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Feasibility of a prospective multi-center prognostication study in critically ill patients with severe traumatic brain injury: The TBI-Prognosis pilot study

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ABSTRACT (298 words)

Objective: Severe traumatic brain injury is a significant cause of morbidity and mortality in young adults. Assessing long-term neurological outcome after such injury is difficult and often characterized by uncertainty. The objective of this pilot study was to establish the feasibility of conducting a large, multicenter prospective study to develop a prognostic model of long-term neurological outcome in critically ill patients with severe traumatic brain injury.

Design: Prospective cohort study.

Setting: Nine Canadian intensive care units enrolled patients suffering from acute severe traumatic brain injury. Clinical, biological, radiological and electrophysiological data were systematically collected during the first week in the intensive care unit. Mortality and functional outcome (Glasgow Outcome Scale extended) were assessed upon hospital discharge, and then 3, 6 and 12 months following injury.

Outcomes: The compliance to protocolized test procedures was the primary outcome. Secondary outcomes were enrolment rate and compliance to follow-up.

Results: We successfully enrolled 50 patients over a 12-month period. Most patients were male (80%), with a median age of 45 years (IQR 29.0 – 60.0), a median Injury Severity Score (ISS) of 38 (IQR 25-50), and a GCS of 6 (IQR 3-7). Mortality was 38% (19/50) and most deaths occurred following a decision to withdraw life-sustaining therapies (18/19). The main reasons for non-enrollment were the time window for inclusion being after regular working hours (35%, n=23) and oversight (24%, n=16). Compliance with protocolized test procedures ranged from 92% to 100% and enrolment rate was 43%. No patients were lost to follow-up at 6 months and 2 were at 12 months. The overall study adherence was 96%.

Conclusion: In this multicenter prospective pilot study, we achieved feasibility objectives pertaining to compliance to test, enrolment and follow-up. We conclude that the TBI-Prognosis prospective multicentre study in severe traumatic brain injury patients in Canada is feasible.

STRENGHT AND LIMITATIONS OF THIS STUDY

- This pilot study involved 9 centers in 5 different provinces in Canada, thus showing the feasibility enrolling in different centers, health care systems and clinical settings.
- We enrolled in all centers but one due to start-up delay secondary to staffing issues.
- The sample size was large enough to allow testing a protocol of test procedures and to identify potential pitfalls to consider for the large scale study.

INTRODUCTION

Severe traumatic brain injuries are catastrophic injuries primarily afflicting young individuals.[1] Mortality ranges from 30 to 50%, while 30% of survivors suffer from severe neurological sequelae.[2-5] Given the majority of victims are young with previous excellent quality of life, substantive human, social and financial repercussions are experienced by survivors.[6]

With regard to victims of severe traumatic brain injury, physicians and families often face important treatment decisions. They must decide to either undertake aggressive care in the hope of the patient will survive with an acceptable quality of life[7-10] or to withdraw life-sustaining therapy considering an unfavourable and undesirable prognosis. Serious concerns have been expressed regarding early decisions made to withdraw life-sustaining therapies in absence of evidence-based prognostic information.[11-13] Recently, we observed significant variations in mortality and in the incidence of withdrawal of life-sustaining therapies following severe traumatic brain injury in Canada.[8, 14] Current prognostic models are of limited clinical utility as they are based on data obtained from small[15-17], single centre[3, 16-22] retrospective studies[16, 21, 23-25] that did not consider secondary brain injury.[3, 16-20, 22, 23, 26-28] Consequently, it is not surprising to observe a wide variation in prognostic evaluation when surveying intensivists, neurosurgeons and neurologists caring for severe traumatic brain injury in Canada.[29] The development of appropriate prognosis tools and models is necessary to help guide the decision making process with families.

The objective of the TBI-Prognosis Pilot Study was to assess the feasibility of a conducting a large-scale, multicentre study to develop a prognostic model to inform long-term prognosis in patients with severe traumatic brain injury.

METHODS

Study design

We conducted a multicentre prospective pilot study in 9 level I trauma centres across Canada. Research Ethics Board approval was obtained from each participating center. Informed consent was obtained from surrogate decision makers prior to enrolment in most centers; deferred consent was permitted by Research Ethics Boards at two centers.

Eligibility criteria

We included critically ill adults (≥18 years of age) with severe traumatic brain injury (Glasgow coma scale (GCS) ≤8) due to blunt-force trauma on day 1 of intensive care unit admission. We excluded patients anticipated to be on mechanical ventilation for less than 48 hours, patients with solid malignancy associated with a life expectancy less than 12 months, liver cirrhosis Child C, chronic heart failure (NYHA class IV), end-stage chronic respiratory disease (O_2 dependent), end-stage renal disease (chronic dialysis), previous neurologic disorder with abnormal findings on radiological imaging (CT-scan, magnetic resonance imaging (MRI)) or electrophysiological tests (electroencephalogram (EEG), somatosensory evoked potentials (SSEP)) or patients who were declared brain-dead when assessed for eligibility. Patients with no fixed address were also excluded due to difficulties in conducting follow-up.

Data collection

Participants underwent a protocolized schedule of clinical, biological, radiological, and electrophysiological prognostic tests or examinations. Tests and examinations used in our study are, for the most part, commonly utilized in the care of patients with severe traumatic brain injury for diagnostic or prognostic purposes. Data were collected daily from intensive care unit admission until the 7th day following the injury, death or until hospital discharge, whichever came first. These included evaluation of serum glucose, complete blood count, creatinine and arterial

blood gases, pupillary reactivity, corneal reflex, episodes of increased intracranial hypertension (>25 mmHg), hypoxemia (arterial oxygen saturation of <90%) and hypotension (systolic blood pressure <90 mm Hg). A schedule of prognostic biological, radiological and electrophysiological tests/examinations was implemented (Figure 1). On intensive care unit day 1, 3 and 7, CT-scans were performed and blood samples were collected to measure serum biomarkers. These timelines were informed by a multicenter retrospective study and a health care survey of Canadian clinicians.[8, 29, 30] On intensive care unit day 7, MRI, SSEP and EEG examinations were performed. We permitted a time window of 24 hours (for CT-scan) and 48 hours (for MRI, SSEP and EEG) to reflect clinical practice and enhance feasibility over weekends.

Outcome measures

Our overarching objective of the research program is to develop a model to predict short (discharge), mid (3 months) and long-term neurological prognosis (6 and 12 months) in patients admitted to intensive care unit with severe traumatic brain injury. The functional outcome was evaluated using the Glasgow Outcome Scale extended (GOSe) (face to face (hospitalized patients) or phone interviews (discharged patients)).[31, 32] Our pilot study was designed to establish the feasibility of a large scale study adequately powered to develop prognostic models to help inform clinical decision-making. Our primary outcome was the compliance rate to the protocolized test procedures (tests performed or not performed). We considered a 90% compliance rate to be acceptable. Secondary outcomes were enrolment rate and compliance to follow-up. We also evaluated the percentage of potentially eligible patients that were excluded, the reasons for exclusion and adverse events related to the protocol.

Sample size

With a sample size of 50 patients we predicted to estimate a compliance to the scheduled test procedures of 90% with a margin of error of 10%.

Statistical Analyses

Descriptive statistics were used to report the data. Data on compliance to the tests procedure, enrolment rate, compliance to follow-up and overall study adherence are presented using proportions. No comparative statistical testing was performed considering the pilot feasibility nature of this study.

RESULTS

Patient enrolment

Over a 12-month period totalising 208 weeks of active enrolment (all centers considered), participating centres screened 530 patients from which 116 were potentially eligible and 50 were enrolled (43%). The two main reasons for non-enrolment were the time-window for inclusion being after regular working hours and personnel oversight (Figure 2). We observed few refusals from surrogate decision makers and physicians, as well as non-enrolment due to the absence of a surrogate decision maker. No patient, once included in the study, was excluded. One center did not succeed to implement the study due to staffing issues and did not contribute any patients to this pilot trial. The majority of recruitment (32 patients, 64%) took place during weekdays; three of the centers enrolled patients on weekends. Informed consent was mostly obtained (41 patients, 82%) between 9:00 am and 6:00 pm.

Patient characteristics

The median age of participants was 45 years (Interquartile range (IQR), 29 – 60 years) and 80% were male (40 patients, 80%). The median GCS at intensive care unit admission was 6 (IQR: 3-7) while the Injury Severity Score (ISS) was 38 (IQR 25-50) (Table 1). In 88% of patients, traumatic brain injury occurred following motor vehicle collision (MVC) or fall.

Table 1. Patients demographic

Characteristics	Patients (n=50)
Age (median, IQR)	45 (29 – 60)
Male (n, %)	40 (80%)
GCS in ER (median, IQR)	6 (3 - 7)
APACHE II score (mean ± SD)	20.2 ± 6.84
ISS score (median, IQR)	38 (25 - 30)
Absent pupillary reactivity (ICU day 1)	36 (72%)
Absent corneal reflex (ICU day 1)	7 (14%)
Cause of trauma (n, %)	
MVC-occupant	21 (42%)
MVC-motorcyclist	9 (18%)
MVC-pedestrian	2 (4%)
Fall	14 (28%)
Assault	2 (4%)
Other	2 (4%)

IQR: Interquartile range; GCS: Glasgow Coma Scale; ER: Emergency room; MVC: Motor vehicle collision SD: Standard Deviation; APACHE: Acute Physiology and Chronic Health Evaluation; ISS: Injury Severity Score, ICU: Intensive care unit

Compliance to test procedures

The compliance to the protocol of test procedures ranged from 92% to 100%, depending on the test performed. Compliance to tests was measured according to the survival status during the time window in which the test was scheduled (Figure 3). We observed 94% compliance for SSEP (3 missed tests), 96% for EEG (2 missed tests), and 92% for MRI (4 missed tests). Day 7 MRI was delayed for 20% (n=10) of the patients, most of them (n=6) due to the presence of

material incompatible with the performance of the MRI procedure. No CT-scans were missed on day 1 and 3, while the compliance for day 7 CT-scans was 96% (2 missed scans). All but one blood sample were collected. The main reason for not conducting a specific test was a change in level of care (palliative care). The main explanation for performing tests outside of the time window was patient instability (hemodynamic or increased intracranial pressure). We observed no adverse events related to this study and tests performed.

Follow-up measures

Two patients were lost to follow-up at 12 months, but none were at 6 months. Overall, 33 patients (66%) had an unfavourable outcome at 12 months (GOSe 1-4). Mortality was 38% (19/50) and most deaths were associated with a decision to withdraw life-sustaining therapies (18/19). No patient died during follow-up after hospital discharge.

INTERPRETATION

In this multicenter prospective pilot feasibility study, we achieved high compliance with the study procedures, an acceptable enrolment rate and had a low rate of loss to follow-up. All except one center achieved acceptable enrolment during the study period. The lessons learned during this multicenter pilot prospective study have informed the design of the TBI-Prognosis multicenter prospective study (NCT02452541), which is currently ongoing.

The high compliance rate to the test procedures observed in our study is a paramount result for the feasibility of the large scale study. Several reasons may explain this high compliance. First, our protocol is straightforward and mainly relies on reminders for timely test procedures. Second, the uniformity of the tests and the flexibility of test timing allow these tests to be included seamlessly into the patient's care continuum. Third, adherence to the test schedule has also

been facilitated by local research coordinators directly interacting with the clinical personnel in the intensive care unit and championing the project,[33] and by clinician guidance and enthusiasm towards the project.[34] Finally, we engaged the clinical personnel working in the intensive care unit by holding information sessions describing the project and by being available to answer their queries and concerns.[33, 35]

Pilot studies are particularly useful in revealing study flaws and design weaknesses.[36-38] In this pilot feasibility study, we also identified some potential challenges for the conduction of the large scale study. One of the challenges identified was the difficulty of enrolling patients admitted outside of regular working hours (evenings or week-ends). Due to budgetary restrictions, but also to the available workforce, it was not always possible to have 24-hour coverage for screening and enrolment in clinical research. Using a deferred consent approach in all centers for the large scale study is one of the avenues considered to handle this potential issue. Another important finding is our follow-up rates at 6 and 12 months that are comparable or better to the ones observed in previous large scale multicenter trials in patient with severe traumatic brain injury.[39, 40] Despite having missed 2 patients for the 12-month follow-up, we were able to follow all patients at 6 months, a result showing the possibility of not missing any patients for the large scale study.

Following this pilot phase of the TBI-Prognosis study, study investigators engaged with local investigators, intensive care unit nurses, and research coordinators, through both informal discussions and survey, to understand their experience participating in the TBI-prognosis pilot study. Recruitment techniques and eligibility criteria were revised and refined to improve clarity in the larger study. Deferred consent was highlighted as being especially helpful given the time constraints and appears to be generally accepted by participants upon regaining the ability to

participate in the shared decision-making consent process.[41, 42] Indeed, the two centers that implemented this method recruited a greater number of patients than the other sites in accordance with the duration of the screening period. Strategies for approaching families in time of stress were also discussed.[37] With much preparatory work completed, the TBI-Prognosis team and the Canadian Critical Care Trials Group are now undertaking the large multicenter prospective cohort study informed by the results of this pilot feasibility study.

In this multicenter prospective pilot study, we successfully enrolled participants following an acceptable enrolment rate, reached our targeted sample size, achieved feasibility objectives pertaining to the compliance to the test procedures, compliance to follow-up, as well as the overall adherence the study protocol. We conclude that a prospective multicentre study in severe traumatic brain injury patients in Canada aiming at developing a prognostic model in the acute phase of care is feasible.

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CONTRIBUTIONS

AFT, FL, RZ, DAF, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, JP, JLG, AL, KR, GP, DZ and LM were involved in conception and design. AFT, FL, RZ, DAF, CL, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, MSh, JP, JLG, AL, KR, DJ, GP, DZ and LM were involved in the acquisition and interpretation of data. AFT, CL and MSh drafted the manuscript. AFT, FL, RZ, DAF, CL, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, MSh, JP, JLG, AL, KR, DJ, GP, DZ and LM were involved in revising the manuscript and approved the version published.

COMPETING INTERESTS

The authors declared no competing interests.

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DATA SHARING

There are no additional unpublished data available.

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Figure 1. TBI-Prognosis test schedule.
The arrows indicate the prescribed time frame to perform tests or take blood samples. The study requested that CT-scans be done on day 1, 3, and 7, with the possibility to conduct the scans 24 hours prior or after the required date. Blood samples were drawn on day 1, 3 and 7. The EEG, SSEP and MRI tests were required on day 7 but could be obtained 48 hours before or after the seventh day.

CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

Figure 2. Reasons for non-enrolment

SDM: Shared Decision Making

Figure 3. Compliance to the scheduled test procedures

CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

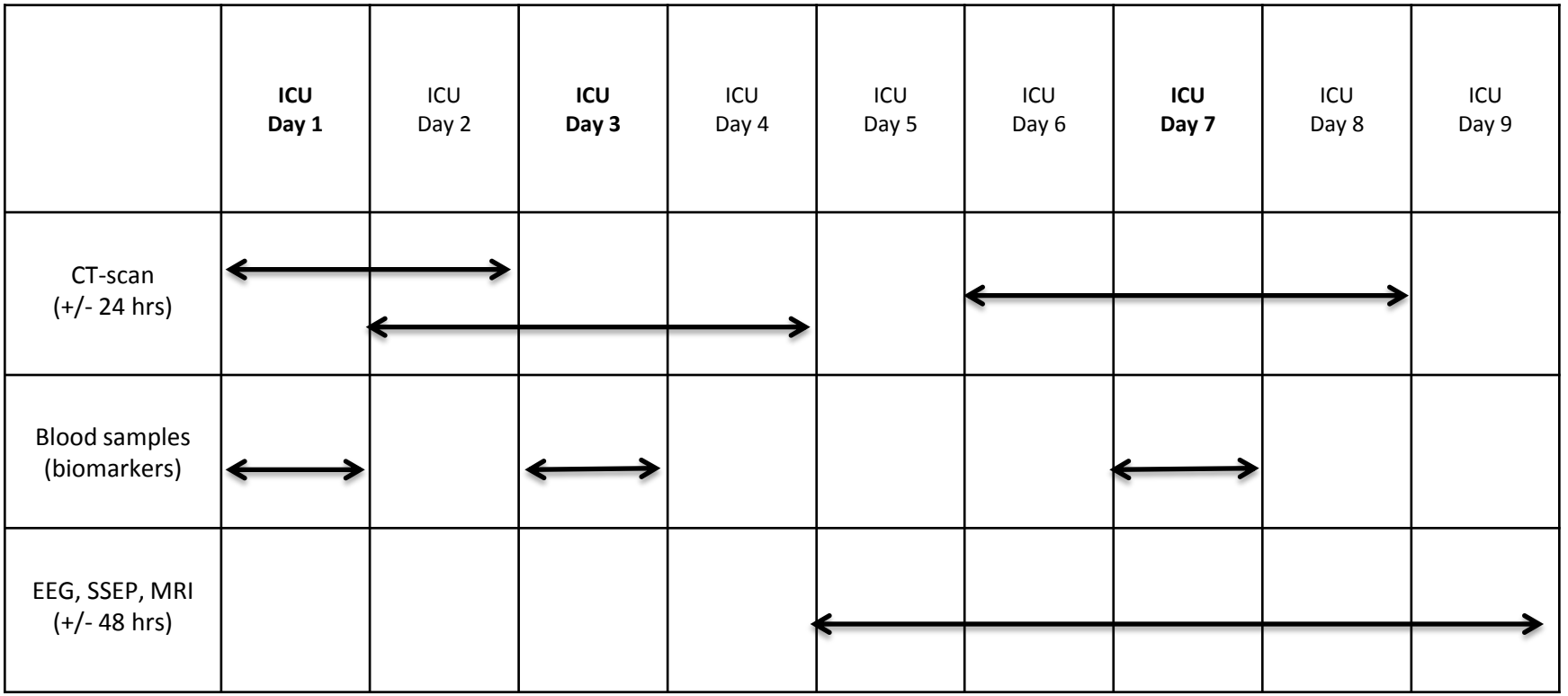

Figure 1. TBI-Prognosis test schedule.
The arrows indicate the prescribed time frame to perform tests or take blood samples. The study requested that CT-scans be done on day 1, 3, and 7, with the possibility to conduct the scans 24 hours prior or after the required date. Blood samples were drawn on day 1, 3 and 7. The EEG, SSEP and MRI tests were required on day 7 but could be obtained 48 hours before or after the seventh day.

CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

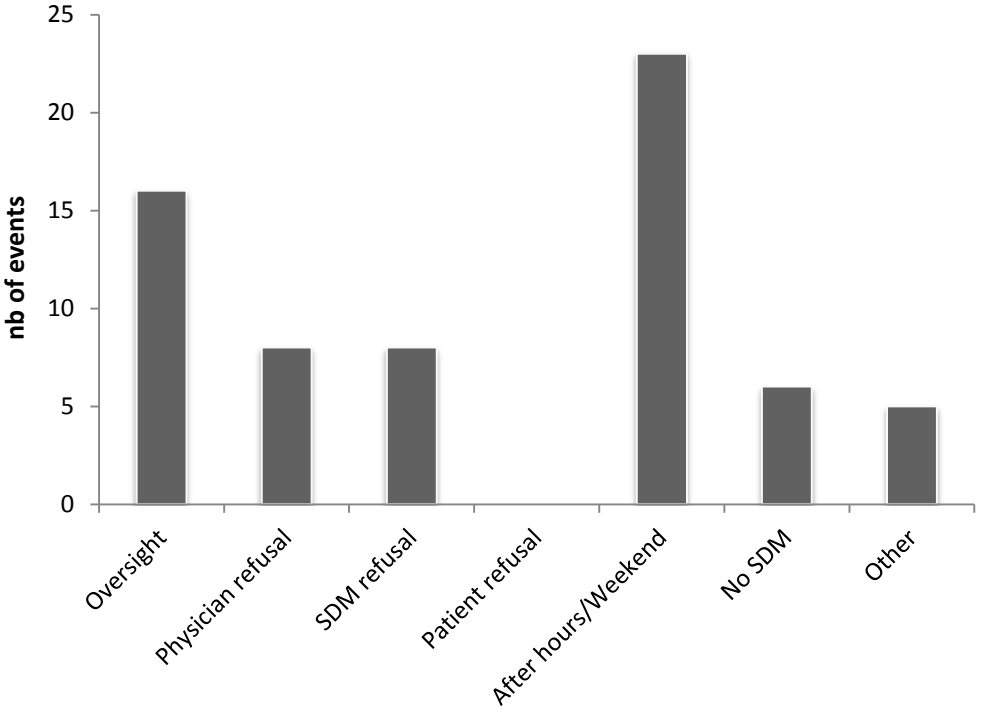

Figure 2. Reasons for non-enrolment
SDM: Shared Decision Making

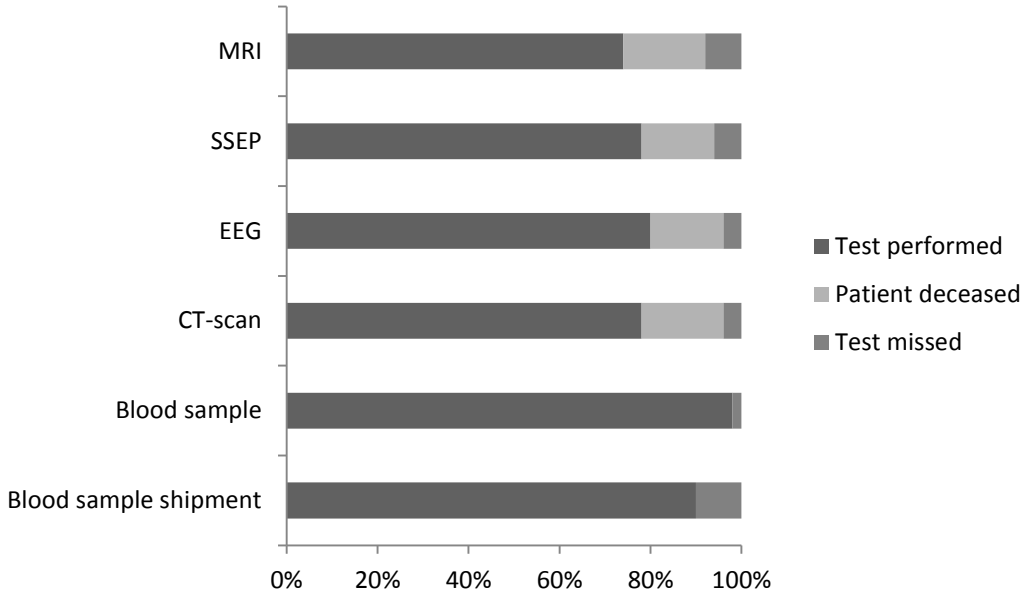

Figure 3. Compliance to the scheduled test procedures
CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8, Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Part of pilot goal
		(*d*) If applicable, explain how loss to follow-up was addressed	Part of pilot goal
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9, Figure 2
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	10, 11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11, 12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prognostication in critically ill patients with severe traumatic brain injury: The TBI-Prognosis multicenter feasibility study

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Epidemiology
Keywords:	Traumatic brain injury, Pilot study, Prognosis, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Outcome

Prognostication in critically ill patients with severe traumatic brain injury: The TBI-Prognosis multicenter feasibility study

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ABSTRACT (292 words)

Objective: Severe traumatic brain injury is a significant cause of morbidity and mortality in young adults. Assessing long-term neurological outcome after such injury is difficult and often characterized by uncertainty. The objective of this feasibility study was to establish the feasibility of conducting a large, multicenter prospective study to develop a prognostic model of long-term neurological outcome in critically ill patients with severe traumatic brain injury.

Design: Prospective cohort study.

Setting: Nine Canadian intensive care units enrolled patients suffering from acute severe traumatic brain injury. Clinical, biological, radiological and electrophysiological data were systematically collected during the first week in the intensive care unit. Mortality and functional outcome (Glasgow Outcome Scale extended) were assessed upon hospital discharge, and then 3, 6 and 12 months following injury.

Outcomes: The compliance to protocolized test procedures was the primary outcome. Secondary outcomes were enrolment rate and compliance to follow-up.

Results: We successfully enrolled 50 patients over a 12-month period. Most patients were male (80%), with a median age of 45 years (IQR 29.0 – 60.0), a median Injury Severity Score (ISS) of 38 (IQR 25-50), and a GCS of 6 (IQR 3-7). Mortality was 38% (19/50) and most deaths occurred following a decision to withdraw life-sustaining therapies (18/19). The main reasons for non-enrollment were the time window for inclusion being after regular working hours (35%, n=23) and oversight (24%, n=16). Compliance with protocolized test procedures ranged from 92% to 100% and enrolment rate was 43%. No patients were lost to follow-up at 6 months and 2 were at 12 months.

Conclusion: In this multicenter prospective feasibility study, we achieved feasibility objectives pertaining to compliance to test, enrolment and follow-up. We conclude that the TBI-Prognosis prospective multicentre study in severe traumatic brain injury patients in Canada is feasible.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Our study involved nine centers in five different provinces in Canada and showed the feasibility of enrolling critically ill patients with severe traumatic brain injury and assess 12-months outcome measures.
- Our study sample size allowed testing a protocol of test procedures and identifying potential pitfalls to consider for a large-scale prognostic study.
- Some eligible patients were missed due to an admission to the intensive care unit outside of working hours or were oversight by the research personnel.

INTRODUCTION

Severe traumatic brain injuries are catastrophic injuries primarily afflicting young individuals.[1] Mortality ranges from 30 to 50%, while 30% of survivors suffer from severe neurological sequelae.[2-5] Given the majority of victims are young with previous excellent quality of life, substantive human, social and financial repercussions are experienced by survivors.[6]

With regard to victims of severe traumatic brain injury, physicians and families often face important treatment decisions. They must decide to either undertake aggressive care in the hope of the patient will survive with an acceptable quality of life[7-10] or to withdraw life-sustaining therapy considering an unfavourable and undesirable prognosis. Serious concerns have been expressed regarding early decisions made to withdraw life-sustaining therapies in absence of evidence-based prognostic information.[11-14] Recently, we observed significant variations in mortality and in the incidence of withdrawal of life-sustaining therapies following severe traumatic brain injury in Canada.[8, 15] Current prognostic models are of limited clinical utility as they are based on data obtained from small[16-18], single centre[3, 17-23] retrospective studies[17, 22, 24-26] that did not consider secondary brain injury.[3, 17-21, 23, 24, 27-28] Consequently, it is not surprising to observe a wide variation in prognostic evaluation when surveying intensivists, neurosurgeons and neurologists caring for severe traumatic brain injury in Canada.[29] The development of appropriate prognosis tools and models is necessary to help guide the decision making process with families.

The objective of the TBI-Prognosis Feasibility Study was to assess the feasibility of a conducting a large-scale, multicentre study to develop a prognostic model to inform long-term prognosis in patients with severe traumatic brain injury. The study was conducted in the

Canadian health care system in which trauma, neurosurgery and critical care are part of a public system with universal health care coverage for all citizens.

METHODS

Study design

We conducted a multicentre prospective feasibility study in 9 level I trauma centres across Canada. Research Ethics Board approval was obtained from each participating center. Informed consent was obtained from surrogate decision makers prior to enrolment in most centers; deferred consent was permitted by Research Ethics Boards at two centers. This study was conducted

Eligibility criteria

We included critically ill adults (≥18 years of age) with severe traumatic brain injury (Glasgow coma scale (GCS) ≤8 following resuscitation) due to blunt-force trauma on day 1 of intensive care unit admission. We excluded patients anticipated to be on mechanical ventilation for less than 48 hours, patients with solid malignancy associated with a life expectancy less than 12 months, liver cirrhosis Child C, chronic heart failure (NYHA class IV), end-stage chronic respiratory disease (O_2 dependent), end-stage renal disease (chronic dialysis), previous neurologic disorder with abnormal findings on radiological imaging (CT-scan, magnetic resonance imaging (MRI)) or electrophysiological tests (electroencephalogram (EEG), somatosensory evoked potentials (SSEP)) or patients who were declared brain-dead when assessed for eligibility. Patients with no fixed address were also excluded due to difficulties in conducting follow-up.

Data collection

Participants underwent a protocolized schedule of clinical, biological, radiological, and electrophysiological prognostic tests or examinations. Tests and examinations used in our study were commonly utilized in the care of patients with severe traumatic brain injury for diagnostic or prognostic purposes except for blood samples. Data were collected daily from intensive care unit admission until the 7th day following the injury, death or until hospital discharge, whichever came first. These included pupillary reactivity, corneal reflex, GCS, episodes of increased intracranial hypertension (>25 mmHg), hypoxemia (arterial oxygen saturation of <90%) and hypotension (systolic blood pressure <90 mm Hg). Data was prospectively collected at the bedside using specific case report forms. We also collected serum glucose (highest and lowest value), complete blood count, INR, prothrombin time, sodium, creatinine, arterial blood gases, also on a daily basis if the data was available as per clinical decision by the medical team. A schedule of prognostic biological, radiological and electrophysiological tests/examinations was implemented (Figure 1). On intensive care unit day 1, 3 and 7, CT-scans were performed and blood samples were collected to measure serum biomarkers. These timelines were informed by a multicenter retrospective study and a health care survey of Canadian clinicians.[8, 29, 30] On intensive care unit day 7, MRI, SSEP and EEG examinations were performed. We permitted a time window of 24 hours (for CT-scan) and 48 hours (for MRI, SSEP and EEG) to reflect clinical practice and enhance feasibility over weekends.

Outcome measures

Our overarching objective of the research program is to develop a model to predict short (discharge), mid (3 months) and long-term neurological prognosis (6 and 12 months) in patients admitted to intensive care unit with severe traumatic brain injury. The functional outcome was evaluated using the Glasgow Outcome Scale extended (GOSe) (face to face (hospitalized patients) or phone interviews (discharged patients)).[31, 32] Our feasibility study was designed to establish the feasibility of a large scale study adequately powered to develop prognostic

models to help inform clinical decision-making. Our primary outcome was the compliance rate to the protocolized test procedures (tests performed or not performed). We considered a 90% compliance rate to be acceptable. Secondary outcomes were enrolment rate and compliance to follow-up. We also evaluated the percentage of potentially eligible patients that were excluded, the reasons for exclusion and adverse events related to the protocol.

Research team at participating centers

At each participating center, a research coordinator and/or research nurse, was involved in the implementation of the study in the intensive care unit, daily screening, enrolment at the bedside, organization of the schedule of tests with the attending medical team and daily data collection. Follow-ups were performed locally with face-to-face questionnaire when patients were still in hospital, or phone questionnaires, when discharged home or to another facility. Follow-ups were made during working hours for most patients.

Start-up meeting

We organize a start-up meeting using virtual technology (video conference) prior to start enrolment in the study. This start meeting was chaired by the study manager at the coordinating center, involved the review of the protocol, the screening, enrolment and consent process, the overall study procedure, and potential pitfalls to avoid during the process.

Central coordination and data monitoring

The study was coordinated centrally by a study manager assisted by a clinical research coordinator. The study manager was responsible for supervising the implementation of the study at each site and was the primary link for the local research team to answer questions and queries during the conduction of the study. Communications through emails and phone calls to participating sites were performed on regular basis to clarify potential issues on enrolment and data collection, as well as to ascertain a close follow-up of sites. The data collection process was monitored centrally at the coordinating center and answers queries sent to the participating

centers before case report forms were considered completed. A newsletter was disseminated every other month to update center on the enrolment in the study, but also to motivate the team and provide information on common queries and questions.

Sample size

With a sample size of 50 patients we predicted to estimate a compliance to the scheduled test procedures of 90% with a margin of error of 10%.

Statistical Analyses

Descriptive statistics were used to report the data. Data on compliance to the tests procedure, enrolment rate, compliance to follow-up and overall study adherence are presented using proportions. No comparative statistical testing was performed considering the feasibility nature of this study.

RESULTS

Patient enrolment

Over a 12-month period (May 2012 to May 2013) totalising 208 weeks of active enrolment (all centers considered), participating centres screened 530 patients from which 116 were potentially eligible and 50 were enrolled (43%). The two main reasons for non-enrolment were the time-window for inclusion being after regular working hours and personnel oversight (Figure 2). We observed few refusals from surrogate decision makers and physicians, as well as non-enrolment due to the absence of a surrogate decision maker. No patient, once included in the study, was excluded. One center did not succeed to implement the study due to staffing issues and did not contribute any patients to this feasibility trial. The majority of recruitment (32

patients, 64%) took place during weekdays; three of the centers enrolled patients on weekends. Informed consent was mostly obtained (41 patients, 82%) between 9:00 am and 6:00 pm.

Patient characteristics

The median age of participants was 45 years (Interquartile range (IQR), 29 – 60 years) and 80% were male (40 patients, 80%). The median GCS at enrolment was 6 (IQR: 3-7) and the Injury Severity Score (ISS) was 38 (IQR 25-50) (Table 1). In 88% of patients, traumatic brain injury occurred following motor vehicle collision (MVC) or fall.

Table 1. Patients demographic

Characteristics	Patients (n=50)
Age (median, IQR)	45 (29 – 60)
Male (n, %)	40 (80%)
GCS (median, IQR)	6 (3 - 7)
APACHE II score (mean ± SD)	20.2 ± 6.84
ISS score (median, IQR)	38 (25 - 30)
Absent pupillary reactivity (ICU day 1)	36 (72%)
Absent corneal reflex (ICU day 1)	7 (14%)
Cause of trauma (n, %)	
MVC-occupant	21 (42%)
MVC-motorcyclist	9 (18%)
MVC-pedestrian	2 (4%)
Fall	14 (28%)
Assault	2 (4%)
Other	2 (4%)

IQR: Interquartile range; GCS: Glasgow Coma Scale; MVC: Motor vehicle collision SD: Standard Deviation; APACHE: Acute Physiology and Chronic Health Evaluation; ISS: Injury Severity Score, ICU: Intensive care unit

Compliance to the daily clinical data collection

Clinical data for episodes of hypotension, hypoxemia and increased intracranial pressure were successfully collected. We had three missing time points for pupillary reaction (2 patients) and one time point for the GCS (1 patient). Data for the corneal reflex was however missed at least for one data point in 29 patients.

Compliance to the test procedures

The compliance to the protocol of test procedures ranged from 92% to 100%, depending on the test performed. Compliance to tests was measured according to the survival status during the time window in which the test was scheduled (Figure 3). We observed 94% compliance for SSEP (3 missed tests), 96% for EEG (2 missed tests), and 92% for MRI (4 missed tests). Day 7 MRI was delayed for 20% (n=10) of the patients, most of them (n=6) due to the presence of material incompatible with the performance of the MRI procedure. No CT-scans were missed on day 1 and 3, while the compliance for day 7 CT-scans was 96% (2 missed scans). All but one blood sample were collected (day 7); all collected blood samples were successfully shipped to the coordinating centers. The main reason for not conducting a specific test was a change in level of care (palliative care). The main explanation for performing tests outside of the time window was patient instability (hemodynamic or increased intracranial pressure). We observed no adverse events related to this study and tests performed.

Follow-up of outcome measures

Two patients were lost to follow-up at 12 months, but none were at 6 months. Overall, 33 patients (66%) had an unfavourable outcome at 12 months (GOSe 1-4). Mortality was 38%

(19/50) and most deaths were associated with a decision to withdraw life-sustaining therapies (18/19). No patient died during follow-up after hospital discharge.

INTERPRETATION

In this multicenter prospective feasibility study, we achieved high compliance with the study procedures, an acceptable enrolment rate and had a low rate of loss to follow-up. All except one center achieved acceptable enrolment during the study period. The lessons learned during this multicenter feasibility prospective study have informed the design of the TBI-Prognosis multicenter prospective study (NCT02452541), which is currently ongoing.

The high compliance rate to the test procedures observed in our study is a paramount result for the feasibility of the large-scale study. Several reasons may explain this high compliance. First, our protocol is straightforward and mainly relies on reminders for timely test procedures. Second, the uniformity of the tests and the flexibility of test timing allow these tests to be included seamlessly into the patient's care continuum. Third, adherence to the test schedule has also been facilitated by local research coordinators directly interacting with the clinical personnel in the intensive care unit and championing the project,[33] and by clinician guidance and enthusiasm towards the project.[34] Finally, we engaged the clinical personnel working in the intensive care unit by holding information sessions describing the project and by being available to answer their queries and concerns.[33, 35]

Pilot and feasibility studies are particularly useful in revealing study flaws and design weaknesses.[36-38] In this feasibility study, we also identified some potential challenges for the conduction of the large-scale study. One of the challenges identified was the difficulty of

enrolling patients admitted outside of regular working hours (evenings or week-ends). This finding that a significant proportion of patients with traumatic brain injury are admitted over the week-end was also observed in a previous cohort study of patients with mild to severe traumatic brain injury in the UK.[39] Due to budgetary restrictions, but also to the available workforce, it was not always possible to have 24-hour coverage for screening and enrolment in clinical research. Using a deferred consent approach in all centers for the large-scale study is one of the avenues considered to handle this potential issue. Another important finding is our follow-up rates at 6 and 12 months that are comparable or better to the ones observed in previous large scale multicenter trials in patient with severe traumatic brain injury.[40, 41] Despite having missed 2 patients for the 12-month follow-up, we were able to follow all patients at 6 months, a result showing the possibility of not missing any patients for the large scale study.

Following this feasibility phase of the TBI-Prognosis study, study investigators engaged with local investigators, intensive care unit nurses, and research coordinators, through both informal discussions and survey, to understand their experience participating in the TBI-prognosis feasibility study. Recruitment techniques and eligibility criteria were revised and refined to improve clarity in the larger study. Deferred consent was highlighted as being especially helpful given the time constraints and appears to be generally accepted by participants upon regaining the ability to participate in the shared decision-making consent process.[42, 43] Indeed, the two centers that implemented this method recruited a greater number of patients than the other sites in accordance with the duration of the screening period. Strategies for approaching families in time of stress were also discussed.[37] With much preparatory work completed, the TBI-Prognosis team and the Canadian Critical Care Trials Group are now undertaking the large multicenter prospective cohort study informed by the results of this pilot feasibility study.

In this multicenter prospective feasibility study, we successfully enrolled participants following an acceptable enrolment rate, reached our targeted sample size, achieved feasibility objectives pertaining to the compliance to the test procedures, compliance to follow-up, as well as the overall adherence the study protocol. Considering our enrolment rate, we considered that three years will be necessary to enrol 315 patients in 17 centers across Canada in the large-scale TBI-Prognosis study. We conclude that a prospective multicentre study in severe traumatic brain injury patients in Canada aiming at developing a prognostic model in the acute phase of care is feasible.

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CONTRIBUTIONS

AFT, FL, RZ, DAF, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, JP, JLG, AL, KR, GP, DZ and LM were involved in conception and design. AFT, FL, RZ, DAF, CL, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, MSh, JP, JLG, AL, KR, DJ, GP, DZ and LM were involved in the acquisition

and interpretation of data. AFT, CL and MSh drafted the manuscript. AFT, FL, RZ, DAF, CL, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, MSh, JP, JLG, AL, KR, DJ, GP, DZ and LM were involved in revising the manuscript and approved the version published.

COMPETING INTERESTS

The authors declared no competing interests.

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DATA SHARING

There are no additional unpublished data available.

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Figure 1. TBI-Prognosis test schedule.
The arrows indicate the prescribed time frame to perform tests or take blood samples. The study requested that CT-scans be done on day 1, 3, and 7, with the possibility to conduct the scans 24 hours prior or after the required date. Blood samples were drawn on day 1, 3 and 7. The EEG, SSEP and MRI tests were required on day 7 but could be obtained 48 hours before or after the seventh day.

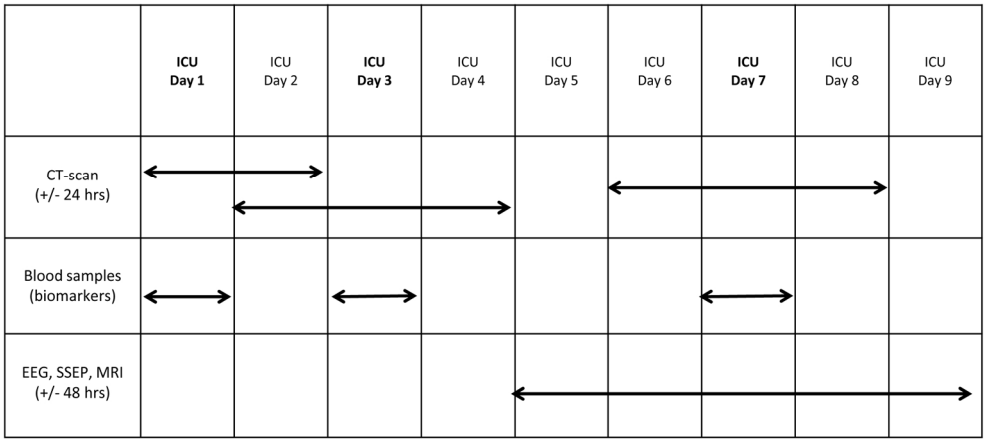
CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

Figure 2. Reasons for non-enrolment

SDM: Shared Decision Making

Figure 3. Compliance to the scheduled test procedures

CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials



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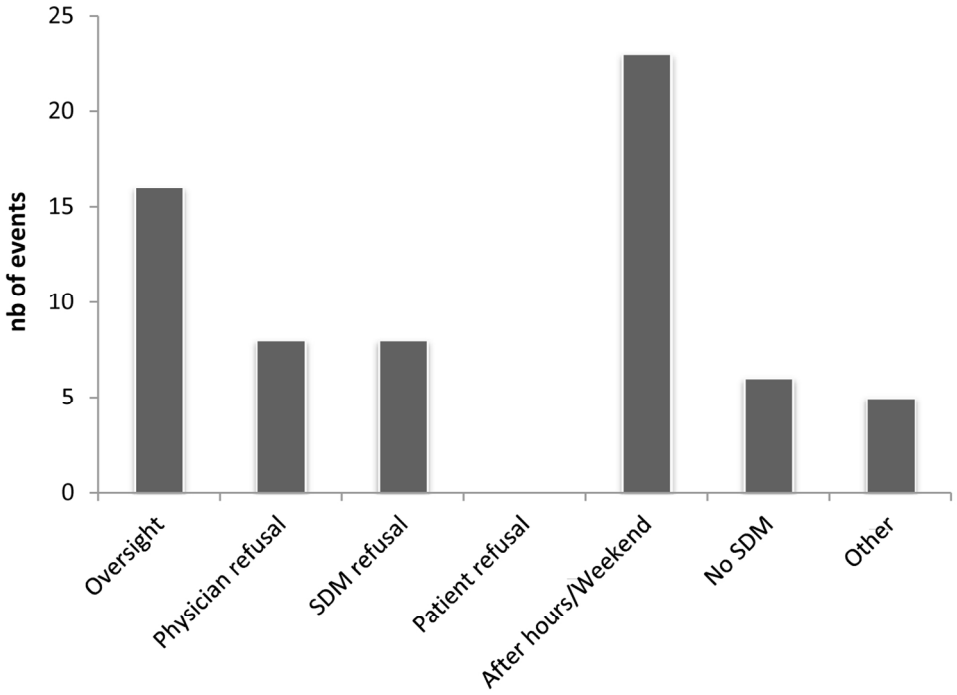

Figure 2. Reasons for non-enrolment.† SDM: Shared Decision Making

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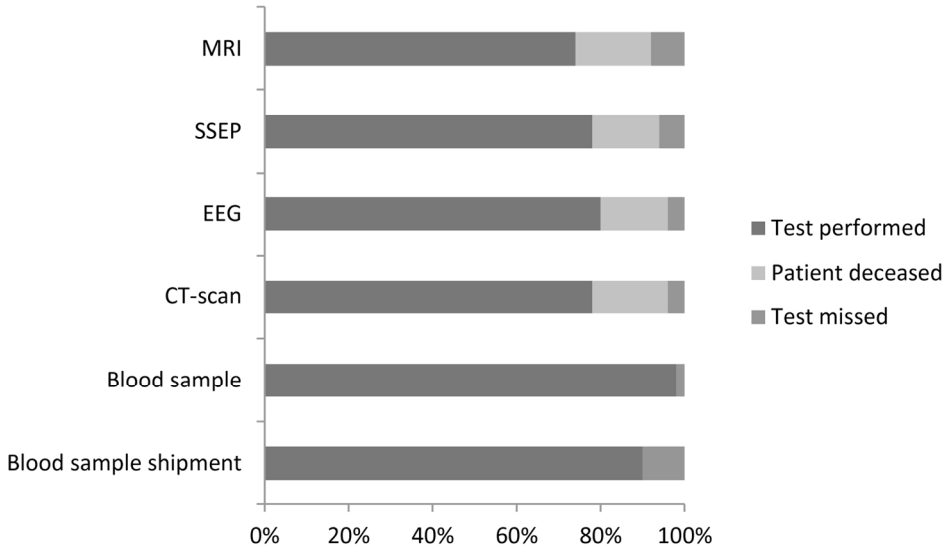

Figure 3. Compliance to the scheduled test procedures. CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8, Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Part of pilot goal
		(*d*) If applicable, explain how loss to follow-up was addressed	Part of pilot goal
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9, Figure 2
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	10, 11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11, 12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Epidemiology
Keywords:	Traumatic brain injury, Pilot study, Prognosis, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Outcome

Prognostication in critically ill patients with severe traumatic brain injury: The TBI-Prognosis multicenter feasibility study

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ABSTRACT (292 words)

Objective: Severe traumatic brain injury is a significant cause of morbidity and mortality in young adults. Assessing long-term neurological outcome after such injury is difficult and often characterized by uncertainty. The objective of this feasibility study was to establish the feasibility of conducting a large, multicenter prospective study to develop a prognostic model of long-term neurological outcome in critically ill patients with severe traumatic brain injury.

Design: Prospective cohort study.

Setting: Nine Canadian intensive care units enrolled patients suffering from acute severe traumatic brain injury. Clinical, biological, radiological and electrophysiological data were systematically collected during the first week in the intensive care unit. Mortality and functional outcome (Glasgow Outcome Scale extended) were assessed upon hospital discharge, and then 3, 6 and 12 months following injury.

Outcomes: The compliance to protocolized test procedures was the primary outcome. Secondary outcomes were enrolment rate and compliance to follow-up.

Results: We successfully enrolled 50 patients over a 12-month period. Most patients were male (80%), with a median age of 45 years (IQR 29.0 – 60.0), a median Injury Severity Score (ISS) of 38 (IQR 25-50), and a GCS of 6 (IQR 3-7). Mortality was 38% (19/50) and most deaths occurred following a decision to withdraw life-sustaining therapies (18/19). The main reasons for non-enrollment were the time window for inclusion being after regular working hours (35%, n=23) and oversight (24%, n=16). Compliance with protocolized test procedures ranged from 92% to 100% and enrolment rate was 43%. No patients were lost to follow-up at 6 months and 2 were at 12 months.

Conclusion: In this multicenter prospective feasibility study, we achieved feasibility objectives pertaining to compliance to test, enrolment and follow-up. We conclude that the TBI-Prognosis prospective multicentre study in severe traumatic brain injury patients in Canada is feasible.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Our study involved nine centers in five different provinces in Canada and showed the feasibility of enrolling critically ill patients with severe traumatic brain injury and assess 12-months outcome measures.
- Our study sample size allowed testing a protocol of test procedures and identifying potential pitfalls to consider for a large-scale prognostic study.
- Some eligible patients were missed due to an admission to the intensive care unit outside of working hours or were oversight by the research personnel.

INTRODUCTION

Severe traumatic brain injuries are catastrophic injuries primarily afflicting young individuals.[1] Mortality ranges from 30 to 50%, while 30% of survivors suffer from severe neurological sequelae.[2-5] Given the majority of victims are young with previous excellent quality of life, substantive human, social and financial repercussions are experienced by survivors.[6]

With regard to victims of severe traumatic brain injury, physicians and families often face important treatment decisions. They must decide to either undertake aggressive care in the hope of the patient will survive with an acceptable quality of life[7-10] or to withdraw life-sustaining therapy considering an unfavourable and undesirable prognosis. Serious concerns have been expressed regarding early decisions made to withdraw life-sustaining therapies in absence of evidence-based prognostic information.[11-14] Recently, we observed significant variations in mortality and in the incidence of withdrawal of life-sustaining therapies following severe traumatic brain injury in Canada.[8, 15] Current prognostic models are of limited clinical utility as they are based on data obtained from small[16-18], single centre[3, 17-23] retrospective studies[17, 22, 24-26] that did not consider secondary brain injury.[3, 17-21, 23, 24, 27-28] Consequently, it is not surprising to observe a wide variation in prognostic evaluation when surveying intensivists, neurosurgeons and neurologists caring for severe traumatic brain injury in Canada.[29] The development of appropriate prognosis tools and models is necessary to help guide the decision making process with families.

The objective of the TBI-Prognosis Feasibility Study was to assess the feasibility of a conducting a large-scale, multicentre study to develop a prognostic model to inform long-term prognosis in patients with severe traumatic brain injury.

METHODS

Study design

We conducted a multicentre prospective feasibility study in 9 level I trauma centres across Canada. Research Ethics Board approval was obtained from each participating center. Informed consent was obtained from surrogate decision makers prior to enrolment in most centers; deferred consent was permitted by Research Ethics Boards at two centers. This study was conducted in the Canadian health care system in which trauma, neurosurgery and critical care are part of a public system with universal health care coverage for all citizens. In Canada, major trauma care is delivered through 10 integrated provincial trauma systems. In Canada, neurocritical care is mainly delivered in combined neuro/general intensive care units.

Eligibility criteria

We included critically ill adults (≥18 years of age) with severe traumatic brain injury (Glasgow coma scale (GCS) ≤8 following resuscitation) due to blunt-force trauma on day 1 of intensive care unit admission. We excluded patients anticipated to be on mechanical ventilation for less than 48 hours, patients with solid malignancy associated with a life expectancy less than 12 months, liver cirrhosis Child C, chronic heart failure (NYHA class IV), end-stage chronic respiratory disease (O_2 dependent), end-stage renal disease (chronic dialysis), previous neurologic disorder with abnormal findings on radiological imaging (CT-scan, magnetic resonance imaging (MRI)) or electrophysiological tests (electroencephalogram (EEG), somatosensory evoked potentials (SSEP)) or patients who were declared brain-dead when assessed for eligibility. Patients with no fixed address were also excluded due to difficulties in conducting follow-up.

Data collection

Participants underwent a protocolized schedule of clinical, biological, radiological, and electrophysiological prognostic tests or examinations. Tests and examinations used in our study were commonly utilized in the care of patients with severe traumatic brain injury for diagnostic or prognostic purposes except for blood samples. Data were collected daily from intensive care unit admission until the 7th day following the injury, death or until hospital discharge, whichever came first. These included pupillary reactivity, corneal reflex, GCS, episodes of increased intracranial hypertension (>25 mmHg), hypoxemia (arterial oxygen saturation of <90%) and hypotension (systolic blood pressure <90 mm Hg). Data was prospectively collected at the bedside using specific case report forms. We also collected serum glucose (highest and lowest value), complete blood count, INR, prothrombin time, sodium, creatinine, arterial blood gases, also on a daily basis if the data was available as per clinical decision by the medical team. A schedule of prognostic biological, radiological and electrophysiological tests/examinations was implemented (Figure 1). On intensive care unit day 1, 3 and 7, CT-scans were performed and blood samples were collected to measure serum biomarkers. These timelines were informed by a multicenter retrospective study and a health care survey of Canadian clinicians.[8, 29, 30] On intensive care unit day 7, MRI, SSEP and EEG examinations were performed. We permitted a time window of 24 hours (for CT-scan) and 48 hours (for MRI, SSEP and EEG) to reflect clinical practice and enhance feasibility over weekends.

Outcome measures

Our overarching objective of the research program is to develop a model to predict short (discharge), mid (3 months) and long-term neurological prognosis (6 and 12 months) in patients admitted to intensive care unit with severe traumatic brain injury. The functional outcome was evaluated using the Glasgow Outcome Scale extended (GOSe) (face to face (hospitalized patients) or phone interviews (discharged patients)).[31, 32] Our feasibility study was designed to establish the feasibility of a large scale study adequately powered to develop prognostic

models to help inform clinical decision-making. Our primary outcome was the compliance rate to the protocolized test procedures (tests performed or not performed). We considered a 90% compliance rate to be acceptable. Secondary outcomes were enrolment rate and compliance to follow-up. We also evaluated the percentage of potentially eligible patients that were excluded, the reasons for exclusion and adverse events related to the protocol.

Research team at participating centers

At each participating center, a research coordinator and/or research nurse, was involved in the implementation of the study in the intensive care unit, daily screening, enrolment at the bedside, organization of the schedule of tests with the attending medical team and daily data collection. Follow-ups were performed locally with face-to-face questionnaire when patients were still in hospital, or phone questionnaires, when discharged home or to another facility. Follow-ups were made during working hours for most patients.

Start-up meeting

We organize a start-up meeting using virtual technology (video conference) prior to start enrolment in the study. This start meeting was chaired by the study manager at the coordinating center, involved the review of the protocol, the screening, enrolment and consent process, the overall study procedure, and potential pitfalls to avoid during the process.

Central coordination and data monitoring

The study was coordinated centrally by a study manager assisted by a clinical research coordinator. The study manager was responsible for supervising the implementation of the study at each site and was the primary link for the local research team to answer questions and queries during the conduction of the study. Communications through emails and phone calls to participating sites were performed on regular basis to clarify potential issues on enrolment and data collection, as well as to ascertain a close follow-up of sites. The data collection process was monitored centrally at the coordinating center and answers queries sent to the participating

centers before case report forms were considered completed. A newsletter was disseminated every other month to update center on the enrolment in the study, but also to motivate the team and provide information on common queries and questions.

Sample size

With a sample size of 50 patients we predicted to estimate a compliance to the scheduled test procedures of 90% with a margin of error of 10%.

Statistical Analyses

Descriptive statistics were used to report the data. Data on compliance to the tests procedure, enrolment rate, compliance to follow-up and overall study adherence are presented using proportions. No comparative statistical testing was performed considering the feasibility nature of this study.

RESULTS

Patient enrolment

Over a 12-month period (May 2012 to May 2013) totalising 208 weeks of active enrolment (all centers considered), participating centres screened 530 patients from which 116 were potentially eligible and 50 were enrolled (43%). The two main reasons for non-enrolment were the time-window for inclusion being after regular working hours and personnel oversight (Figure 2). We observed few refusals from surrogate decision makers and physicians, as well as non-enrolment due to the absence of a surrogate decision maker. No patient, once included in the study, was excluded. One center did not succeed to implement the study due to staffing issues and did not contribute any patients to this feasibility trial. The majority of recruitment (32

patients, 64%) took place during weekdays; three of the centers enrolled patients on weekends. Informed consent was mostly obtained (41 patients, 82%) between 9:00 am and 6:00 pm.

Patient characteristics

The median age of participants was 45 years (Interquartile range (IQR), 29 – 60 years) and 80% were male (40 patients, 80%). The median GCS at enrolment was 6 (IQR: 3-7) and the Injury Severity Score (ISS) was 38 (IQR 25-50) (Table 1). In 88% of patients, traumatic brain injury occurred following motor vehicle collision (MVC) or fall.

Table 1. Patients demographic

Characteristics	Patients (n=50)
Age (median, IQR)	45 (29 – 60)
Male (n, %)	40 (80%)
GCS (median, IQR)	6 (3 - 7)
APACHE II score (mean ± SD)	20.2 ± 6.84
ISS score (median, IQR)	38 (25 - 30)
Absent pupillary reactivity (ICU day 1)	36 (72%)
Absent corneal reflex (ICU day 1)	7 (14%)
Cause of trauma (n, %)	
MVC-occupant	21 (42%)
MVC-motorcyclist	9 (18%)
MVC-pedestrian	2 (4%)
Fall	14 (28%)
Assault	2 (4%)
Other	2 (4%)

IQR: Interquartile range; GCS: Glasgow Coma Scale; MVC: Motor vehicle collision SD: Standard Deviation; APACHE: Acute Physiology and Chronic Health Evaluation; ISS: Injury Severity Score, ICU: Intensive care unit

Compliance to the daily clinical data collection

Clinical data for episodes of hypotension, hypoxemia and increased intracranial pressure were successfully collected. We had three missing time points for pupillary reaction (2 patients) and one time point for the GCS (1 patient). Data for the corneal reflex was however missed at least for one data point in 29 patients.

Compliance to the test procedures

The compliance to the protocol of test procedures ranged from 92% to 100%, depending on the test performed. Compliance to tests was measured according to the survival status during the time window in which the test was scheduled (Figure 3). We observed 94% compliance for SSEP (3 missed tests), 96% for EEG (2 missed tests), and 92% for MRI (4 missed tests). Day 7 MRI was delayed for 20% (n=10) of the patients, most of them (n=6) due to the presence of material incompatible with the performance of the MRI procedure. No CT-scans were missed on day 1 and 3, while the compliance for day 7 CT-scans was 96% (2 missed scans). All but one blood sample were collected (day 7); all collected blood samples were successfully shipped to the coordinating centers. The main reason for not conducting a specific test was a change in level of care (palliative care). The main explanation for performing tests outside of the time window was patient instability (hemodynamic or increased intracranial pressure). We observed no adverse events related to this study and tests performed.

Follow-up of outcome measures

Two patients were lost to follow-up at 12 months, but none were at 6 months. Overall, 33 patients (66%) had an unfavourable outcome at 12 months (GOSe 1-4). Mortality was 38%

(19/50) and most deaths were associated with a decision to withdraw life-sustaining therapies (18/19). No patient died during follow-up after hospital discharge.

INTERPRETATION

In this multicenter prospective feasibility study, we achieved high compliance with the study procedures, an acceptable enrolment rate and had a low rate of loss to follow-up. All except one center achieved acceptable enrolment during the study period. The lessons learned during this multicenter feasibility prospective study have informed the design of the TBI-Prognosis multicenter prospective study (NCT02452541), which is currently ongoing.

The high compliance rate to the test procedures observed in our study is a paramount result for the feasibility of the large-scale study. Several reasons may explain this high compliance. First, our protocol is straightforward and mainly relies on reminders for timely test procedures. Second, the uniformity of the tests and the flexibility of test timing allow these tests to be included seamlessly into the patient's care continuum. Third, adherence to the test schedule has also been facilitated by local research coordinators directly interacting with the clinical personnel in the intensive care unit and championing the project,[33] and by clinician guidance and enthusiasm towards the project.[34] Finally, we engaged the clinical personnel working in the intensive care unit by holding information sessions describing the project and by being available to answer their queries and concerns.[33, 35]

Pilot and feasibility studies are particularly useful in revealing study flaws and design weaknesses.[36-38] In this feasibility study, we also identified some potential challenges for the conduction of the large-scale study. One of the challenges identified was the difficulty of

enrolling patients admitted outside of regular working hours (evenings or week-ends). This finding that a significant proportion of patients with traumatic brain injury are admitted over the week-end was also observed in a previous cohort study of patients with mild to severe traumatic brain injury in the UK.[39] Due to budgetary restrictions, but also to the available workforce, it was not always possible to have 24-hour coverage for screening and enrolment in clinical research. Using a deferred consent approach in all centers for the large-scale study is one of the avenues considered to handle this potential issue. Another important finding is our follow-up rates at 6 and 12 months that are comparable or better to the ones observed in previous large scale multicenter trials in patient with severe traumatic brain injury.[40, 41] Despite having missed 2 patients for the 12-month follow-up, we were able to follow all patients at 6 months, a result showing the possibility of not missing any patients for the large scale study.

Following this feasibility phase of the TBI-Prognosis study, study investigators engaged with local investigators, intensive care unit nurses, and research coordinators, through both informal discussions and survey, to understand their experience participating in the TBI-prognosis feasibility study. Recruitment techniques and eligibility criteria were revised and refined to improve clarity in the larger study. Deferred consent was highlighted as being especially helpful given the time constraints and appears to be generally accepted by participants upon regaining the ability to participate in the shared decision-making consent process.[42, 43] Indeed, the two centers that implemented this method recruited a greater number of patients than the other sites in accordance with the duration of the screening period. Strategies for approaching families in time of stress were also discussed.[37] With much preparatory work completed, the TBI-Prognosis team and the Canadian Critical Care Trials Group are now undertaking the large multicenter prospective cohort study informed by the results of this pilot feasibility study.

In this multicenter prospective feasibility study, we successfully enrolled participants following an acceptable enrolment rate, reached our targeted sample size, achieved feasibility objectives pertaining to the compliance to the test procedures, compliance to follow-up, as well as the overall adherence the study protocol. Considering our enrolment rate, we considered that three years will be necessary to enrol 315 patients in 17 centers across Canada in the large-scale TBI-Prognosis study. We conclude that a prospective multicentre study in severe traumatic brain injury patients in Canada aiming at developing a prognostic model in the acute phase of care is feasible.

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CONTRIBUTIONS

AFT, FL, RZ, DAF, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, JP, JLG, AL, KR, GP, DZ and LM were involved in conception and design. AFT, FL, RZ, DAF, CL, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, MSh, JP, JLG, AL, KR, DJ, GP, DZ and LM were involved in the acquisition

and interpretation of data. AFT, CL and MSh drafted the manuscript. AFT, FL, RZ, DAF, CL, LAM, FB, AR, KB, DG, RG, DCS, MOM, MS, MSh, JP, JLG, AL, KR, DJ, GP, DZ and LM were involved in revising the manuscript and approved the version published.

COMPETING INTERESTS

The authors declared no competing interests.

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DATA SHARING

There are no additional unpublished data available.

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Figure 1. TBI-Prognosis test schedule

The arrows indicate the prescribed time frame to perform tests or take blood samples. The study requested that CT-scans be done on day 1, 3, and 7, with the possibility to conduct the scans 24 hours prior or after the required date. Blood samples were drawn on day 1, 3 and 7. The EEG, SSEP and MRI tests were required on day 7 but could be obtained 48 hours before or after the seventh day.

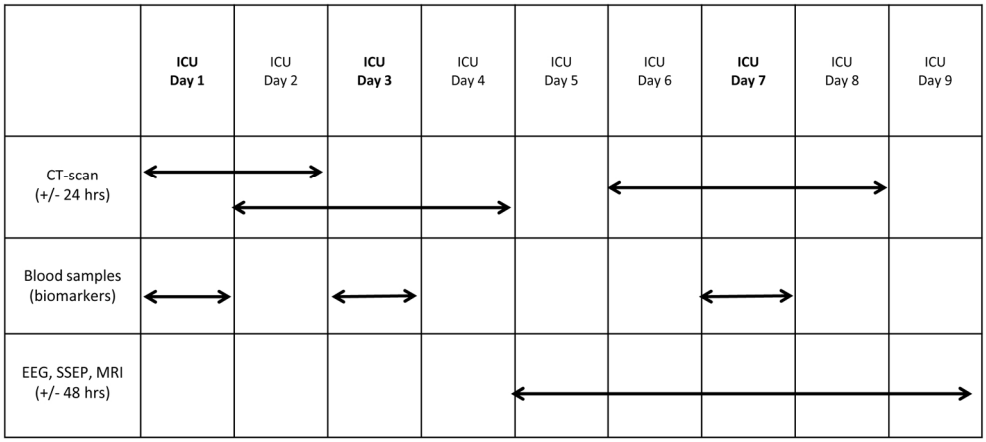
CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

Figure 2. Reasons for non-enrolment

SDM: Shared Decision Making

Figure 3. Compliance to the scheduled test procedures

CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials



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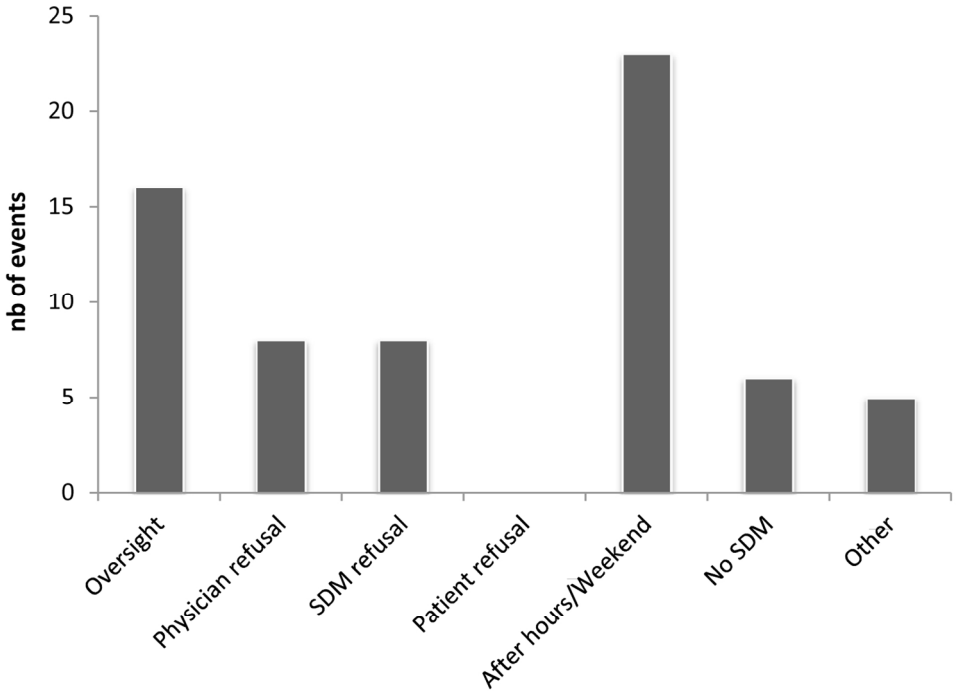

Figure 2. Reasons for non-enrolment.† SDM: Shared Decision Making

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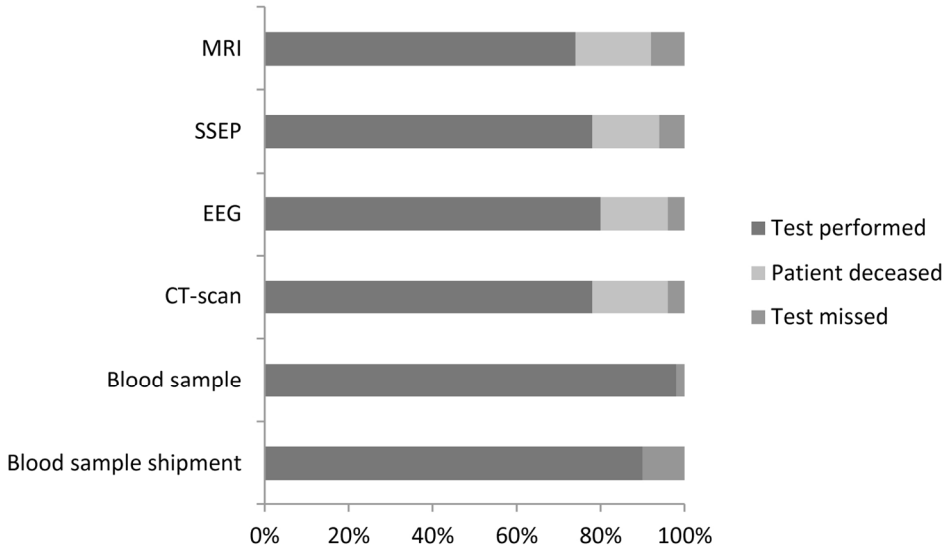

Figure 3. Compliance to the scheduled test procedures. CT-scan: Computed Tomography Scan; EEG: Electroencephalogram; ICU: Intensive Care Unit; MRI: Magnetic Resonance Imaging; SSEP: Somatosensory Evoked Potentials

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8, Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Part of pilot goal
		(*d*) If applicable, explain how loss to follow-up was addressed	Part of pilot goal
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9, Figure 2
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	10, 11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11, 12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.