THE UNIVERSITY OF CALGARY

Non-neurological Organ Dysfunction in Severe Traumatic Brain Injury

by

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ABSTRACT

Our objective was to describe the incidence of non-neurological organ dysfunction and its association with outcome in patients with severe traumatic brain injury (sTBI) admitted to intensive care (ICU).

This was a historical prospective cohort study of 209 consecutive patients with sTBI. Ninety-six organ system failures were identified in 74 patients (35%). In a multivariate model, non-neurological organ dysfunction was independently associated with hospital mortality ($OR_{\text{hospital mortality}}$: 1.63; 95% CI: 1.34, 1.98 for each maximum modified MOD score point). Dichotomized Glasgow outcome score, as a measure of neurological outcome, was also independently associated with the degree of non-neurological organ dysfunction. The timing of the organ dysfunction did not appear to be important in the prediction of outcome.

Non-neurological organ dysfunction is common in patients with sTBI and is independently associated with worse outcome.

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DEDICATION

To Heather, Julia and Alex

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A. INTRODUCTION

Critically ill patients, who require multisystem management including advanced physiological monitoring and support and advanced nursing care with small nurse-patient ratios, are cared for in intensive care units (ICU). Common to most critically ill ICU patients is the presence of a systemic inflammatory response (SIRS) manifest by characteristic physiologic and laboratory abnormalities.[1] This inflammatory response—the body's mechanism for tissue repair—will often become dysregulated. In doing so, the inflammatory response will result in damage to organs and physiologic systems that were otherwise normal at the time of ICU admission.[2-4] This progressive and sequential damage resulting in secondary organ dysfunction, which if present in multiple organs, is known as multiple organ dysfunction syndrome. Approximately 50% of patients admitted to ICU develop multiple organ dysfunction syndrome, and approximately 40% of these patients will die from the consequences of multiple organ dysfunction syndrome.[5] Therefore, multiple organ dysfunction syndrome is the major cause of death in multisystem ICU patients.

Neurologically injured patients represent a distinct subset of critically ill patients. Similar to all critically ill ICU patients, patients with severe neurological injury are at risk for the development of multiple organ dysfunction syndrome. However, neurological injury has been associated with non-neurological organ dysfunction in the absence of systemic infection or injury. Further, therapy used to support the cerebral circulation in severe neurological injury may result in non-

neurological organ dysfunction. Thus, severe neurological injury represents an additional risk factor for the development of the multiple organ dysfunction syndrome. The incidence of non-neurological organ dysfunction in severe traumatic brain injury and its effect on outcome has not been previously described.

B. LITERATURE REVIEW

1. Multiple Organ Dysfunction in Critical Care

In 1973, Tilney and colleagues described the postoperative course of a series of patients with ruptured aortic aneurysm, massive blood loss and shock (a clinical consequence of aortic rupture), successful resuscitation and surgical repair, but postoperative organ failure and death.[6] Baue subsequently coined the term in an article entitled "Multiple, Progressive, or Sequential Systems Organ Failure: a Syndrome of the 1970's".[7] Subsequent authors in case series describing their own local experience provided further detail on which organ systems were most likely to fail. In 1980, Fry provided the first classification system for identifying patients with "Multiple Organ Failure".[8] Many other authors have subsequently published "Organ Failure" scoring systems. These systems have in common the identification of organ failure in 6-8 physiologic systems, and the use of physiologic and/or laboratory variables to identify the presence or absence of organ failure.

There have been 3 large multicentre studies that have assessed the association of organ failure and ICU patient survival. The first study examined 5677 ICU admissions at 13 US hospitals between 1979 and 1982.[9] Of these admissions, 2724/5677 (48%) developed one or more organ system failures. A single organ system failure (OSF) persistent for >1 day was independently associated with a mortality rate of ~40%, 2 or more OSFs for >1 day was associated with a mortality rate of 60%, and the mortality rate for 99 patients with

3 or more OSFs lasting ≥3 days was 98%. These results were subsequently replicated in 2405 ICU admissions at 27 French hospitals.[10] Approximately 10 years following the first study, the same authors conducted the third study involving 10,427 patients admitted to 60 ICU's in 53 U.S. hospitals.[11] They confirmed the initial results in patients with one or two organ system failures. However, the last study did demonstrate a slightly lower mortality rate for patients with 3 or more OSFs (30/192 survived, or an 84% hospital mortality rate). An important secondary analysis demonstrated a variation in risk of death dependent on the organ system involved with cardiovascular and neurological failure being associated with the highest mortality.

2. Multiple Organ Dysfunction Scoring Systems

Many organ dysfunction scales have been developed to measure the severity and course of organ dysfunction. Ideal variables for describing organ dysfunction should possess several important characteristics. These variables should be objective, simple and easily available but reliable. They should be specific for the organ system being considered and of a continuous nature. In addition, they should also be independent of patient type and therapeutic intervention. In the mid 1990's, at relatively the same time, four organ dysfunction scores were developed that met these 'optimal' characteristics for a variable, used rigorous albeit disparate methodology in variable/score development, and included or had subsequent attempts to assess the validity

and operating characteristics of the scores. The Sequential Organ Failure Assessment (SOFA) score, Multiple Organ Dysfunction (MOD) Score, and the Logistic Organ Dysfunction (LOD) score have received the most attention in the literature while the Brussels Score remains only in abstract form. The SOFA and MOD score, the most commonly applied scores, will be reviewed here including the methodology of creation, characteristics of each score, and the validation of each score.

MOD SCORE

The MOD score was developed and validated on a cohort of 692 patients admitted to a tertiary Canadian surgical ICU.[12] The principles of validity (construct, content, and criterion), reproducibility, and responsiveness guided an extensive literature search, which served as the basis for the selection and evaluation of variables. The first 336 patients served as a development set for the calibration of variables. Each organ system was scored from 0 to 4. Thresholds were determined based on mortality rate. A score of 0 represented a mortality rate of <5% while a score of 4 represented a mortality of >50%. Intermediate intervals were established so the ranges for each point were approximately equal and a given score in one system would predict an equivalent mortality for the same score in another system. The subsequent 356 patients served as a validation set to test the reproducibility of the intervals derived from the development set. The MOD score is presented in Appendix 1.

An increasing MOD score correlated with ICU mortality. Patients with scores > 20 had a mortality rate of 100%. A mortality rate of 25% was observed for patients with a score of 9 –12, 50% for a score of 13 – 16, and 75% for a score of 17 – 20. In logistic regression analysis, the neurological and renal had largest contribution to predictive capacity while the hepatic component did not significantly contribute to the prediction of mortality. This logistic regression model (component scores as independent variables and ICU mortality as the dependent variable) had excellent discriminative power in both the development set (area under the ROC 0.936) and the validation set (area under the ROC 0.928). The MOD score at admission and delta MOD score (the difference between the maximum MOD score and the admission MOD score which represents the amount of organ dysfunction acquired during ICU stay) independently predicted ICU mortality in a logistic regression analysis (admission MOD score OR 1.47, delta MOD score OR 1.59. The delta MOD score contributed slightly more than the admission MOD score to the predictive capacity of the model.

Other investigators have described the use of the MOD score. Barie and colleagues measured daily MOD scores in a large prospective cohort of surgical ICU patients.[13, 14] MOD score was significantly correlated with ICU length of stay. The MOD score also significantly predicted mortality in their multiple logistic regression analysis. Jacobs *et al* compared the MOD score to the APACHE II score in a prospective cohort of 39 patients with septic shock admitted to a

medicosurgical ICU.[15] The MOD score at admission was not statistically different between survivors and non-survivors. This was also true for the admission APACHE II score. However, the maximum MOD score calculated during the ICU stay was significantly higher in non-survivors than survivors. The corresponding value for APACHE II was not statistically different between survivors and non-survivors. The relatively small number of patients limits the interpretation of this study. Recently, a Canadian group studied the MOD component scores in a cohort of 1200 patients admitted to 16 multi-system ICUs.[16] The goal of the study was to examine the relationship between the six components of the MOD score with time to death in the ICU. Cox regression analysis determined that only four organ systems were associated with ICU mortality: cardiovascular, respiratory, renal, and neurological. The relative risk of mortality was found to be time-dependent for the respiratory system (baseline and serial components) and the serial component of the hepatic system. Baseline hepatic score was not related to mortality. The characteristics of the maximum MOD score were not described in this study. Further, the MOD score in this study utilized a different cardiovascular variable than described above. Instead of the pressure-adjusted heart rate, the cardiovascular component was scored as follows: 0 = heart rate < 120; 1 = heart rate > 120, <140; 2 = heart rate > 140; 3 = need for inotropes > dopamine 3 μg/kg/min; 4 = lactate > 5 mmol/L.

SOFA SCORE

The SOFA score, presented in Appendix 2, was developed by consensus conference of the European Society of Intensive Care Medicine (ESICM) in Paris in 1994.[17] The purpose behind development was two-fold: to improve the understanding of the natural history of organ dysfunction and be able to assess the effects of new therapies on the course of organ dysfunction. The SOFA score consists of 6 organ systems each scored from 0 to 4 with 0 representing normality and 4 representing the most severe dysfunction. The cardiovascular, respiratory, coagulation, hepatic, central nervous and renal systems were chosen for inclusion with the worst physiological value for each day recorded. J. L. Vincent *et al*, on behalf of the working group on "sepsis-related problems" of the ESICM, published the first prospective evaluation of the SOFA score.[18] This international cohort study described organ dysfunction as measured by the SOFA in 1449 patients admitted to one of 40 ICUs during May 1995. Using a subset of patients staying at least a week in the ICU (544 patients), they found 44% of non-survivors increased their SOFA score compared to 20% of survivors. Further, 33% of survivors decreased their total score compared with 21% of non-survivors. Infected patients had more severe organ dysfunction compared with those without infection. Supporting the validity of the SOFA score as a surrogate ICU outcome measure, mortality was correlated with SOFA. Mortality was 9% for patients without organ failure and 83% for those with four or more organs failing (organ failure defined as $\geq$3). A maximum SOFA of >15 was associated with a

90% mortality rate. A proportional hazards analysis suggested the values within the cardiovascular, neurological and renal systems contribute the most to the risk of death.

Two further analyses of this dataset examining the characteristics of the SOFA score have been published. The first examined the development of organ dysfunction in the subset of 181 trauma patients.[19] Those trauma patients who did not survive were significantly older and had significantly higher mean SOFA scores during the first week of ICU care. A higher SOFA score was independently associated in multiple regression analysis with a longer ICU length of stay (LOS). Evaluation of these regression coefficients revealed the contribution of SOFA to ICU LOS decreased over the first 5 days. The additive coefficient for each SOFA point on day 0 was 0.85 days compared to 0.66 days at day 4. Non-survivors had more severe admission respiratory, coagulation, cardiovascular, and neurological scores than survivors. A SOFA score of greater than or equal to 5 was associated with a death rate 2.7 times greater than a SOFA score less than 5. After the first 4 days, only respiratory dysfunction has significant prognostic value in the trauma patient.

The second publication analyzed the association of total maximum SOFA score and delta SOFA score to ICU mortality.[20] A patient's total maximum SOFA score was calculated by summing the worst scores for each of the 6 component scores. The delta SOFA score was defined the difference between the total maximum SOFA score and the admission SOFA score. The mean total

maximum SOFA score was significantly higher for non-survivors than survivors (13.6±4.8 vs. 6.7±4.5). The discriminative power, the ability of the scores to discriminate between survivors and non-survivors, for each maximum component SOFA score, total maximum SOFA score, admission SOFA score, and the delta SOFA score was determined using the area under the Receiver Operating Characteristic curve (AuROC). Of the component scores, the cardiovascular score had the best discriminative power (AuROC 0.802). However, when compared with the individual component scores, delta SOFA score, and admission SOFA scores, the total maximum SOFA score performed the best in terms of discriminative power (AuROC 0.847). In logistic regression analysis, the cardiovascular component score was found to have the highest relative contribution to outcome {Odds Ratio (OR) 1.683, 95% Confidence Interval (CI): 1.488-1.905} while the hepatic component did not significantly contribute to the prediction of outcome (p=0.192). Further logistic regression analysis revealed the degree of organ dysfunction at admission (admission SOFA score) and the degree of organ dysfunction developing during the ICU stay (delta SOFA score) significantly and independently contributed to the prediction of outcome with a similar weight (admission SOFA OR 1.361, 95% CI 1.303 – 1.421; delta SOFA OR 1.367, 95% CI 1.303 – 1.432).

The total maximum SOFA score has been further validated in 303 consecutive patients admitted to a medical ICU in Germany.[21] In this study, the total maximum SOFA score again showed very good discriminative power

(AuROC 0.86) despite the fact that the patients were significantly different when compared with the multicentre trial described above, (this study was comprised primarily of medical patients with an overall hospital mortality of 14.5% while the multicentre study included a large proportion of surgical patients and described a 26% overall hospital mortality). The SOFA score has also been scrutinized in other patient populations. In a sample of critically ill patients with cirrhosis, Wehler *et al* found day 1 SOFA score to have excellent discriminative power (AuROC 0.94), which was superior to the APACHE II and Child-Pugh systems.[22] Recently, Ferreira and colleagues published a study of 352 consecutive patients admitted to a medicosurgical ICU in Belgium.[23] They found mean SOFA score (sum of all daily SOFA scores divided by the ICU LOS) correlated best with mortality in univariate analysis (OR 3.06 95% CI: 2.36 – 3.97) and had a very good discriminative power (AuROC curve 0.88). However, the variable with the best discriminative power was the highest SOFA score (AuROC 0.90). Supporting previous work, the change in SOFA score during the patient's ICU stay was independently predictive of outcome. For those with an initial SOFA of >11, a mean SOFA that increased or stayed the same was associated with a 91% mortality rate.

3. Mechanisms of Non-Neurological Organ Dysfunction in Patients with Significant Neurological Injury

Patients with severe neurological injury represent a distinct group of critically ill patients in whom organ dysfunction may develop. In addition to the causes of organ dysfunction experienced by general critical care patients, neurologically injured patients may develop non-neurological organ dysfunction as a result of brain specific mechanisms or as a complication of brain targeted therapies.

Neurogenic myocardial dysfunction and neurogenic pulmonary edema (NPE) are two well described brain specific causes of non-neurological organ dysfunction. Cardiac abnormalities in patients with subarachnoid hemorrhage (SAH) have been described for over 50 years.[24] Numerous case series have described both global myocardial dysfunction and regional wall motion abnormalities following SAH.[25-30] The cardiac abnormailities seen following SAH have been primarily linked to catecholamines. Naredi and colleagues found evidence of prolonged and massive sympathetic nervous activation following SAH.[31] Norepinephrine spill-over to the plasma increased by a factor of three. This increase was sustained for 10 days, but follow up at 6 months revealed normal levels. Catecholamines released in response to experimental SAH in dogs caused cardiac lesions observed by electron microscopy within 4 hours of hemorrhage.[32] Connor has described human autopsy evidence of myocytolysis and contraction-band necrosis of the heart in neurosurgical patients, including

those with SAH.[33] These lesions were considered to be similar to those caused by catecholamines. Patterns of myocardial dysfunction observed following SAH are not compatible with a coronary artery etiology and angiography has not been revealing in these patients.[27] Zaroff *et al* recently described an apex-sparing pattern of myocardial dysfunction which correlates with the distribution of the myocardial sympathetic nerve terminals.[34] Less is known about myocardial dysfunction following severe traumatic brain injury. After brain death, Dujardin found 17/41 (41%) of patients with traumatic brain injury had echocardiographic evidence of myocardial dysfunction.[35] Fifty-three percent had segmental dysfunction while 47% had global dysfunction. It is not known if this dysfunction was present before brain death or occurred after declaration.

NPE was first described in 1908[36] and has been described following SAH, traumatic brain injury, status epilepticus and intracranial hemorrhage. It has been observed to develop within seconds of neurological insult but can occur any time during the first 14 days after injury, most commonly occurs on day 3.[37] Based on pulmonary edema fluid analysis, both hydrostatic edema and permeability edema may be present in patients with NPE.[38] This mixture of types of edema may be due to the fact that intense pulmonary constriction initially causes increased capillary pressures and hydrostatic edema but then disrupts the basement membrane finally resulting in a permeability edema. Similar to the neurocardiac injury, the primary etiological theory of NPE revolves around catecholamines. Catecholamines increase transmural pulmonary pressures[39] and the largest

initial effect is increased pulmonary venous pressure.[40] Extravascular lung water in increased in patients with SAH and is correlated with alveolar-arterial oxygen difference.[41]

Other potential brain specific mechanisms of non-neurological organ dysfunction have recently been described. Dys-regulated inflammatory mechanisms are thought to play a crucial role in the development of multiple organ dysfunction syndrome. Although the brain was previously thought to be immunologically inactive, recent evidence suggest local inflammation may be an important mediator of secondary injury following brain injury. Elevated cerebral spinal fluid cytokine levels have been identified in adult and children following traumatic brain injury and SAH.[42-44] Importantly, there appears to be delivery of these cytokines to the systemic circulation.[45-47] It is possible these inflammatory mediators contribute to the development of non-neurological organ dysfunction following major neurological injury. Recently, modulation of the coagulation system with activated protein C has been shown to improve outcome in those with septic shock.[48] Those patients treated with activated protein C showed significantly faster resolution of cardiovascular and respiratory dysfunction and significantly slower onset of hematological organ dysfunction compared with placebo patients.[49] Although activated protein C is not a viable option for most with severe neurological injury due to the risk of intracranial bleeding, it is clear that patients with severe traumatic brain injury have abnormalities of the coagulation system that may contribute to non-neurological organ dysfunction.

Severe head injury induces an initial hypercoagulable state.[50, 51] This hypercoagulable state may be followed by increased fibrinolytic activity[52] which may progress to symptomatic disseminated intravascular coagulation. Systemic microthrombi formation due to a dys-regulated coagulation system may predispose to multiple organ dysfunction.[53, 54] Takahashi and colleagues have suggested neutrophil elastase may play a role in the development of symptomatic disseminated intravascular coagulation following head injury.[55]

In addition to the above described brain specific mechanisms, non-neurological organ dysfunction may arise as a complication of therapies aimed at support of the cerebral circulation. A primary focus in the treatment of severe traumatic brain injury is the control of intracranial hypertension. Barbiturates and induced hypothermia significantly reduce intracranial pressure. However, barbiturates cause immunosuppression[56] which may be mediated through inhibition of tumor necrosis factor alpha-induced activation of nuclear factor kappaB through suppression of kappaB kinase activity.[57] These acquired immune defects are a potential explanation for the increase incidence of pneumonia seen in patients treated with barbiturates.[58] Similarly, induced hypothermia leads to an increased risk of pneumonia in patients with head injury.[59] Pneumonia is frequent cause of organ dysfunction in intensive care. Cerebral perfusion pressure (CPP) management has recently come under scrutiny because of an association with acute respiratory distress syndrome (ARDS). In a randomized controlled trial of two management strategies,

Robertson *et al* found a fivefold increase in the occurrence of ARDS in the group managed with a higher CPP threshold (70 vs. 50 mm Hg).[60] In a secondary analysis, independent risk factors for the development of ARDS included administration of epinephrine, administration of dopamine in a larger than median dose, and a history of drug abuse.[61]

4. Impact of Non-Neurological Organ Dysfunction on Outcome in Patients with Significant Neurological Injury

Three studies have addressed the impact of non-neurological organ dysfunction in patients with subarachnoid hemorrhage. Gruber studied 242 patients with SAH and found extracerebral organ system dysfunctions were significantly and independently related to poor neurological outcome.[62] Solenski found that 41.8% of all deaths after SAH (except prehospital mortalities) were due to extracerebral organ dysfunctions.[63] Zygun and colleagues retrospectively studied patients with severe traumatic brain injury or SAH in an academic neurocritical care unit in the United Kingdom.[64] Despite identifying a high incidence of cardiopulmonary failure, no influence of non-neurological organ dysfunction cold be identified. However, this study was limited by a relatively small sample size.

C. OBJECTIVES

1. Primary Question

What proportion of patients with severe traumatic brain injury experience at least one non-neurological organ failure during admission to the intensive care unit (ICU)?

2. Secondary Questions

Is there an association between degree of non-neurological organ dysfunction and hospital mortality in patients with severe traumatic brain injury?

Is there an association between the degree of non-neurological organ dysfunction and neurological outcome in patients with severe traumatic brain injury?

Does the timing of maximal organ dysfunction [early (<5days) vs. late (≥5 days)] have an effect on the association of non-neurological outcome and outcome?

Is the method of assessment of non-neurological organ dysfunction an important factor in the association of organ dysfunction and outcome (mortality and neurological outcome)?

D. METHODS

1. Study Design

This study is a historical cohort study comprised of data merged from three prospectively collected databases. Patients with severe traumatic brain injury were identified from the Trauma Services database maintained by the Division of Trauma, Department of Surgery at FMC. The Department of Critical Care Medicine TRACER database prospectively collected both SOFA and MOD scores on all patients admitted to ICU for each day of ICU stay and mortality status. The FMC Rehabilitation database and Trauma Services database provided neurological outcome.

2. Study Sample

In the CHR, adult trauma services are regionalized to the Foothills Medical Centre (FMC) that is the only adult tertiary care trauma center servicing southern Alberta, Canada. All adult patients (≥16 years of age) with severe traumatic brain injury admitted to the intensive care unit of FMC during the period from May 1, 2000 to April 30, 2003 with an ICU length of stay (LOS) > 48 hours were included. Severe traumatic brain injury was defined as a traumatic brain injury resulting in at least one of 1) an initial resuscitated (systolic blood pressure > 90 mm Hg and SaO_2 > 90%) Glasgow Coma Score (GCS) of 8 or less at first contact with medical services, or 2) a post-resuscitation GCS at presentation to the trauma centre of 8 or less in the absence of sedation, or 3) the requirement

for intracranial pressure (ICP) monitoring, or 4) the presence of clinical or radiographic herniation.

3. Data Measurement

Non-Neurological Organ Dysfunction Scores

The SOFA and MOD scores were collected daily based on the recommendations in the original publications.[18, 65] An electronic patient information system (Quantitative Sentinel (QS), GE-Marquette Medical Systems Inc. interfaced to all bedside devices collects physiologic data, and this data was validated (accepted by the system) by nursing or respiratory therapy staff on at least an hourly basis by examining the representativeness and sensibility of the data. An HL-7 interface with the regional laboratory information system (Cerner PathNet Classic version 306 (Kansas City, MO)) was utilized to collect all laboratory data. Two programs were developed in Visual Basic (Microsoft VBL, Microsoft Corporation, Seattle WA) to examine all physiologic and laboratory values in each 24-hour period, measured daily from 0000-2359 hours. For the SOFA score, one Visual Basic program determined the most abnormal value for each parameter. The program then calculated the appropriate SOFA value (range 0-4), which was then exported to a local longitudinal ICU database known as TRACER (Microsoft Access, Microsoft Corporation, Seattle WA). Missing values were replaced between a preceding and subsequent value with the lower of the two scores. In the absence of a preceding or subsequent value, the score

was calculated at zero. In the second Visual Basic program, the least abnormal value at 0700±2 hours was used to calculate the appropriate MOD score. The calculation of each component system value and the total values for both SOFA and MOD scores were manually checked (C. Doig) for their accuracy by comparing to the laboratory or physiologic data recorded in the QS system over a one month period (683 patient days) prior to the start of the study; no errors were found in the calculation of either score.

Outcome Measures

Survival status was determined at the time of hospital discharge. Neurological outcome was determined at discharge from the inpatient rehabilitation program. The Functional Independence Measure (FIM) is the most widely accepted functional assessment measure in the rehabilitation community. The FIM emerged from a thorough developmental process, sponsored by the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation. A National Task force reviewed 36 published and unpublished functional assessment scales before agreeing on an instrument. Granger and colleagues developed the FIM as a measure of disability using average daily minutes of direct assistance from another person as a criterion for validity.[66] The FIM measures independent performance in self-care, sphincter control, transfers, locomotion, communication, and social cognition. The FIM employs 18 items in which a patient's degree of disability and burden of

care are assessed. Each item is rated according to a seven-level classification. A score of one indicates complete dependence while a score of 7 indicates complete independence. Scores falling below six require another person for supervision or assistance. By adding the points for each item, the total possible score ranges from 18 (lowest) to 126 (highest) level of independence. The interrater reliability of the FIM has been shown to be between 0.86 and 0.97.[66, 67] It has been shown to have high internal consistency and adequate discriminative capabilities for brain injured rehabilitation patients. It is responsive to functional change over time and provides a good indication of burden of care.[68] The FIM has been extensively studied and validated specifically in those suffering from traumatic brain injury.[69-72] The FIM score was determined through a collaborative effort of the Brain Injury rehabilitation team at the time of discharge from the rehabilitation program. This team consists of physiotherapists, occupational therapists, nurses and physiatrists and all members have undergone formal training in the application of the FIM score.

In addition, hospital discharge Glasgow Outcome Scores (GOS, Appendix 3), which were determined based on chart review by Trauma Services, were also employed in the analysis. The GOS was developed to allocate people who have suffered head injury into broad outcome categories. Its primary strength is to allow the outcome of different groups of patients to be compared in a simple and easily interpreted fashion.[73] It has been recommended as a measure of outcome for clinical trials[74] and has been widely adopted for this purpose.

Clinical Data

Patient demographics, injury details, and post-resuscitation GCS were included in the Trauma Services database. ICU and hospital length of stay were included in the TRACER database.

4. Data Analysis

General Considerations

Descriptive statistics and boxplots were used to analyze each variable separately. Analyses of continuous, normally distributed variables within and between groups were undertaken using the appropriate Student's t-test. Non-normally distributed continuous variables were analyzed using the Mann Whitney U test. Categorical variables were analyzed using Fisher's exact test. A P-value of less than 0.05 was considered significant. All statistical tests were two-sided.

Primary Outcome

The primary outcome was the proportion of patients with at least one non-neurological organ failure during the intensive care phase of the management of patients with severe traumatic brain injury. An organ failure was defined as a MOD component score ≥ 3. In addition, the number of organs failing during ICU was determined for each patient and the proportion of patients experiencing two, three, four and five non-neurological organ failures were calculated.

Secondary Outcomes

The contribution of non-neurological organ dysfunction to hospital mortality was determined by calculation of the modified maximum MOD (maximum mMOD) score which is defined as the sum of the most abnormal non-neurological MOD component scores obtained by each patient during ICU management. Patients were categorized by quartile of maximum mMOD score and comparisons between survivors and non-survivors were accomplished using the Fisher's exact test. To determine if mortality is associated with non-neurological outcome present at admission or with non-neurological organ dysfunction acquired during ICU stay, the admission modified MOD score (admission mMOD), defined as the sum of the non-neurological MOD component scores on the patient's day of admission to ICU, and the modified delta MOD score (delta mMOD), defined as the difference between the maximum mMOD score and the admission mMOD score, was calculated. Patients were categorized by median admission and delta mMOD scores and comparisons of these categories between survivors and non-survivors were performed using the Fisher's exact test. To determine if the association of mortality and non-neurological organ dysfunction was independent of the known association with age and post-resuscitation GCS, a logistic regression model was created that also included ICU LOS as this represents the time at risk for the development of non-neurological organ dysfunction.

To determine if the association of neurological outcome and non-neurological organ dysfunction was independent of the known association with age and post-resuscitation GCS, a logistic regression model was created that also included ICU LOS as this represents the time at risk for the development of non-neurological organ dysfunction. In this model, GOS was dichotomized into favorable outcome (GOS 4, 5) and unfavorable outcome (GOS 1, 2, 3).

Comparison of the SOFA and MOD score determination of organ dysfunction for each organ system was examined by calculating the proportion of patients with SOFA and MOD component score defined organ failure. The proportion of patients who did not survive to hospital discharge was calculated for each level of dysfunction within each component score and the results for SOFA and MOD scores were compared. Organ systems with discrepant results were further analyzed by calculating the odds ratio for hospital mortality of SOFA or MOD defined organ failure. Ability to discriminate hospital mortality was judged by calculating the AuROC.

We speculated organ dysfunction derived from neurological injury will occur early in the patient's course (< 5 days) and organ dysfunction related to ICU complications (ventilator associated pneumonia, line sepsis, etc) would occur later (≥5days). Therefore, the timing of maximal non-neurological organ dysfunction may be important with respect to its relationship to outcome. In the subset of patients with ICU LOS≥10 days, patients were classified as having maximal organ dysfunction early or late. The Fisher's exact test will be used to

assess the proportion of patients with early (cf. late) maximal organ dysfunction between survivors and non-survivors.

E. ETHICAL CONCERNS

All data was collected from the three databases. Prior to data acquisition, ethical review and approval was attained from the Ethics Review Board of the Calgary Health Region. Collaborating researchers include Dr. C. Doig (Intensive Care), Dr. J. Kortbeek (Trauma and Intensive Care), and Dr. C. McGovern (Rehabilitation) who have clinical and administrative responsibilities for these patients. However, to further protect patient confidentiality, only data from the index hospital admission was accessed. Personal identifiers were removed from the data wherever possible and the data was password protected at all times. Data was stored in a locked cupboard in a locked office

F. RESULTS

1. Patient Characteristics

A total of 209 patients were identified as having sustained a severe traumatic brain injury and required at least 48 hours of ICU care during the study period. The criteria for the diagnosis of severe traumatic brain injury are detailed in Table 1. The characteristics of these patients are detailed in Table 2.

TABLE 1. Method of Diagnosis Of Severe Traumatic Brain Injury

Criteria for the Diagnosis of Severe Traumatic Brain Injury	Percentage of Patients
GCS Alone	49%
Herniation Alone	4%
ICP Alone	9%
GCS & Herniation	7%
GCS & ICP	20%
Herniation & ICP	4%
GCS & Herniation & ICP	7%

TABLE 2. Patient Characteristics

Patient Characteristic	
Number	209
Age [Median, (Range)]	36 (16-90)
Male Gender	78%
Injury Severity Score (Mean±SD)	32.6±10.8
Mechanism of Injury	
Motor Vehicle Collision	50%
Fall	33%
Assault	5%
Suicide	3%
Pedestrian vs. Motor Vehicle	5%
Bicycle Collision	1%
Snowboarding/Skiing	1%
Unknown	1%
Post-Resuscitation Glasgow Coma Score [Median (Intraquartile Range)]	5 (3-7)
Admission APACHE II (Mean±SD)	18.5±6.4
Percentage of Patients with the Following Injuries on CT Head:	
Subdural Hematoma	54%
Extradural Hematoma	16%
Subarachnoid Hemorrhage	55%
Diffuse Axonal Injury	31%
Intraventricular Hemorrhage	32%
Parenchymal Hematoma	28%
Percentage of patients with maximum AIS ≥ 3 for the following systems:	
Chest	87%
Abdomen/Pelvic Contents	39%
Pelvis/Extremities	63%
ICU Length of Stay [Median (IQR)]	7 (3,13)
Hospital Length of Stay [Median (IQR)]	19 (6,50)
Hospital Mortality	32%

2. Non-Neurological Organ System Failure

Ninety-six organ system failures were identified in 74 patients (35%). One quarter of non-neurological organ system failures were identified in the first 24

hours of ICU admission. The majority of patients (55/74) developed failure of only one non-neurological organ system. Seventeen patients developed 2 non-neurological organ system failures. Three and four non-neurological organ system failures were experienced by one patient each.

Respiratory failure was the most common non-neurological organ system failure occurring in 23% of patients while cardiovascular failure occurred in 18%. Eight patients (4%) had failure of the coagulation system. One patient had renal failure while no patient developed hepatic failure.

3. Mortality and Non-neurological Organ Dysfunction

Sixty seven patients (32%) patients died prior to discharge from hospital. Characteristics of survivors and non-survivors are presented in Table 3.

TABLE 3. Patient Characteristics by Survival Status

Characteristic	Survivors	Non-Survivors	P-value
Age [Median (IQR)]	35 (22,50)	38 (23,53)	0.54
Male Gender	114/142	49/67	0.28
ICU LOS [Median (IQR)]	8 (2,8)	4 (2, 8)	<0.0001
APACHE II (Mean±SD)	17±5	22±7	<0.0001
Post-Resuscitation GCS [Median (IQR)]	6 (3,7)	4 (3,6)	0.02
ISS	32±11	33±10	0.47

Non-survivors had more non-neurological organ dysfunction during intensive care than survivors as determined by the maximum mMOD score. Non-survivors had more non-neurological organ dysfunction at admission to ICU as

determined by the admission mMOD score (Table 4). In addition, they developed more non-neurological organ dysfunction than survivors during ICU stay as determined by the delta mMOD score. The proportion of survivors and non-survivors by quartile of maximum mMOD score is shown in Table 5. There was no difference in hospital mortality among patients with greater than median admission mMOD scores compared to those patients with less then the median (P=0.08). Hospital mortality was significantly greater in those patients with delta mMOD scores above the median (51%) compared to patients with delta mMOD scores less than the median (P=0.036). The day of ICU admission on which the patient's highest daily mMOD score occurred was not significantly different between survivors and non-survivors (P=0.9).

TABLE 4. Non Neurological Organ Dysfunction

	Survivors	Non-Survivors
Maximum mMOD [Median (IQR)]	3 (1, 5)	4 (2, 7)
Admission mMOD [Median (IQR)]	0 (0, 2)	1 (0, 2)
Delta mMOD [Median (IQR)]	2 (0, 3)	3 (1, 5)

TABLE 5. Hospital Mortality by Quartile of Maximum MOD Score

Maximum mMOD Score	0 - 1	2 – 3	4 - 5	6 - 12
Survivors (%)	44 (80)	42 (67)	32 (71)	24 (52)
Non-Survivors (%)	11 (20)	21 (33)	13 (29)	22 (48)

P=0.028

The proportion of patients who did not survive to hospital discharge increased with increasing number of non-neurological organ system failures (Table 6).

TABLE 6. Number of Organ System Failures and Mortality

Number of Organ System Failures	Proportion of Patients Not Surviving to Hospital Discharge	Number of Patients
0	0.26	135
1	0.40	55
2	0.47	17
3	1.0	1
4	1.0	1

A logistic regression model was created to determine if the association between the degree of non-neurological organ dysfunction (maximum mMODS) was independent of the known prognostic factors age and post-resuscitation GCS. Because organ dysfunction was only measured in ICU, ICU LOS was included in the model as it represents the time the patient was at risk for acquiring organ dysfunction. The model is presented in Table 7 and represented schematically by:

$$g = \ln\left\{\frac{\rho}{1-\rho}\right\} = \beta_0 + \beta_{Max\_mMOD}(Max\_MMOD) + \beta_{GCS}(GCS) + \beta_{ICULOS}(ICULOS) + \beta_{Age}(Age)$$

where ρ represents probability, Max_mMOD represents the maximum mMOD score, GCS represents post-resuscitation GCS, and ICULOS represents ICU LOS.

TABLE 7. Multivariable Logistic Regression Model: Hospital Mortality and Organ Dysfunction

	Coefficient	Standard Error	95% Confidence Interval	P-value
Constant	-0.359	0.607	-1.549, 0.831	0.554
Maximum mMOD Score	0.489	0.100	0.293, 0.686	<0.001
Post-Resuscitation GCS	-0.191	0.071	-0.331, -0.051	0.007
ICU Length of Stay	-0.249	0.050	-0.348, -0.150	<0.001
Age	0.019	0.010	-0.001, 0.039	0.058

N=191, LR X^2(4df)=58.62, P<0.0001

This model can be interpreted as follows for the contribution of non-neurological organ dysfunction to the prediction of hospital mortality. Assuming the same post-resuscitation GCS, ICU length of stay and age, the following is obtained for a one point difference in maximum mMOD score:

$$g(Max\_mMOD+1)-g(Max\_mMOD)=$$
$$\left[\beta_0+\beta_{Max\_mMOD}(Max\_MMOD+1)+\beta_{GCS}(GCS)+\beta_{ICULOS}(ICULOS)+\beta_{Age}(Age)\right]$$
$$-\left[\beta_0+\beta_{Max\_mMOD}(Max\_MMOD)+\beta_{GCS}(GCS)+\beta_{ICULOS}(ICULOS)+\beta_{Age}(Age)\right]$$
$$=\beta_{Max\_mMOD}$$

Thus:

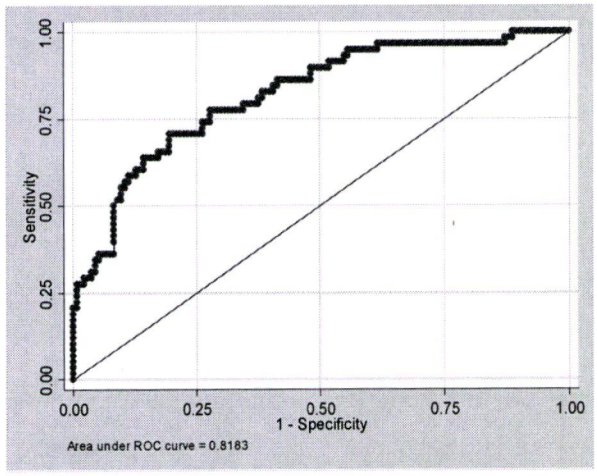
$$\Psi(Max\_mMOD+1, Max\_mMOD)=e^{\beta_{MAX\_mMOD}} \Rightarrow \hat{\beta}=e^{0.489}=1.63$$

Therefore, for every increase of 1 point in maximum mMOD score, the odds of hospital mortality increases 1.63 times.

The fit of the model was assessed using the Hosmer-Lemesow goodness of fit test. There was no evidence of lack of fit ($\hat{C}_{(8df)}$=10.65, P=0.22). This model

was found to have excellent discrimination as determined by the area under the Receiver Operator Characteristic curve of 0.81 (See Figure 1).

FIGURE 1. Area under the Receiver Operating Characteristic Curve: Association of Hospital Mortality and Non-Neurological Organ Dysfunction



Examination of a the plot of Pearson residuals against the predicted probability with points sized based on Pregibon's dbeta, a measure of influence revealed two outlying patients with potential influence (Figure 2 and Table 8).

FIGURE 2. Plot of Pearson Residuals Against Predicted Probability

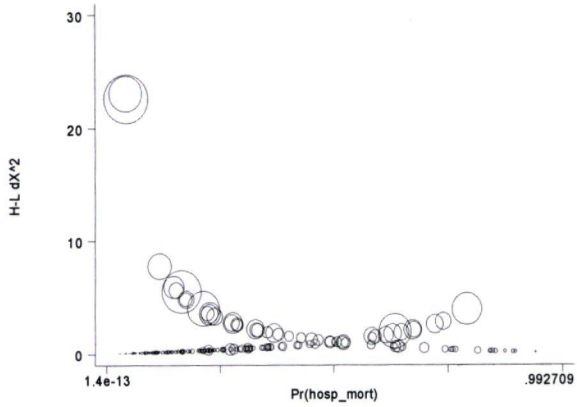


TABLE 8. Covariate Pattern for Outlying Patients

Patient ID	Age (years)	Post-Resuscitation GCS	ICU Length of Stay (days)	Maximum mMOD Score
9262321	42	3	16	2
9323836	54	9	24	8

Exclusion of these 2 patients did not affect the model's significance or alter the coefficients substantially.

In a post-hoc assessment, hospital mortality was found to be associated with diagnostic category in univariate comparison. Therefore, diagnostic category was added to the multivariate model in an exploratory analysis. Addition of this categorical variable into the model improved its discriminatory ability (AuROC 0.89). Nested model likelihood ratio testing suggested addition of this variable also improved the predictive ability of the model ($P<0.01$). However, the coefficient and its significance for the maximum mMOD score did not change significantly (0.502 vs. 0.489). Thus, there was no evidence that diagnostic category confounded the association of hospital mortality and non-neurological organ dysfunction.

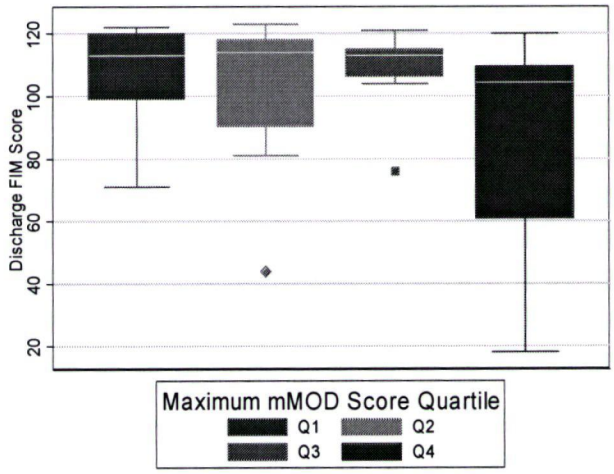
4. Neurological Outcome and Non-Neurological Organ System Failure

FIM Score

Forty-four of 142 survivors (31%) were admitted to the Foothills rehabilitation program making available discharge FIM scores. Discharge FIM

score was performed a median (IQR) of 83.5 (46.5,117.5) days after injury. Median (IQR) discharge FIM score was 110 (100, 116). Although a slight trend to lower discharge FIM scores was noted in the quartile of patients with the highest degree of non-neurological organ dysfunction, no statistically significant association between maximum mMOD score and discharge FIM score could be demonstrated (Figure 3).

FIGURE 3. Boxplot Comparison of Discharge FIM Score by Maximum mMOD Quartile



Glasgow Outcome Score

Discharge GOS were available for 147 patients (70%). For survivors, GOS was determined a median (IQR) of 31(15-55) days following injury. Neurological outcome was dichotomized into favorable (GOS 4, 5) and unfavorable (GOS 1, 2, 3). One third of patients (49/147) had favorable neurological outcome. Maximum mMOD score was lower in those with favorable neurological outcome. This was

due to both lower admission mMOD scores and the development of less non-neurological organ dysfunction during ICU (Table 9).

TABLE 9. Non Neurological Organ Dysfunction and Neurological Outcome

	Favorable Neurological Outcome	Unfavorable Neurological Outcome
Maximum mMOD Score [Median (IQR)]	2 (1, 4)	4 (2, 6)
Admission mMOD Score [Median (IQR)]	0 (0, 1)	1 (0, 2)
Delta mMOD Score [Median (IQR)]	1 (0, 2)	2, (1, 4)

The proportion of patients with favorable and unfavorable outcome by quartile of maximum mMOD score is shown in Table 10. There was a significant difference in the proportion of patients attaining a favorable neurological outcome among patients with greater than median admission mMOD scores (14%) compared to those patients with less then the median admission mMOD score (P=0.001). The proportion of patients with favorable neurological outcome was significantly lower in those patients with delta mMOD scores above the median (20%) compared to patients with delta mMOD scores less than the median delta mMOD score (42%) (P=0.007).

TABLE 10. Neurological Outcome by Quartile of Maximum MOD Score

Maximum mMOD Score	0 - 1	2 – 3	4 - 5	6 - 12
Favorable (%)	23 (58)	12 (29)	9 (30)	5 (14)
Unfavorable (%)	17 (43)	30 (71)	21 (70)	30 (86)

P=0.001

Analogous to the hospital mortality analysis, a multivariate model was created to assess the independent association of non-neurological organ dysfunction and neurological outcome. The model is presented in Table 11.

TABLE 11. Multivariable Logistic Regression Model: Favorable Neurological Outcome and Organ Dysfunction

	Coefficient	Standard Error	95% Confidence Interval	P-value
Constant	-0.764	0.667	-0.543, 2.072	0.252
Maximum mMOD Score	-0.426	0.114	-0.650, -0.202	<0.001
Post-Resuscitation GCS	0.167	0.080	0.012, 0.324	0.036
ICU Length of Stay	0.076	0.037	0.002, 0.150	0.042
Age	-0.041	0.013	-0.066, -0.015	0.001

N=133, LR X^2 (4df)=31.15, P<0.0001

There was no evidence of lack of fit of the model using the Hosmer-Lemeshow goodness of fit test. The discrimination of the model was adequate as judged by the AuROC (0.77). Residual analysis did not reveal outlying data points with significant influence and leverage. A post-hoc analysis did not reveal a confounding or modifying effect of the timing of the determination of the GOS on the association of maximum mMOD and dichotomized neurological outcome.

5. The Effect of the Timing of Organ Dysfunction on Outcome

A stratified analysis was performed to examine the effect of timing of maximal organ dysfunction on the association of non-neurological organ dysfunction and outcome. For both hospital mortality and dichotomized neurological outcome, the timing of maximal organ dysfunction [early (<5days) vs. late (≥5days)] did not significantly modify the effect of non-neurological organ dysfunction on outcome if patient with ICU length of stay 10 days or longer. In a post hoc analysis, the timing of maximal organ dysfunction was explored in *all* patients. Again, the timing of non-neurological organ dysfunction did not modify or confound the association of non-neurological outcome and outcome. The results of logistic regression modeling with non-neurological organ dysfunction entered as a continuous variable confirmed the results of the stratified analysis.

6. A Comparison of Modified MOD and SOFA Scores

The percentage of patients with SOFA and MOD component score defined organ failure is presented in Table 12. For four of the five non-neurological organ systems, SOFA component scores identified organ failure in a higher proportion of patients.

TABLE 12. Percentage of Patients with Component Score Defined Organ Failure

Component Score	SOFA	MOD
Cardiovascular	56%	18%
Respiratory	43%	23%
Coagulation	6%	4%
Renal	0.5%	0.5%
Hepatic	1%	0%

The relationship of hospital mortality and component SOFA and MOD scores are presented in Table 13.

TABLE 13. Relationship of Hospital Mortality and Component SOFA and MOD Scores

Maximum SOFA Component Score			Hospital Mortality	Maximum MOD Component Score		
CV Component Score	Proportion of Non-Survivors	N		CV Component Score	Proportion of Non-Survivors	N
0	0	20		0	0.17	100
1	0.09	70		1	0.43	37
2		0		2	0.44	34
3	0.43	14		3	0.52	21
4	0.53	105		4	0.47	17
Respiratory Component Score	Proportion of Non-Survivors	N		Respiratory Component Score	Proportion of Non-Survivors	N
0	0.17	6		0	0.31	39
1	0.21	24		1	0.32	57
2	0.30	90		2	0.27	64
3	0.28	57		3	0.44	41
4	0.56	32		4	0.25	8
Coagulation Component Score	Proportion of Non-Survivors	N		Coagulation Component Score	Proportion of Non-Survivors	N
0	0.30	93		0	0.28	134
1	0.24	58		1	0.32	44
2	0.39	46		2	0.43	23
3	0.5	10		3	0.57	7
4	1.0	2		4	1.0	1
Renal Component Score	Proportion of Non-Survivors	N		Renal Component Score	Proportion of Non-Survivors	N
0	0.30	195		0	0.31	193
1	0.5	10		1	0.38	13
2	0.67	3		2	0.5	2
3	1.0	1		3	1.0	3
4		0		4		0
Hepatic Component Score	Proportion of Non-Survivors	N		Hepatic Component Score	Proportion of Non-Survivors	N
0	0.32	180		0	0.32	192
1	0.33	24		1	0.33	15
2	0.33	3		2	0.50	2
3	0.5	2		3		
4		0		4		

Mortality increased with increasing SOFA cardiovascular component score. However, there was no significant difference in mortality between MOD cardiovascular component scores greater than zero. The distribution of patients differed dramatically between the SOFA and MOD cardiovascular component scores. The majority of patients (105) were identified by SOFA cardiovascular component score to have the most severe degree of cardiovascular dysfunction while the MOD cardiovascular component score determined almost half of the patients (100) to have normal cardiovascular function. Patients who developed SOFA defined cardiovascular failure were at significantly higher risk of death than those patients who did not (OR 14.7; 95% CI: 5.9 – 36.3; p>0.001). The development of SOFA defined cardiovascular failure was a reasonable discriminator of hospital mortality (AuROC=0.75).Those patients who developed MOD defined cardiovascular failure had a slightly increased risk of hospital mortality (OR 2.6; 95% CI 1.24 – 5.26; p=0.01). The development of MOD defined cardiovascular failure was a poor discriminator of hospital mortality (AuROC=0.57).

In general, an increasing SOFA respiratory component score was associated with an increasing mortality. This was not the case for the MOD

respiratory component score. In fact, the highest MOD respiratory component score was associated with the lowest mortality. Respiratory organ failure defined by either score was not statistically associated with increased risk of death prior to hospital discharge. For the renal, coagulation and hepatic component scores, there was little difference between the SOFA and MOD scoring systems.

The relationship of dichotomized neurological outcome and component SOFA and MOD scores are presented in Table 14.

TABLE 14. Association of Dichotomized Neurological Outcome and Component SOFA and MOD Scores

Maximum SOFA Component Score				Maximum MOD Component Score		
CV Component Score	Proportion with Unfavorable Outcome	N		CV Component Score	Proportion with Unfavorable Outcome	N
0	0.27	11		0	0.49	65
1	0.42	43		1	0.70	27
2		0		2	0.84	25
3	0.70	10		3	0.93	15
4	0.84	83		4	0.80	15
Respiratory Component Score	Proportion with Unfavorable Outcome	N		Respiratory Component Score	Proportion with Unfavorable Outcome	N
0	0.33	3		0	0.50	30
1	0.37	19		1	0.66	38
2	0.63	60		2	0.67	45
3	0.74	39		3	0.86	29
4	0.88	26		4	0.60	5
Coagulation Component Score	Proportion with Unfavorable Outcome	N		Coagulation Component Score	Proportion with Unfavorable Outcome	N
0	0.62	68		0	0.62	94
1	0.51	39		1	0.66	32
2	0.91	32		2	0.93	15
3	0.83	6		3	0.80	5
4	1.0	2		4	1.0	1
Renal Component Score	Proportion with Unfavorable Outcome	N		Renal Component Score	Proportion with Unfavorable Outcome	N
0	0.65	135		0	0.66	137
1	0.78	9		1	0.75	8
2	1.0	2		2	1.0	1
3	1.0	1		3	1.0	1
4		0		4		0
Hepatic Component Score	Proportion with Unfavorable Outcome	N		Hepatic Component Score	Proportion with Unfavorable Outcome	N
0	0.67	128		0	0.66	136
1	0.63	16		1	0.70	10
2	0.50	2		2	1.0	1
3	1.0	1		3		0
4		0		4		0

Similar to the data regarding hospital mortality, distribution of patients and proportion of patients with unfavorable neurological outcome differed between SOFA and MOD cardiovascular component cardiovascular scores. Developing cardiovascular failure as defined by SOFA was associated with a greater risk of unfavorable neurological outcome (OR 7.6; 95% CI 3.5 - 16.3, p>0.001) than developing MOD defined cardiovascular failure (OR 4.1; 95% CI 1.3 – 12.4; p=0.006). SOFA defined cardiovascular failure was a better discriminator of dichotomized neurological outcome than MOD defined cardiovascular failure (AuROC 0.73 vs. 0.59). For the renal, coagulation and hepatic component scores, there was little difference between the SOFA and MOD scoring systems.

Because of the discrepancy between the SOFA and MOD scoring systems for the cardiovascular and respiratory component scores, further analysis was undertaken. Patients were categorized as having SOFA and MOD defined cardiovascular failure, SOFA but not MOD defined cardiovascular failure, MOD but not SOFA defined cardiovascular failure, and patients without SOFA or MOD defined cardiovascular failure. This categorization was tabulated in association with hospital mortality, the most robust endpoint of this study. A similar process was repeated for the respiratory component scores.

The results for cardiovascular failure are presented in Table 15.

TABLE 15. Relationship of SOFA and MOD Defined Cardiovascular Failure to Mortality

Cardiovascular Failure Defined by:	N	Hospital Mortality
SOFA and MOD	33	56%
SOFA not MOD	86	49%
MOD not SOFA	5	0%
Neither	85	7%

Patients with SOFA and MOD defined cardiovascular failure suffered the highest hospital mortality but this was not significantly different from those patients with SOFA but not MOD defined cardiovascular failure. This suggests little additive contribution of MOD defined cardiovascular failure if there patients have SOFA defined cardiovascular failure. Further, all 5 patients with MOD but not SOFA defined cardiovascular failure survived. This mortality was not significantly different from those patients without cardiovascular failure. Age and post-resuscitation GCS was not significantly different among the four categories.

The results for respiratory failure are presented in Table 16.

TABLE 16. Relationship of SOFA and MOD Defined Respiratory Failure to Mortality

Respiratory Failure Defined by:	N	Hospital Mortality
SOFA and MOD	49	41%
SOFA not MOD	40	35%
MOD not SOFA	0	
Neither	120	28%

MOD defined respiratory failure did not occur in the absence of SOFA defined respiratory failure. Patients with SOFA and MOD defined respiratory failure suffered the highest hospital mortality but this was not significantly different from those patients with SOFA but not MOD defined respiratory failure. This again suggests little additive contribution of MOD defined organ failure if there patients have SOFA defined failure. Age and post-resuscitation GCS were not significantly different among the four categories.

G. LIMITATIONS OF THE STUDY

Adjustment for potential confounding factors of age and post-resuscitation GCS was undertaken for logistic regression model involving hospital mortality and dichotomized neurological outcome. There are other known prognostic factors such as pupillary abnormalities, CT scan appearance, and episodes of hypoxemia and hypotension. These variables were not included in the dataset and, therefore, adjustment could not be made. The importance of these variables on the association of non-neurological organ dysfunction with outcome in the multivariable models is unknown. However, one would expect a certain degree of co-linearity of these addition variables with post-resuscitation GCS. Another limitation of the study involves the significant proportion of missing data with respect to neurological outcome. It is plausible that this missing data was significantly associated with a particular neurological outcome. Further, the neurological determination was determined by chart review and was not accomplished at a standardized time post-injury but rather at hospital discharge. It is known that patients with severe traumatic brain injury can continue to improve over time following hospital discharge. Thus, we cannot rule out the differential timing of the determination of neurological outcome may have influenced our results.

H. DISCUSSION

In this cohort of patients with severe traumatic brain injury who required ICU care for at least 48 hours, non-neurological organ dysfunction was found to be common. Thirty-five percent of patients developed failure of at least one non-neurological organ system. This is comparable to the 43% of patients who developed at least one organ failure (which included neurological system failure) reported in the original description and validation of the MOD score.[12] However, our patients were considerably younger (mean age 36 vs. 61) and therefore would have been expected to have fewer co-morbidities that would predispose to organ dysfunction. Gruber and colleagues[62] found a slightly lower incidence of single non-neurological organ failure at 26%. Congruent with Gruber's report in patients with SAH, our data suggests only a small proportion of patients experience 3 or more non-neurological organ system failures, but this portends a grave prognosis as no patient in either study survived. Compared to the Gruber's data, almost twice as many patients in our study developed 2 organ system failures but experienced half the mortality. Potential reasons for this difference include the possibility that direct organ system trauma which likely partially contributed to the development of non-neurological organ dysfunction in our study has a different prognosis than the non-neurological organ dysfunction found in patients with subarachnoid hemorrhage. Indeed, it is not known if the same neurogenic mechanisms causing organ dysfunction are present in SAH and traumatic brain injury.

A significant association was found between the degree of non-neurological organ dysfunction and outcome, both hospital mortality and neurological outcome, that appeared to be independent of the severity of primary injury (post-resuscitation GCS) and age of the patient. This has several important implications in the management of these patients. Firstly, non-neurological organ dysfunction should be included in the evaluation of new brain-directed therapies. Further, the failure of previous brain-directed therapies may need to be re-evaluated as the lack of success could be attributed to an increase in non-neurological organ dysfunction. If this non-neurological organ dysfunction can be prevented perhaps a benefit to these therapies could be demonstrated. Sirvent *et al* demonstrated that prophylactic cefuroxime at time of intubation in patients with structural coma decreases the incidence of ventilator-associated pneumonia.[75] Although evidence for unselected administration of topical antibiotics to eradicate nasal *Staphylococcus aureus* colonization to prevent infection is lacking, some authors have suggested treatment in the head injured patient, a group at high risk of *Staphylococcus aureus* infection.[76] Given our data indicate non-neurological organ dysfunction is an important contributor to outcome in this patient population, it is imperative further study address the prevention and management of non-neurological organ dysfunction in patients with severe traumatic brain injury.

This study has implications for the organizational aspects of care of the patients. Historically, patients with severe traumatic brain injury have been

primarily taken care of by neurosurgeons. Although no one will debate the importance of neurosurgeons in the care of these patients, the high incidence of non-neurological organ dysfunction and its effect on outcome suggest a team-based approach which includes intensivists, neurosurgeons, and allied health care members may provide optimal care. Many academic centres have already created focused neurocritical care teams and there is preliminary evidence that this has improved outcome at these centres.[77-79]

This is the first comparison of SOFA and MOD score measurement of organ dysfunction in patients with major neurological injury. Of particular interest in this group is the determination of cardiovascular dysfunction. Patients in this study, like most patients in North America, were treated with CPP targeted therapy. This often requires volume loading and inotropic support. Thus, distinction between cardiovascular failure and cerebral circulatory support is difficult. This is of particular concern with the SOFA cardiovascular component score which is therapy dependent. The MOD cardiovascular component score is overtly more attractive because of its therapy independence (except for the placement of a central venous pressure monitor which is routine in almost all patients with severe traumatic brain injury). However, our data support the use of the SOFA cardiovascular component score due to it larger contribution to outcome prediction and better discriminatory ability. Similar to our results, in a relatively large study comparing SOFA and MOD scores in a mixed ICU population Peres Bota and colleagues also found the SOFA cardiovascular

component score to be superior to the MOD cardiovascular component score in the discrimination of outcome.[80]

I. CONCLUSIONS

Non-neurological organ dysfunction is common in patients who have sustained a severe traumatic brain injury and who require ICU care for 48 hours or longer. The development of non-neurological organ failure in this patient population is independently associated with worse outcome. Clinicians need to develop strategies to prevent and treat this organ dysfunction with careful consideration of the effect of these treatments on the brain.

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APPENDIX 1. MOD SCORE

Organ System	Score				
	0	1	2	3	4
Respiratory PaO_2/FiO_2	>300	226-300	151-225	76-150	≤75
Renal Creatinine(μmol/L)	≤100	101-200	201-350	251-500	>500
Hepatic Bilirubin (μmol/L)	≤20	21-60	61-120	121-240	>240
Cardiovascular PAR[a]	<10.0	10.1-15	15.1-20.0	20.1-30.0	>30.0
Hematologic Platelet Count	>120	81-120	51-80	21-50	≤20
Neurologic Glasgow Coma Score	15	13-14	10-12	7-9	≤6

[a]Pressure-Adjusted Heart Rate: product of the heart rate multiplied by the ratio of the right atrial pressure to the mean arterial pressure

APPENDIX 2. SOFA SCORE

Organ System	Score				
	0	1	2	3	4
Respiratory PaO_2/FiO_2	>400	≤400	≤300	≤200	≤100
Renal Creatinine (µmol/L)	≤110	110-170	171-299	300-440 Urine Output ≤500 ml/d	>440 Urine Output<200ml/d
Hepatic Bilirubin (µmol/L)	≤20	20-32	33-101	102-204	>204
Cardiovascular Hypotension	No hypotension	MAP<70 mm Hg	Dopamine ≤ 5*, Dobutamine (any dose)	Dopamine >5* or epinephrine ≤0.1* or norepinephrine ≤0.1*	Dopamine >15* or epinephrine >0.1* or norepinephrine >0.1*
Hematologic Platelet Count	>150	≤150	≤100	≤50	≤20
Neurologic Glasgow Coma Score	15	13-14	10-12	6-9	<6

*adrenergic agents administered for at least one hour (doses given are in mcg/kg/min)

APPENDIX 3. GLASGOW OUTCOME SCORE

5	Good Recovery	Resumption of normal life despite minor deficits
4	Moderate Disability	Disabled but independent. Can work in sheltered setting
3	Severe Disability	Conscious but disabled. Dependent for daily support
2	Persistent vegetative	Minimal responsiveness
1	Death	Non survival

APPENDIX 4. Ethical Approval

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

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2003-10-01

Dr. C.J. Doig
Division of Critical Care
Room EG23, Foothills Hospital
Calgary, Alberta

Dear Dr. Doig:

RE: Non-neurological Organ Dysfunction in Severe Traumatic Brain Injury

Grant-ID: 17397

The above-noted thesis proposal has been submitted for Committee review and found to be ethically acceptable. Please note that this approval is subject to the following conditions:

(1) a copy of the informed consent form must have been given to each research subject, if required for this study;
(2) a Progress Report must be submitted by 2004-10-01, containing the following information:
    (i) the number of subjects recruited;
    (ii) a description of any protocol modification;
    (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
    (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
    (v) a copy of the current informed consent form;
    (vi) the expected date of termination of this project;
(3) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Ian Mitchell, MA, MB, FRCPC
Acting Chair, Conjoint Health Research Ethics Board

c.c. Adult Research Committee
Dr. P. Boiteau (information)
Dr. D. Zygun
Research Services