Published in final edited form as:

Crit Care Med. 2018 November ; 46(11): 1792–1802. doi:10.1097/CCM.0000000000003361.

Intracranial pressure trajectories: A novel approach to informing severe TBI phenotypes

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Author Conflict of Information:

RMJ reports no conflicts and discloses NIH grants: K23NS101036 (NINDS), KL2-TR001856 (NCATS), KL2-TR000146 (NCATS)

JE reports no conflicts and discloses NIH grants: 1K23NS097629 (NINDS)

BEZ reports no conflicts

SD reports no conflicts

AMP reports no conflicts and discloses NIH grant: R00 NR013176 (NINR)

DOO reports no conflicts

SYP reports no conflicts

LAS reports no conflicts

JSW reports no conflicts

YPC reports no conflicts and discloses NIH grant: R01NR013342 (NINR)

PMK reports no conflicts

Author contributions:

Ruchira M. Jha was involved in study concept, design, data analysis and interpretation and manuscript generation. Jonathan Elmer was involved in data and statistical analysis, group-based trajectory modeling and interpretation, and critical revision of the manuscript. Ava M. Puccio, David O. Okonkwo, Benjamin E. Zusman and Shashvat Desai were involved in acquisition of data and patient samples. Seo-Young Park was involved in statistical analysis and review. Jessica Wallisch, and Lori A. Shutter were involved in content expertise and critical revision of the manuscript. Yvette P. Conley was involved genetics content expertise, supervision and critical review of the manuscript. Patrick M. Kochanek was involved in study concept, design, data interpretation, supervision and critical revision of the manuscript.

Copyright form disclosure: Dr. Jha's institution received funding from the National Institutes of Health (NIH) grants K23NS101036 (NINDS), KL2-TR001856 (NCATS), KL2-TR000146 (NCATS). Drs. Jha, Elmer, Park, Wallisch, Conley, and Kochanek received support for article research from the NIH. Dr. Elmer's institution received funding from NIH 1K23NS097629 (NINDS). Dr. Puccio received funding from NIH grant R00 NR013176 (NINR). Dr. Conley's institution received funding from NIH grant R01NR013342 (NINR). Dr. Kochanek's institution received funding from the NIH and the Department of Defense, and he received funding from the Society of Critical Care Medicine/World Federation of Pediatric Intensive Critical Care Societies as Editor-in-Chief of Pediatric Critical Care Medicine, numerous lectures as a guest professor at a number of academic institutions, from serving as an expert witness on several cases relevant to pediatric neurocritical care, and as one of the editors of the Textbook of Critical Care Medicine (honorarium). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Abstract

Objective—Intracranial pressure (ICP) in traumatic brain injury (TBI) is dynamic and influenced by factors like injury patterns, treatments and genetics. Existing studies use time-invariant summary ICP-measures thus potentially losing critical information about temporal trends. We identified longitudinal ICP-trajectories in severe-TBI and evaluated whether they predicted outcome. We further interrogated the model to explore whether *ABCC8*-polymorphisms (a known cerebral-edema regulator), differed across trajectory-groups.

Design—prospective observational cohort

Setting—single-center academic medical center

Patients—404 severe-TBI patients.

Interventions—none

Measurements—We used group-based trajectory modeling to identify hourly ICP trajectories in days 0–5 post-TBI incorporating risk-factor adjustment (age, sex, GCS-score, craniectomy, primary hemorrhage pattern). We compared six-month outcomes (Glasgow Outcome Scale(GOS), Disability Rating Scale(DRS), mortality) and *ABCC8* tag-single-nucleotide polymorphisms associated with cerebral edema (rs2237982, rs7105832) across groups. Regression models determined whether trajectory-groups predicted outcome.

Results—A six trajectory-group model best fit the data, identifying cohorts differing in initial ICP, evolution, and number/proportion of spikes >20 mmHg. There were pattern differences in age, hemorrhage type, and craniectomy rates. *ABCC8* polymorphisms differed across groups. GOS ($p=0.006$), DRS ($p=0.001$), mortality ($p<0.0001$) and rs2237982 ($p=0.035$) differed across groups. Unfavorable outcomes were surprisingly predicted by both low ICP-trajectories and sustained intracranial hypertension. ICP-variability differed across groups ($p<0.001$) and may reflect preserved/impaired intracranial elastance/compliance.

Conclusions—We employed a novel approach investigating longitudinal/dynamic ICP patterns in TBI. In a risk adjusted model, six groups were identified and predicted outcomes. If validated, trajectory modeling may be a first step towards developing a new, granular approach for ICP phenotyping in conjunction with other phenotyping tools like biomarkers and neuroimaging. This may be particularly relevant in light of changing TBI demographics towards the elderly.

Keywords

intracranial pressure trajectory (ICP); traumatic brain injury (TBI); group based trajectory modeling (GBTM); *ABCC8*/sulfonylurea receptor 1

INTRODUCTION

Intracranial hypertension is a key prognosticator of unfavorable outcome in severe traumatic brain injury (TBI). Its management remains a cornerstone of TBI guidelines (1–4). However, this relationship is complex. Intracranial pressure (ICP) is a dynamic product of multiple factors including an individual's cerebral elastance/compliance, mechanisms underlying cerebral edema generation/resolution, vascular dysregulation/blood volume, impact characteristics, and injury complex(4–6). It is further influenced by non-modifiable factors like demographics and genetics(5). Studies, including large trials, use single/summary ICP measures to classify patients and determine treatment efficacy(5, 7–11). Considering ICP as a time-invariant average value potentially obscures temporal trends. Point-values may also be insufficient to distinguish between an increasingly heterogeneous TBI population: the recent demographic shift towards elderly patients with increased cerebral atrophy/CSF space, comorbidities, lower physiologic reserve and reduced neuroplasticity, may yield fundamentally different ICP patterns, optimal thresholds, and prognostic implications(4, 6). In an era of precision medicine, individual variations in ICP trajectories may thus contribute to accurately phenotyping TBI. Classifying ICP trajectory may be a valuable *first step* in a new approach. It lays the foundation for future studies to potentially identify patients at risk for unfavorable trajectories, ultimately providing opportunities for early, or preventive interventions. Thus, we had three goals for this exploratory study: 1) to characterize temporal patterns of ICP evolution in our cohort of severe TBI patients, 2) to evaluate whether these patterns informed outcome, and 3) whether trajectory analysis added insight beyond conventional thresholds.

Group-based trajectory modeling (GBTM) is an established analytical method identifying clusters of individuals that follow a similar progression of some measure over time(12–14). It is increasingly utilized in medical research(12–14). We use GBTM to define longitudinal ICP trajectories and identify potentially distinct patterns in severe TBI. We examined the utility of generated ICP-trajectory groups as outcome predictors. To interrogate the model, we explored a potential genetic contribution to group variation. Since *ABCC8* encodes sulfonylurea-receptor-1 (Sur1), a putative regulator of cerebral edema in TBI, we evaluated whether *ABCC8* polymorphisms with reported cerebral edema associations differed across ICP trajectory-groups(15, 16).

METHODS

Study Design

This prospectively enrolled cohort (2000–2014) included 446 patients from a single academic medical-center with severe TBI (Glasgow Coma Scale (GCS) score ≤ 8 on presentation, and ICP monitoring per standard care with an external ventricular drain (EVD) and intra-parenchymal monitor). Brain death on presentation, pregnancy, and those without ICP recordings were excluded producing a cohort of 404 patients. Patients were treated as per the standard institutional protocol (Supplementary Materials). If care was withdrawn, no further ICP measurements were obtained and monitoring was discontinued as per standard clinical procedure. Informed consent was obtained from health-care proxies. University of Pittsburgh's IRB approved the study.

Clinical Data Collection

Demographic and clinical information (age, gender, GCS score), primary hemorrhage patterns, and hourly ICP were collected by research assistants blinded to *ABCC8* genotypes. Primary injury/hemorrhage patterns (subdural, subarachnoid, intraparenchymal-contusion, epidural, intraventricular, and diffuse axonal injury (DAI)) were determined from final radiology reports of initial CT scans and confirmed with review by a trained research assistant. For patients with >1 pattern of primary injury, the two most prominent patterns were recorded with no ordinance. Punctate CT hemorrhages suspicious for DAI were confirmed with MRI. Hourly ICP measurements from hours 1–120 (standard duration per our institutional protocol) after monitor placement were obtained from clamped EVD recordings (n=353) or intra-parenchymal monitors (n=51). For EVDs, the pressure transducer was placed at the level of the tragus. Outcomes were determined by binary six-month Glasgow Outcome Scale (GOS) score (unfavorable=GOS<4; favorable=GOS 4), six-month Disability Rating Scale (DRS) score (continuous), and six-month all-cause mortality. Outcomes were determined telephonically using standard forms for GOS and DRS by trained research technicians supervised by a licensed neuropsychologist.

DNA Collection, Tag-SNP Genotyping and Selection

DNA was obtained as previously reported(5). 23 *ABCC8* tag-SNPs were identified using HapMap(Build-36) with the tagger-algorithm pairwise approach, $r^2 \geq 0.8$ and minor allele frequency >0.20. Genotyping using iPlex-Gold was performed (Agena Compact MassArray with Nanodispenser, Genomics Research Core). Genotype analysis was performed using Typer-4.0 Assay. After quality control (Supplemental Methods), 410 samples were available. 2 tag-SNPs, rs2237982 and rs7105832 potentially associate with traditional cerebral edema markers (15) and were selected to assess associations with ICP-trajectories.

GBTM and Statistical Analysis

We used GBTM with a censored normal distribution (0–40 mmHg) to build ICP trajectories over the initial 120h. We used standard methods informed by Bayesian Information Criteria to select the optimal number of groups, and iteratively eliminated non-significant polynomial terms by performing a stepwise reduction of polynomial level to achieve the simplest final model where each trajectory group is significant at $\alpha=0.05$ (Supplementary-Table 1) (12–14, 17). Our model included time-invariant risk factor adjustment for age, sex, initial GCS score, emergent craniectomy, and primary hemorrhage pattern. We repeated this procedure restricted to patients who did not undergo craniectomy, and also included subsequent models where specific CT characteristics were included as risk factors (herniation, basal cistern effacement, ventricular effacement, sulcal effacement, degree of midline shift).

Analysis of variance F-test and Fisher's exact test were used to compare outcomes between groups. Pairwise comparisons were adjusted (Bonferroni's method). For final trajectory groups identified by multivariable risk-adjusted GBTM, we used logistic and linear regression models to determine whether groups (encoded as categorical variables) predicted outcome. Hosmer-Lemeshow tests determined goodness of fit. The largest trajectory-group was used as the reference group. For comparison, traditional multivariable linear and logistic

regression models predicting 6-month outcomes from average-ICP. Analyses were performed using Stata 14.0(StataCorp, TX).

RESULTS

ICP-trajectory groups

Six distinct trajectory groups were identified by our final model (Figure 1). The mean posterior-probability of group membership was 0.90 indicating excellent grouping(12). Table 1 summarizes clinical and demographic characteristics. Age, emergent craniectomy and primary injury pattern but not gender or initial GCS score differed between groups. Conventionally reported values (mean ICP, median number and proportion of ICP spikes, also differed between groups (Table 1, Supplementary-Tables 2A–E). GBTM classification had more nuanced pattern differences and prognostic implications vs. point measurements (presented subsequently).

A: ICP characteristics—Longitudinal ICP-trajectories were progressively higher with each group (Figure 1A). *Group 1* (n=34) had low ICPs that gradually rose over time. *Group 2* (n=88) had higher ICPs vs. 1 but remained persistently low. *Group 3* (n=93) had double-digit ICPs with rare spikes>20mmHg. *Group 4* (n=116) was the largest group, and had intermittent ICP spikes>20mmHg. ICPs in group 4 were higher than 3 over the entire monitoring-period with more frequent spikes (Figure 1, Supplementary-Figure 1, Table 1). *Group 5* (n=60) had persistently elevated ICPs-frequently between 20–30 mmHg (mean 19.19 ± 0.11 mmHg). *Group 6* (n=13) was a small cohort with early severe intracranial hypertension that continued to rise over the first 48h. Collated individual ICP measurements are shown in Supplementary-Figure 1. Figure 1C summarizes general characteristics within each ICP trajectory-group.

B: Clinical characteristics—Median age in groups 1 (49.5) and 2 (48) was higher than other groups (Table 1). Radiographic and craniectomy differences between groups were also evaluated.

(i) Injury patterns: The three most common primary injury patterns in all trajectory groups were subdurals, contusions, and subarachnoid hemorrhages (Supplementary-Figure 2). 257 patients had > one injury pattern on initial CT. In all ICP trajectory groups, frontal and diffuse injuries were most common (Supplementary-Figure 2B). While there appeared to be a slightly larger proportion of subdural hematomas in group-6 versus others, this was not significant ($p=0.084$). Lesion volumes were similar across groups-although epidural hematomas appeared larger in group-5 this was not significant ($p=0.35$, Supplementary-Figure 2C). Sample sizes in subgroups were too small for meaningful trajectory modeling or comparisons within each lesion type. Group-3 appeared to harbor an asymmetric proportion of patients with DAI and IVH: >50% of DAI and > 70% of IVH patients were in group 3. Supplementary Figure 2A suggests that intra-group proportions of DAI appear higher in groups 1 and 3 vs other groups (not statistically significant) despite these groups having different odds of favorable outcome (see section on Outcomes).

(ii) Radiographic edema: The proportion of patients demonstrating any one sign of acute CT edema (defined as midline shift, basal cistern effacement, sulcal effacement, ventricular effacement, herniation) was different between groups ($p=0.001$, Supplementary-Figure 3A)—group-6 had the highest proportion of patients with edema, group-1 had the lowest; groups 2–5 were similar. Distribution of the individual signs of acute CT edema within each trajectory group is shown in Supplementary Figure 3B. Degree of midline shift ($p=0.09$) and evidence of herniation ($p=0.087$) were not different between groups, however basal cistern effacement was ($p=0.002$) with group-6 having the highest proportion (Supplementary-Figure 3B). Risk-adjusted models including *any* sign of CT edema, or a constellation of potentially deleterious signs (degree of midline shift, basal cistern compression, herniation) did not change ICP trajectory patterns (Supplementary-Figure 3C–D).

(iii) Craniectomy: Majority of craniectomies in all groups were performed within 24 hours of presentation (Supplementary-Figure 4). In group 1, 17.65% underwent craniectomy. Groups 2 (47.73%) and 6 (53.85%) had a high proportion of patients undergoing craniectomy

Interestingly, a 6-group model, even in a sub-cohort without craniectomies; resulted in ICP-trajectory groups that were almost identical (Figure 1B, Supplementary Table 3) suggesting, surprisingly, that the rapid decline in ICP after hour 60–75 in group-6 of this cohort was not due to a surgical intervention but potentially the natural evolution of ICP based on pathophysiologic pathways in these patients with early severe intracranial hypertension. Furthermore, although craniectomy was acute (<24 hours) in $\sim 75\%$ of the cohort, it was acute in 100% of patients who underwent craniectomy in group 6 (Supplementary-Figure 4A). ICP trajectory group 5 was the only group where the distribution of craniectomies was similar across the first 72 hours—this group had consistent intracranial hypertension both before and after craniectomy. Late craniectomies were also performed consistent with the clinical significance of late ICP rises (18–20). GBTM replacing craniectomy from a binary risk-factor adjustment variable, to a continuous variable (to evaluate how this influenced trajectory patterns) confirmed the robustness/stability of our model (Supplementary Figure 4B).

(iv) Other characteristics: Withdrawal of care was different across trajectory groups ($p=0.02$) with the highest proportion of withdrawal in group-2; inter-group comparisons were not significant after Bonferroni's correction (Supplementary Figure 5A). There was no difference in injury severity scores across trajectory groups (Supplementary Figure 5B). Temporal ICP variability/fluctuation between serial measurements was different between groups ($p<0.001$, Figure 2) with a higher variance in groups 3 and 4 vs. others ($p<0.001$).

Six-month TBI outcomes differ across ICP-trajectory groups

Unfavorable six-month GOS ($p=0.006$), DRS ($p=0.0003$) and mortality ($p<0.0001$) differed across trajectory groups (Table 2, Figure 3A–B). Comparisons within ICP-trajectory groups revealed that groups 1 (median age 49.5, low rising ICPs), 2 (median age 48, high proportion of craniectomy, persistently low ICPs), 5 (median age 27, persistently elevated ICP) and 6 (severe/refractory intracranial hypertension) had higher proportions of unfavorable GOS

(Figure 3A, all $p < 0.001$). Groups 3 and 4 (intermittent ICP spikes, higher variability) had higher proportions of survivors (Figure 3B, both $p < 0.0001$).

ICP-trajectory group membership predicted six-month outcome in all assessed measures (Table 2, Figure 3A–B, Supplementary Figure-6). Groups 1, 2, 5 and 6 had higher DRS and increased odds of unfavorable GOS despite being at opposite extremes in terms of absolute ICP (Figure 1, Table 2). Surprisingly, these results persisted even in patients without craniectomy (Supplementary Table-4A) and in a risk-adjusted model that included radiographic signs of deleterious CT edema (degree of midline shift, basal cistern effacement, herniation; Supplementary Table-4B). Groups 1 and 5 continued to predict morbidity in patients aged ≥ 50 (Supplementary Results-ii).

Our cohort is robust in that conventional models in these patients validate previously reported predictors of unfavorable outcome such as age, initial GCS score, average ICP and proportion of ICP measurements > 20 and 25 mmHg (Supplementary Tables-4C–F)(21). Our cohort further corroborates that this predictive value does not hold for survivors (average ICP $p = 0.77$, proportion of ICP > 20 mmHg $p = 0.22$, Supplementary Tables 4C,E) (21, 22). GBTM classification suggests that point-value based models may fail to detect important differences (Supplementary Results-i-ii, Supplementary Table 4): trajectory groups remain predictive of unfavorable outcome even in survivors, and groups with lower mean-ICPs/and minimal frequent spikes > 20 or 25 mmHg had increased odds of unfavorable outcome.

ABCC8-tag SNP rs2237982 genotype differs across ICP-trajectory groups

Rs2237982 and rs7105832 have previously been associated with traditional measures of edema in TBI, including CT edema(15). Genotype frequencies for rs2237982 ($p = 0.035$) but not rs7105832 ($p = 0.135$) differed across ICP-trajectory groups (Supplementary-Table 5, Supplementary-Figure 6 C–D). Rs2237982 heterozygotes were different across ICP-trajectory groups ($p = 0.013$, Figure 3D) with an overrepresentation of heterozygotes in group 1 (67.7%). Supplemental Results-ii presents additional *post-hoc* differences.

DISCUSSION

Understanding and managing ICP remains fundamental to TBI care and thus crucial to its phenotyping. We employed a novel, dynamic ICP-measurement approach to investigate ICP patterns in TBI. This classification system addresses contemporary TBI demographics, adds nuance to time-invariant point values, and may provide a foundation toward eventually developing new insights into ICP-based clinical care, patient-selection, and prognostication in severe TBI.

(i) ICP-trajectory groups as a novel classification strategy

The six distinct ICP-trajectory groups identified in this study were distinguished by variable ICP patterns and clinical characteristics in the risk-adjusted model. ICP-trajectory groups were independent predictors of six-month outcome across multiple measures and questioned conventional dogma/pathophysiology. Unexpectedly, a six-group model yielded almost identical results in terms of trajectory pattern and outcome prediction for the sub-cohort of patients who did not undergo craniectomy, and; group-membership remained constant for

most patients except for those in ICP-trajectory group 3 and to a lesser extent those in group 4—all of whom transitioned to group 3 in the no-craniectomy cohort (Supplementary Table-3). This potentially indicates a component of innate unmeasured differences between groups, that if validated, warrant characterization. The extent to which innate differences versus therapeutic maneuvers influences ICP trajectory group membership remains unknown, as is the degree to which group-membership is manipulable. These factors affect whether similar vs different ICP trajectories would be seen in patient cohorts from different centers. Our study lays the foundation to explore these important questions in future work.

Current evidence suggests intracranial hypertension (variably defined as ICP 20–25 mmHg) and proportion of ICP spikes are associated with mortality but not morbidity in survivors(21–24). Traditional models in our cohort confirm this finding. However, trajectory-based classification results identify two surprising cohorts of patients with unfavorable outcome despite low ICP (groups 1 and 2). The reason for this association remains unknown and beyond the scope of this manuscript; however these groups may harbor uncaptured metrics such as differences in atrophy, cerebral compliance, neuroplasticity, neurovascular-coupling. While the association may be partially attributed to higher median ages in these groups, in group-1, the association with unfavorable outcome and mortality was true even for patients < 50 years. Differences between trajectory-groups may thus reflect other important unmeasured variability in cellular dysfunction and physiology(21, 25, 26). Additionally, unlike mean-ICP(21, 22), ICP-trajectory groups 1 and 5 predicted unfavorable outcome in survivors. We therefore posit that the dogma of using point values and identical thresholds for all patients may be insufficient to distinguish complex and dynamic physiologies after TBI: classifying patients into ICP trajectory groups serves as an initial step towards recognizing the potential importance of longitudinal temporal trends and more nuanced differences between patient-groups, thus identifying potential sets of patients for future study.

The value of patterns vs. point-measurements has been explored. Refractory ICP predicts outcome better than absolute values(27). ICP dose (>20 mmHg) may influence outcome(28). Our trajectory-group classification supports these concepts. Groups 5 and 6 had persistent intracranial hypertension and markedly increased odds of unfavorable outcome. However, these patterns do not explain the relationship between groups 1 and 2 (low ICPs) and unfavorable outcome. We hypothesize that ICP ‘variability’ may be an important predictive consideration indicative of phenomenon such as a healthier/more responsive elastance, or intact neurovascular-coupling – these potentially represent an early phenotyping opportunity that warrants further exploration. Previous studies have demonstrated an association between responsiveness of physiologic parameters/manifestations of intact autoregulation and TBI outcome (29)-whether this relates purely to homeostatic integrity or is influenced by interventions/systemic factors remains unknown. Thus, analogous to the prognostic value of EEG variability/reactivity, or Pressure-Reactivity Index indicating cerebrovascular reactivity(30, 31), healthier brain tissue may have more variation in ICP measurement (groups 3 and 4). Another potential explanation is that ‘stiffer’/distressed brains are predictive of unfavorable outcome. Our findings may also, in a manner yet to be fully characterized, reflect response to therapy.

A high-resolution temporally-dynamic ICP classification system if validated, may, in conjunction with other phenotyping parameters, ultimately contribute towards informing patient-selection for trials, minimization of treatment-effect dilution, pre-specified subgroup analyses/adaptive-design trials, promoting biomarker discovery to predict trajectory, and guiding differences in thresholds for clinical care based on individual phenotypes. This will need to occur in combination with other integral (and inter-related) physiological parameters including cerebral perfusion pressure, pressure reactivity indices/autoregulatory status, and brain tissue oxygenation. It may be valuable to explore these additional parameters using longitudinal trajectory analysis in future studies. While we did not explore *a priori* prediction of ICP-trajectory groups, our results provide the framework for such a study.

(ii) Age and ICP-trajectory group

The TBI landscape has evolved over the recent decades. One of the starkest differences between patients on whom clinical guidelines are based vs current epidemiology, is the shift towards elderly patients(4, 6). This is associated with different injury mechanisms, age-related comorbidities, use of preinjury antiplatelet/anticoagulants, physiologic reserve/pathophysiologic responses (including compliance, ICP), clinical courses and outcomes. These differences may yield dissimilar ICP patterns, optimal thresholds, and prognostic implications. Groups 1 and 2 had higher median ages vs. others and were independent predictors of unfavorable outcome. Group 1 retained its predictive ability even in patients <50 years however group 2 did not. In both, there were minimal-no episodes of intracranial hypertension. These results raise provocative questions including the utility of ICP monitoring in patients of a certain age group/injury profile, or the need for alternative treatment thresholds(4). Lower ICP thresholds have been proposed in patients > 55 years. Modest increases in ICP may reflect more severe injury in older patients due to age-related atrophy and/or lower compliance(4, 30). Reduced ICP monitoring in elderly patients has also been proposed however needs to be balanced with unjustified nihilistic attitudes towards this population, who can have favorable outcomes after aggressive care(4, 6).

(iii) Genetics and ICP-trajectory

Genetic contributions to TBI outcome are increasingly appreciated(4, 6, 32–34). These data on cerebral edema are limited but evolving, and have face validity(5, 35). Encoded by *ABCC8*, Sur1 mediated water influx represents a unique pathway of cerebral edema(7, 16, 36, 37). Inhibition with glyburide has shown promise in edema reduction in a phase-II trial of stroke, and *ABCC8* variation is associated with cerebral edema and TBI outcome(5, 15, 38). It thus appeared logical to test whether *ABCC8* polymorphisms (rs7105832, rs2237982) that have previously been associated with traditional cerebral edema measures (mean/peak ICP, CT edema) varied across ICP-trajectory groups. In our analysis, rs2237982 genotypes differed across groups. The *ABCC8*/Sur1 pathway is one example of the role of genetic diversity in this process. We selected it because *ABCC8* polymorphisms are likely examples of a greater pool of genetic variability in pathways influencing cerebral edema/neuroprotection. ICP-trajectory group-based classification may ultimately provide a more granular reflection of molecular, genetic and pathophysiological differences in TBI cohorts.

(iv) Limitations

This study establishes groundwork to explore methods of early trajectory prediction; defining the minimum duration of ICP-trajectory observation necessary to predict group membership was beyond the scope of this analysis. This current clinical limitation, in terms of immediate translation to bedside utility of patient categorization, is an important consideration for future work. Higher resolution data (with waveform analysis or automated minute-to-minute measurements) may provide additional potentially useful phenotyping. Our findings do not identify methods for early patient classification, targets for intervention, or analyze how different interventions may cause patients to switch trajectory groups. Serial autocorrelation lags may also be interesting to evaluate within each group since these may be indicators of the typical time-scales of underlying biological processes. However, these questions cannot be answered without first identifying/characterizing trajectory patterns informing outcome. Our results lay the foundation for future phenotyping studies and biomarker development to explore biological substrates that could a) identify patient trajectories earlier in their courses b) provide insight into pathophysiological/molecular/genetic differences between trajectory-groups and c) evaluate early/preventive therapies, and potentially inform patient selection for clinical-trials.

This was a single-center study prone to selection/institutional biases. However, it has the advantage of a therapeutic consistency. Replication in other centers would be informative: consistent results may indicate innate differences whereas pattern variation may implicate management effects. Manual ICP recordings may be less sensitive than automated data(21). Although majority of emergent craniectomies at our institution are for mass lesions rather than refractory intracranial hypertension, our data did not distinguish this, or include information regarding the proportion of prophylactic craniectomies, or craniectomy size. Measures of therapeutic intensity were unavailable to potentially distinguish groups (particularly 4 and 5) with regards to management variation (e.g. use of hypertonic saline, extent of craniectomy). This is a major limitation since this could modulate the ICP levels/patterns noted, as well as the impact of these trajectories on outcomes. Although ICP-trajectory groups are influenced by treatment prospective analysis of unbiased trajectories would be unethical. Nonetheless, almost identical trajectory-group classification resulted in all-patients vs. those without craniectomies. Late ICP rises which may be clinically important were missed (19, 20). Our data are also subject to potential intangible chronological biases - however the same protocol has been in place since 2006 and the only significant change between this and the earlier version was the institution of PbtO₂ monitor placement (unlikely to significantly influence ICP trajectories).

Although GBTM is valuable for longitudinal predictive strategies, it forces data to be fit by smooth polynomials which can be unphysiologic. To provide limits for the model, ICP>40 mmHg was treated as equivalent-ICP over this threshold may increase mortality risk(27). Our model was risk-adjusted for injury severity and primary injury pattern – however, sample size limitations prohibited meaningful statistical comparisons within subgroups of injury patterns/locations. More granular study of these variables in future studies may reveal an additional influence on outcome distinct from ICP trajectories. Larger studies, powered with sufficient patients in each subgroup, are important to discern interactions between ICP

trajectory groups and injury patterns or locations, and their relative effects on outcome. There may also be other (currently unknown) contributors influencing both outcome and ICP trajectories not currently captured by our model, like neurovascular uncoupling, cerebral compliance, brain tissue oxygenation/cerebral metabolic demand. For example, an earlier pediatric study yielded an interesting patient population with low-ICP and low brain-tissue oxygenation(39); analyzing a longitudinal interaction between ICP-trajectory groups and brain-tissue oxygenation could provide further insight into patient sub-populations. Thus, while ICP-trajectory groups provide valuable, high-resolution information, ICP (and therefore this analysis) is limited to *one piece of a complex puzzle of TBI variability*- our results provide an initial basis for future analyses to explore this in conjunction with other important physiologic variables in TBI such as cerebral perfusion pressure data, autoregulatory status, waveform analysis, brain tissue oxygenation, injury pattern and location, or EEG data. Combination of ICP trajectories with other parameters is likely essential for maximal value in TBI phenotyping.

CONCLUSION

We report a novel ICP-trajectory based classification approach as a first-step to understanding dynamic longitudinal patterns of this metric in TBI. Six ICP-trajectory groups were identified that supplemented insight into the relationship between ICP and TBI outcome versus point-measurements. In our risk-adjusted model, ICP-trajectory groups predicted six-month mortality and disability-unexpectedly, groups with low ICP trajectories also predicted unfavorable outcome. ICP variability may reflect the state of intracranial compliance/elasticity and differed across trajectory-groups with favorable vs. unfavorable outcomes. This approach to ICP establishes groundwork for future studies to evaluate early identification of trajectory-groups, pathophysiological differences, biomarker development and effects of intervention. If validated and refined, ICP-trajectory modeling combined with other parameters including neuroimaging, biomarkers, autoregulatory status, multimodal data, and electrophysiologic data, may contribute to clinical-trial design, precision-medicine driven care and prognostication in TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the following grants to which we are grateful: NIH(NINDS) K23NS101036 (RMJ), NIH(NINDS) 1K23NS097629 (JE) NINR R01NR013342 (YPC), NINR R00 NR013176 (AMP), NCATS KL2-TR000146 (RMJ), NCATS KL2-TR001856 (RMJ), UPP Foundation award (RMJ), University of Pittsburgh School of Medicine Dean's Faculty Advancement Award (RMJ).

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Figure 1. ICP Trajectory Group Characteristics

1A ICP Trajectory Group Classification:

Trajectory plots demonstrating collective ICP measurements across the six different ICP-trajectory groups identified by group-based trajectory modeling. ICP values (mmHg) are plotted over the monitoring course of 120 hours (5 days) from monitor placement. A legend in the top right corner identifies the individual trajectory groups.

1B ICP Trajectory Groups in patients without craniectomy.

Trajectory plots as in 1A in a subcohort of patients who did not undergo craniectomy. ICP values (mmHg) are plotted over the monitoring course of 120 hours (5 days) from monitor placement. A legend in the top right corner identifies the individual trajectory groups.

1C ICP Trajectory Group Descriptive Characteristics:

this chart descriptively summarizes demographic, pattern, and outcome differences between the trajectory groups. It highlights that in group 1, the primary hemorrhage pattern is intraparenchymal contusion (IPC), subdural (SDH) or subarachnoid (SAH), ICP values remain low with a gradual rise over time and have minimal beat-beat variability. This group predicts unfavorable outcome. SDH is the primary hemorrhage pattern in Group 2. ICP values are persistently low, with minimal beat-beat variability. A high proportion of these patients undergo craniectomy and this group also predicts unfavorable outcome. Group 3 comprises of patients with intermittent ICP spikes and high variability between measurements. While IPH and SDH constitute the majority of this group, DAI and IVH are disproportionately represented. Group 3 predicts favorable outcome. Group 4 patients have high, frequent ICP spikes. ICP variability is also high in this group. IPH and SDH are the predominant patterns and this group is predictive of favorable outcome. Group 5 patients have persistent intracranial hypertension and low variability. SDH and IPH are the most common hemorrhage patterns and the proportion of craniectomy is low. Group 5 is highly predictive of unfavorable outcome. Group 6, the smallest cohort, has severe/refractory intracranial hypertension, a high proportion of craniectomy, and unfavorable outcome.

Temporal Variability in Serial ICP Measurements by Trajectory Group

Figure 2. ICP variability across ICP-Trajectory Groups

Scatter plots of the difference between consecutive ICP measurements (Δ ICP) organized by trajectory group. In group 1, there is minimum variability/fluctuation between serially recorded ICP measurements – this slightly increases in group 2. Groups 3 and 4 appear to have the most variability between consecutively recorded ICP measurements. Group 5 variability appears similar to group 2. There are too few values in group 6 to make any determinations.

Figure 3. Distribution of 6-month Outcomes and Genotypes across ICP-Trajectory Groups

3A 6-month GOS across ICP-Trajectory Groups:

These bar graphs show the proportion of patients with favorable (GOS ≥ 4, blue) vs unfavorable (GOS < 4, gray) six-month outcome by ICP-trajectory groups. Fisher's exact test showed that the proportion of unfavorable six-month GOS was different across trajectory groups ($p=0.006$). For each trajectory group, Fisher's exact test was performed to determine whether the proportion of favorable vs unfavorable outcome was significantly different (p-value adjusted using Bonferroni's correction). Groups 1, 2, 5 and 6 had significantly higher proportions of unfavorable outcome.

3B 6-month Mortality across ICP-Trajectory Groups:

These bar graphs show the proportion of patients alive (blue) vs dead (gray) at six months, classified by ICP-trajectory groups. Fisher's exact test showed that the proportion of mortality was different across trajectory groups ($p<0.0001$). For each trajectory group, Fisher's exact test was performed to determine whether the proportion of alive vs. dead was significantly different (p-value adjusted using Bonferroni's correction). Groups 3 and 4 had significantly higher proportions of patients alive at six months.

Table 1

Patient characteristics in the ICP Trajectory Groups

	ICP Trajectory Group						Overall
	1	2	3	4	5	6	
Patient Characteristics							
Frequency (%)	34 (8.42%)	88 (21.78%)	93 (23.02%)	116 (28.71%)	60 (14.85%)	13 (3.22%)	404 (100%)
Median age in years (IQR)	49.5 (33–69)	48 (34–62)	33 (24–45)	29 (22–43)	27 (20–40.5)	36 (26–54)	35 (23–50)
Initial GCS $\pm$ SE	5.79 $\pm$ 0.25	6.05 $\pm$ 0.14	6.08 $\pm$ 0.15	5.61 $\pm$ 0.14	5.75 $\pm$ 0.21	5.08 $\pm$ 0.45	5.83 $\pm$ 0.07
% male (per group)	73.53 %	79.55 %	78.49 %	73.28 %	83.33 %	84.62 %	77.78%
% requiring craniectomy (per group)	17.65 %	47.73 %	20.43 %	30.17 %	35.00 %	53.85 %	32.35%
Median # of ICP > 20 mmHg (IQR) *	0 (0–1)	0 (0–0)	1 (0–3)	6 (2.5–12)	25 (16.5–35)	33 (21–39)	2 (0–10)
Proportion of ICP > 20 mmHg % $\pm$ SE *	0.64 $\pm$ 0.2%	0.69 $\pm$ 0.17%	3.1 $\pm$ 0.47%	10.7 $\pm$ 0.71%	39.8 $\pm$ 2.1%	78.0 $\pm$ 4.7%	12.7 $\pm$ 1.0%
Median # of ICP > 25 mmHg (IQR) *	0 (0–0)	0 (0–0)	0 (0–1)	1.5 (0–3)	8 (4–15.5)	22 (17–38)	0 (0–3)
Proportion of ICP > 25 mmHg % $\pm$ SE *	0.15 $\pm$ 0.067%	0.27 $\pm$ 0.08%	1.39 $\pm$ 0.35%	3.26 $\pm$ 0.35%	16.23 $\pm$ 1.4%	66.94 $\pm$ 7.4%	6.13 $\pm$ 0.74%
Mean ICP (mmHg) $\pm$ SE \$	5.8 $\pm$ 0.09	7.7 $\pm$ 0.05	10.4 $\pm$ 0.06	14.2 $\pm$ 0.06	19.3 $\pm$ 0.11	31.1 $\pm$ 0.44	11.62 $\pm$ 0.04

* Kruskal-Wallis test between groups p=0.0001. Dunn's post-hoc correction for multiple comparisons between groups presented in Supplementary Tables 2B–E

\$ ANOVA between groups p=0.0000. Bonferroni's post hoc correction for multiple comparisons between groups presented in Supplementary Tables 2A

Table 2

Outcomes in the ICP Trajectory Groups

<i>Unfavorable 6-month Outcome</i>	<i>ICP Trajectory Group</i>						<i>p-value</i>
	1	2	3	4	5	6	
% mortality (per group)	39.29%	40%	22.5%	25.4%	39.66%	83.33%	<i>p<0.0001</i>
Logistic regression odds ratio for mortality (95% CI, p-value)	1.89 (0.79–4.54, p=0.15)	1.95 (1.03–3.68, p=0.04)	0.85 (0.43–1.68, p=0.64)	Reference	1.92 (0.97–3.8, p=0.06)	14.62 (3.01–71.01, p=0.001)	
% GOS < 4 (per group)	82.14%	73.33%	62.50%	57.54%	79.31%	91.67%	<i>p=0.006</i>
Logistic regression odds ratio for GOS<4 (95% CI, p-value)	3.39 (1.20–9.61, p=0.02)	2.03 (1.07–3.85, p=0.03)	1.23 (0.68–2.23, p=0.50)	Reference	2.83 (1.35–5.94, p=0.006)	8.11 (1.01–65.15, p=0.05)	
Median DRS (IQR)	18 (6–30)	14 (4–30)	6 (2–22)	6 (2–30)	20 (4–30)	30 (30–30)	<i>p=0.0003</i>
Linear regression DRS β -coefficient (95% CI, p-value)	5.65 (0.48–10.81, p=0.03)	3.80 (0.14–7.45, p=0.04)	–1.04 (–4.64–2.56, p=0.57)	Reference	4.09 (0.15–8.03, p=0.04)	14.22 (6.9–21.5, p<0.0001)	