.011
minCPP	.209	.531	1.23	.44, 3.49	86.767	.693
MaxICP	.496	.542	1.64	.57, 4.75	86.064	.359
Lpupil rxn	1.011	.818	2.75	.55, 13.67	83.725	.217
CPP cluster 1						.723
CPP cluster 2 (vs.1)	.539	.748	1.71	.40, 7.45	85.575	.471
CPP cluster 3 (vs.1)	.188	.746	1.21	.28, 5.21		.801
ICP cluster 1						.712
ICP cluster 2 (vs.1)	.511	.769	1.67	.37, 7.53	86.262	.507
ICP cluster 3 (vs. 1)	.616	.754	1.85	.42, 8.11		.413
TIL cluster 1						.202
TIL cluster 2 (vs.1)	.934	.655	2.55	.71, 9.19	83.572	.154
TIL cluster 3 (vs.1)	1.014	.726	2.76	.67, 11.44		.162

* p-value from two-sided Fisher's Exact Test

In a multiple logistic regression model containing all cluster membership information, age, mGCS, presence or absence of CPP less than 70 mmHg and

ICP greater than 20 mmHg, and presence or absence of a fixed pupil, age and mGCS were the only two variables found to be significant.

Examination of the crosstabs of created variables consisting of Low ICP/Low TIL; High ICP/Low TIL; Low ICP/High TIL; and High ICP/High TIL groups (and similar construction for CPP cluster membership) yielded no findings of significance ($p = .224$), however there did appear to be a trend across cells for the high TIL groups to have a better outcome than did the low TIL groups. Similar findings (although with less significance, $p = .296$) were seen in the variables using the CPP. The above variables were also entered into logistic regression models, with no significance noted, other than the previously identified age and mGCS. No interesting changes in these odds ratios were noted.

Discussion

The results of this study demonstrate that the K-means clustering analyses did successfully cluster the subjects appropriately, utilizing the richness of all of the datapoints within the selected time period. Each cluster profile also provided a reasonable representation of the cluster members that was also clinically meaningful. This method of analysis is of potential interest to researchers, as this provides an intriguing and important method to enable the researcher to be able to utilize all of the data collected on study subjects, rather than being limited to the use of a few datapoints.

The finding that the TIL cluster membership most closely approached significance in predicting outcome was interesting, particularly in the analyses of the ICP and CPP stratified by TIL cluster. Although the findings were not significant at the .05 level, it was interesting to note that those patients who received a higher, more aggressive level of therapy tended to have better outcomes, regardless of the ICP or CPP course. It can certainly be observed in the course of clinical treatment that the level of therapy given a patient varies, depending almost as much on the clinician involved as on the severity of injury of the patient. This analysis could suggest that the use of more aggressive therapy can be beneficial to patient outcomes.

Although neither ICP nor CPP cluster membership was found to be significant, it might be noted that in each instance, the ICP clusters were more highly associated with the outcome than the CPP clusters.

There are several possible reasons for the non-significant findings seen in this study. One that might be the most plausible is that the sample size of this study is too small to allow differences in the prediction of outcome to be detected. In a post hoc power analysis, it was seen that an estimated odds ratio of 4.6 was required in order to be able to detect a significant difference at a power of .80 for this sample size (n=72). To detect an odds ratio of 2.0 with a power of .80, a sample size of 400 subjects was required (Hintze, J., 2001).

Another possible explanation is that many of the previous studies of TBI outcomes include those patients who do not survive the initial injury. This has been estimated to represent between 20% and 30% (Struchen et al., 2001). It is possible that if a patient survives the initial TBI, the ICP or CPP course over time does not predict outcome. In addition, many of the previous studies on outcome were done using the prediction of mortality as the outcome variable, which raises the question of whether or not there is a difference in the predictive ability of the variables, depending on whether the outcome measured is mortality or good outcome.

A final reason for possible non-significant findings might be that the hours used in this analysis are not those which have the most impact on outcome, although it is generally believed that the first few days are the most important in the course of a patient's treatment. However, because the first 8 hours were not available for

Limitations

This study has several limitations, foremost of which is that the study has a fairly small sample size (n = 72). Another significant limitation is that data were missing in non-random patterns, with most of the earliest hours after injury (a potentially crucial time period) missing and not available for inclusion in the analyses. While later datapoints were able to be imputed, these earliest datapoints could not.

Conclusion and Future Research

The K-means clustering technique could be valuable in utilizing the rich and complex data that is frequently available but not used in many TBI studies. Cluster membership as assigned by the K-means technique does appear to be able to cluster subjects into clinically meaningful groups that are reasonable representations of the individual members of the clusters.

Future study of this technique in larger projects is recommended, and will be helpful in determining if cluster membership is predictive of outcome in this population, even in the presence of other known predictors of outcome.

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