Partners

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**CREACTIVE**
Collaborative REsearch on ACute Traumatic brain Injury in intensive care medicine in Europe
All ICUs already participating in the PROSAFE project and hospitalized patients with traumatic brain injury are invited to take part in CREACTIVE. For each patient with TBI, the centres have to fill out the case report form, which is already part of the PROSAFE database.

Follow-up will be performed six months after the trauma event, and will be two-tiered:
1. by telephone call for all patients;
2. by full patient examination to be performed in a selected subgroup of ICUs only.

In a subset of ICUs, clinical images carried out during routine clinical practice will be collected and centralized for all recruited patients. Images will undergo computer analysis, with a view to developing automatic or semi-automatic reading systems, thereby facilitating evaluation of the brain injury.

Biological samples will be collected and centralized in a subset of ICUs for phenotypic biomarker analysis. The choice of markers to be studied will be made after analysis of the images has suggested the most promising pathophysiological process to investigate.

The project involves 7 partners from Cyprus, Greece, Hungary, Israel, Italy, Poland and Slovenia.
CREACTIVE started on 1st October, 2013 and will run until 30th September, 2018.

An annual report of the results will be produced in both aggregate and customized form for each participating centre. This will enable the centres to compare their data with those of the entire data set. Accordingly, different quality indicators will be developed (SMR, Calibration Belt, VLAD) in order to statistically adjust comparisons for differences in patient severity. An analysis plan based on the propensity score will be used to identify the most effective therapeutic interventions. Based on the data collected, it is expected to enrol 7000 patients with moderate-to-severe traumatic brain injury in approximately 125 units, of which at least 80 Italian, by the end of the study, scheduled for September 2018.
Il progetto è finanziato dalla Commissione Europea nell’ambito del VII Programma Quadro Europeo con contratto nr. 602714.
Obiettivi dello studio

- Consolidare la rete preesistente PROSAFE, basata su una raccolta dati prospettica nei reparti di terapia intensiva (TI).
- Descrivere l’epidemiologia del trauma cranico (TBI) moderato-grave in 7 paesi.
- Studiare le conseguenze del TBI nei bambini, attraverso una valutazione multidimensionale degli esiti.
- Realizzare una biobanca (sangue e fluidi derivati, liquor) e una banca immagini cliniche per i pazienti con TBI.
- Costruire un modello prognostico basato su dati clinici e biologici per prevedere i risultati a breve e lungo termine nei pazienti con TBI.
- Identificare gli interventi clinici più efficaci per il trattamento dei pazienti con TBI.
- Riconoscere i centri di eccellenza nel trattamento dei pazienti con TBI.
- Condividere i dati raccolti con altri gruppi di ricerca internazionali aderenti alla rete InTBIR.

Il progetto coinvolge 7 partner da Cipro, Grecia, Israele, Italia, Polonia, Slovenia e Ungheria.

CREACTIVE ha avuto inizio il 1° Ottobre 2013 e terminerà il 30 Settembre 2018.

Tutte le TI che partecipano al progetto PROSAFE e che ricoverano pazienti con trauma cranico sono invitate a partecipare a CREACTIVE. Per ciascun paziente con trauma cranico si dovrà compilare la scheda di raccolta dati che è parte del database PROSAFE.

A distanza di sei mesi dal trauma cranico, verrà effettuato un follow-up dei pazienti, per valutare l’esito a medio termine. Sono previsti due livelli: 1. telefonico su tutti i pazienti; 2. ambulatoriale su un sottogruppo di pazienti e di TI.

In un sottoinsieme di reparti verranno raccolte e centralizzate le immagini cliniche effettuate durante la normale pratica clinica, per tutti i pazienti reclutati. L’obiettivo è quello di sviluppare sistemi di lettura automatici o semi-automatici, che facilitino la valutazione della lesione cerebrale.

In un sottoinsieme di reparti verranno raccolte e centralizzate campioni biologici per le analisi dei biomarcatori fenotipici. La scelta dei marcatori da analizzare verrà effettuata dopo che l’analisi delle immagini avrà suggerito quale sia il processo fisiopatologico più promettente da indagare.

Le analisi

Verrà preparato un report annuale sui risultati conseguiti, che sarà prodotto sia in forma aggregata sia personalizzata per ogni centro partecipante. I centri avranno quindi la possibilità di confrontare i propri dati con quelli dell’intero collettivo. Verranno sviluppati diversi indicatori di qualità dell’assistenza (SMR, banda di calibrazione, VLAD) al fine di aggiustare statisticamente i confronti per le differenze nella gravità dei pazienti. Per quanto riguarda l’individuazione degli interventi terapeutici più efficaci, verrà utilizzato uno schema di analisi basato sul propensity score.

Sulla base dei dati raccolti, si prevede l’arruolamento di 7.000 pazienti con trauma cranico moderato-grave in circa 125 reparti, di cui almeno 80 italiani, entro la fine dello studio.

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Banda di calibrazione GiViTI per la valutazione e lo sviluppo di modelli prognostici con esito dicotomico.
Ανάλυση Αποτελεσμάτων

Ετήσια αναφορά αποτελεσμάτων τόσο συνολικά όσο και για την εκάστοτε Μονάδα. Επιτηρείται ότι οι Μονάδες θα έχουν τη δυνατότητα σύγκρισης των αποτελεσμάτων τους με το σύνολο των Μονάδων του δικτύου. Θα δημιουργηθεί ένα σύνολο δεικτών το οποίο θα συμβάλει στην πιο αποτελεσματική σύγκριση των Μονάδων σε συνάρτηση με τη σαφιότητα της κατάστασης του κάθε ασθενούς.

Η ανάλυση της τάσης των αποτελεσμάτων θα καθορίζει τις πιο αποδοτικές παρεμβάσεις όσον αφορά στη θεραπεία των ασθενών της εκάστοτε ομάδας.

Βάσει των στοιχείων που έχουν συγκεντρωθεί μέχρι το Σεπτέμβριο του 2014, αναμένεται να ενταχθούν στο πρόγραμμα 9000 ασθενείς από 125 Μονάδες Εντατικής Θεραπείας μέχρι το Σεπτέμβριο του 2018.

Ολες οι Μονάδες Εντατικής Θεραπείας που ήδη συμμετέχουν στο δίκτυο PROSAFE και νοσηλεύουν ασθενείς με ΚρανιοΕγκεφαλική Κάκωση είναι ευπρόσδεκτες να συμμετάσχουν στο CREACTIVE. Για τον κάθε ασθενή με ΚΕΚ, τα κέντρα πρέπει να συμπληρώνουν το έντυπο αναφοράς περιστατικού που βρίσκεται στην ήδη υπάρχουσα βάση δεδομένων PROSAFE.

Θα γίνεται αξιολόγηση της έκβασης της νόσου 6 και 12 μήνες μετά το συμβάν με δύο τρόπους:
1. Τηλεφωνική επικοινωνία και συμπλήρωση ερωτηματολόγιου.
2. Πληρής κλινική αξιολόγηση που θα περιλαμβάνει κλινική έξεταση και εξετάσεις στο εξής:

Σ’ ένα υποσύνολο Μονάδων Εντατικής Θεραπείας θα συλλέγονται οι απεικονιστικές εξετάσεις για κάθε ασθενή που θα συμμετέχει στο πρόγραμμα. Θα τυχόν τεχνικής επεξεργασίας και θα αποδηκτείται ανώνυμα σε ηλεκτρονικό αρχείο, με σκοπό τη δημιουργία ενός αυτόματου ή εμπιστοσύνης συστήματος αξιολόγησης.

Θα γίνεται μελέτη βιολογικών δειγμάτων για πιθανότητα ανάλυση του φαινότυπου, καθώς και ανάλυση επιλεγμένων βιοδεικτών με σκοπό τη μέλετη τυχόν προδιαθεσιακών παραγόντων για την ανταπόκριση στη θεραπεία και την έκβαση της νόσου.

Στο πρόγραμμα συμμετέχουν 7 χώρες: Κύπρος, Ελλάδα, Ουγγαρία, Ισραήλ, Ιταλία, Πολωνία και Σλοβενία.

Το πρόγραμμα CREACTIVE ξεκίνησε την 1η Οκτωβρίου 2013 και αναμένεται να ολοκληρωθεί στις 30 Σεπτεμβρίου 2018.

Στόχοι Προγράμματος

⇒ Εξαίρεση υφιστάμενου δικτύου PROSAFE βάσει της συνεχούς συλλογής δεδομένων στις Μονάδες Εντατικής Θεραπείας (MEB).
⇒ Περιγραφή επιδημιολογίας μέτρησης και βαρίας κρανιοεγκεφαλικής κάκωσης σε 7 χώρες.
⇒ Αξιολόγηση συνεπειών της κρανιοεγκεφαλικής κάκωσης σε παιδία μέσω πολυδιάστατης διερεύνησης της έκβασης της νόσου.
⇒ Εγκαθίσταση κεντρικής βιοτράπεζας (αίματος και παράγοντων υγείας, CSF) και τράπεζας κλινικογραφικών και απεικονιστικών δεδομένων για ασθενείς με κρανιοεγκεφαλικές κάκωσες.
⇒ Δημιουργία προγνωστικού μοντέλου βασιζούμενου σε κλινικά και βιολογικά δεδομένα, για την πρόβλεψη των βραχυπρόθεσμων και μακροπρόθεσμων επιπλοκών ασθενών με κρανιοεγκεφαλική κάκωση.
⇒ Εξέλιξη αποτελεσματικών παρεμβάσεων για τη βέλτιστη θεραπεία ασθενών με κρανιοεγκεφαλική κάκωση.
⇒ Αναγνώριση κέντρων αισθητικών που αφορούν στη θεραπεία ασθενών με κρανιοεγκεφαλική κάκωση.
⇒ Δημιουργία κοινής βάσης δεδομένων με άλλες διεθνείς ερευνητικές ομάδες που συμμετέχουν στο δίκτυο InTBIR.
CREATIVE
(Collaborative REsearch on ACute Traumatic brain Injury in intensiVe care medicine in Europe)

Προοπτική Μελέτη Συλλογής Δεδομένων & Σύγκρισης Αποτελεσματικότητας σε Ασθενείς με ΚρανιοΕγκεφαλική Κάκωση (ΚΕΚ) στις Μονάδες Εντατικής Θεραπείας

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Επικοινωνία

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A rally for traumatic brain injury research

When members of the International Initiative for Traumatic Brain Injury Research (InTBIR) met in Vancouver (BC, Canada) on Oct 17–18, 2013, some notable stakeholders from the US National Institutes of Health (NIH) could not join them. The temporary shutdown of the US federal government had just been put to an end the night before. But the attendees’ feeling of frustration about the absence of some collaborators did not cloud their enthusiasm, and the InTBIR network reaffirmed its pledge to improve patients’ outcomes by 2020.

Traumatic brain injury (TBI) research has historically been neglected and underfunded. The major funding agencies behind InTBIR (The European Commission’s Health Directorate, NIH, and the Canadian Institutes of Health Research, and their military partners) have now aligned their national programmes and dedicated more than US$80 million to the initiative. Such an unprecedented coordinated strategy reflects the urgent need to tackle a global public-health crisis. In Europe alone, TBI causes an estimated 75 000 deaths per year and more than 1 million hospital admissions; but these estimates are thought to be even higher in other continents. Warfare, violence and terrorism, and road traffic accidents contribute to the huge global burden of TBI; long-term sequelae are both psychological and physical. Furthermore, recurring mild TBI can lead to chronic traumatic encephalopathy—evidence that is starting to affect policies of sports organisations.

As documented in a Personal View, adding to the complexity of a disease for which heterogeneity is an intrinsic feature, substantial differences in patient management exist even among specialist centres in the setting of clinical trials. Not surprisingly then, given the lack of guidelines based on high-quality evidence, inconsistencies in management of both paediatric and adult patients are pervasive. For instance, a recent study of paediatric TBI centres in France, Spain, the UK, and the USA found a great deal of variability in key therapy goals, such as those set up at individual centres on intracranial hypertension and metabolic therapies, or brain monitoring of partial pressure of oxygen.

In Vancouver, Graham Teasdale (University of Glasgow, UK) reminded attendees of the need to strike the right balance between aiming to improve standardised versus personalised clinical care. Without denying that challenge, InTBIR members emphasised the opportunities to exploit heterogeneity in presentation, care, and outcomes, by means of rigorous observational studies and comparative effectiveness analyses to tackle both standardised and personalised care. Four major InTBIR studies in the civilian population have either started recruitment or will do so soon: the Approaches and Decisions for Acute Pediatric TBI (ADAPT) study, an observational comparative effectiveness study of 1000 children with severe TBI; the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI), a longitudinal study to characterise disease phenotypes and compare clinical care in more than 5000 patients, with a concurrent registry to collect data from up to 40 000 patients; the Collaborative Research on Acute Traumatic Brain Injury in Intensive Medicine in Europe (CREACTIVE) study, an epidemiological and comparative effectiveness study of patients with moderate-to-severe TBI in more than 100 intensive care units; and the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, which will enrol 3000 patients for further analyses of comparative effectiveness and diagnostic and prognostic markers. Although each of these studies (plus a plethora of smaller projects also part of InTBIR) should provide a wealth of data, unique potential lies in their synergies. The integrated analysis of findings will be feasible because data collection is standardised according to NIH common data elements (CDEs). And the newly implemented Federal Interagency TBI Research (FITBIR) Informatics System will equip the initiative with a data sharing platform. However, the difficulties of establishing a transnational, open-access research culture are not to be underestimated, and the most heated discussions in Vancouver covered the intricacies of the use of CDEs, legal and ethical barriers to data sharing, and the effects of data sharing in the current academic system of rewards.

The InTBIR community is nevertheless committed to address these obstacles over the next few months. In doing so, they will not only accelerate progress in TBI, but also facilitate the integration of InTBIR with other brain research networks for swift public health improvements. The next meeting of the consortium to review progress will take place in 2 years—hopefully political disruption in Washington, or elsewhere, won’t hold any investigator back on that occasion. ■ The Lancet Neurology
CREATIVE
A EUROPEAN ENDEAVOR TO IMPROVE OUTCOME OF PATIENTS WITH TRAUMATIC BRAIN INJURY

Authors: Guido Bertolini, Giulia Paci, Luca Antiga, Akos Csomos, Rafael Kaps, Isaac Lazar, Malgorzata Mikaszewska, Matteo Mondini, Nektaria Xirouchaki, Roberto Latini, Primoz Gradisek, Joanne Fleming, Theodoros Kyprianou

Background
Traumatic Brain Injury (TBI) is an alteration in brain function, or other evidence of brain pathology, caused by an external force \(^1\). For many years, a myriad of epidemiological and clinical studies have documented the huge burden of TBI for patients, their relatives, and the whole of society, in terms of unexpected death, long-lasting or permanent disability in previously healthy persons, diminished or even a sharp drop in quality of life, massive direct and enormous indirect costs \(^2\)–\(^3\). Nevertheless, TBI research has historically been neglected and underfunded \(^4\), thus it is not surprising that the therapeutic armamentarium to improve outcome of TBI patients is far from being satisfactory \(^5\).

Recently, however, the International Initiative for Traumatic Brain Injury (InTBIR) has been set up with the long term goal of improving the clinical outcomes of these patients and lessening the global burden of the disease by 2020. InTBIR is an unprecedented consortium of three major funding agencies (the European Commission’s Health Directorate, the NIH’s National Institute of Neurological Disorders and Stroke, and the Canadian Institutes of Health Research Institute of Neurosciences, Mental Health and Addiction), which opted to align their national programs to accelerate progress in TBI research. Within this common endeavor, the three agencies have independently launched a number of funding calls focused on basic and clinical TBI research, for a total investment of about US$90 million \(^4\).

Four major studies and a number of smaller projects have been funded and are now in the starting blocks: the Approaches and Decisions for Acute Pediatric TBI (ADAPT) study; the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI); the Collaborative REsearch on ACute Traumatic brain Injury in intensiVe care medicine in Europe (CREATIVE) study; the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. Despite differing in many ways, but being committed to render the resulting databases accessible to the research community, all these studies will collect at least the same core data, the so-called Common Data Elements (CDEs) \(^6\)–\(^8\), thus laying the foundations for a unique international research collaboration.

Here we present the protocol of CREATIVE, an observational study that will involve about 100 intensive care units (ICUs) in seven countries: Cyprus, Greece, Hungary, Israel, Italy, Poland, and Slovenia. While mild TBI patients are variably managed in the different health services, most moderate and almost all severe TBI patients who manage to reach a hospital are admitted to an ICU. Although these patients represent only 20% of the total, they carry the main burden of the disease. Some permanent disability is estimated to occur in 10% of mild, 66% of moderate, and 100% of severe TBIs \(^9\)–\(^11\). Estimated in-hospital mortality is <5% in mild TBI, while it increases to 21% in moderate, and 46% in severe
cases at six months. Hence, the ICU is in an ideal position to adequately evaluate and monitor the bulk of the burden of the disease, identify and assess the most effective clinical interventions, and recognize excellence in TBI management.

**Aims of the CREACTIVE study**
The CREACTIVE project has several aims: 1) to better describe the epidemiology of moderate-to-severe TBI in the participating countries; 2) to establish centralized repositories of clinical data (CDEs+), biological samples (blood and derived fluids, cerebrospinal fluid) and clinical imaging data, to be exploited for prognostic purposes; 3) to build a prognostic model based on clinical and biological data to predict short- and long-term outcome; 4) to identify the most effective clinical interventions for optimally treating TBI patients; 5) to recognize the determinants of optimal vs. suboptimal performance.

**Progress beyond the state-of-the-art**

**Epidemiology of TBI**
The existing PROSAFE network, recently established through EU funding (PHEA 2007331), will be consolidated through the CREACTIVE project. The PROSAFE network was created to export the experience gained with the Italian Margherita Project in establishing clinical audit to improve the quality of care in the ICU setting. In 2012, 242 ICUs, mainly from Italy, had joined PROSAFE, recruiting 85,965 patients in total. Of these ICUs, 199 admitted at least one TBI patient, totaling 3,344 cases. On the basis of these statistics, the network expects to recruit about 7,000 moderate to severe TBI patients over a period of 4 years.

Two features of the PROSAFE project are particularly valuable for CREACTIVE from an epidemiological perspective. First, all kinds of healthcare facilities will be involved, from secondary to tertiary, to quaternary care level centers. This is extremely important, considering that the representativeness of the sample matters even more than its size. At the present, a large fraction of moderate to severe TBI patients continue, perhaps inevitably, to be admitted to peripheral, secondary care centers, where it is often hard to decide whether to centralize a patient to a tertiary or even a quaternary care facility. On this premise, if InTBIR is actually to be able to improve outcome of TBI patients, it is mandatory to know what happens in secondary centers. Second, all admitted patients will be registered in the PROSAFE Case Report Form, while those with TBI will be registered in both the CREACTIVE and PROSAFE forms. This is of paramount importance for many reasons: it will provide a general picture of the case mix of the ICUs and their general performance, which can be taken into account in explaining variability in TBI patient management; it will be possible to monitor the participation of each ICU in the study; the software will alert the presence of eligible patients, thereby avoiding any selection bias; and, ultimately, this will foster familiarity with data collection and promote the overall quality of the information gathered.

Finally, from the patient perspective, given the importance of TBI-related disabilities, mortality cannot be considered the only outcome to assess the impact of the condition. Accordingly, a follow-up will be performed six months after the trauma event, and will be two-tiered. The first level will be administered over the phone and consist of the extended version of the Glasgow Outcome Scale (GOS) to assess disability and the QOLIBRI-OS to evaluate the health-related quality of life. The second level will encompass a full patient examination. In the case of children, this will include a dedicated sleep disturbances study. The second level follow-up will be performed in a selected subgroup of ICUs only.

**Bio-bank and bank of clinical imaging**
The damage occurring after trauma is the consequence of two distinct, partially independent mechanisms, namely primary and secondary injury. Whilst the first is directly caused by the impact, the second is governed by a complex set of cellular processes and biochemical cascades that occur in the minutes to days following the trauma. Through different pathways, the most critical results of secondary injury are the progression of the hemorrhagic lesion and/or the cytotoxic and vasogenic edema (swelling of the brain), which ultimately cause a rise in intracranial pressure. Since this accounts for the greatest number of TBI deaths occurring in hospital, the main aim of treatment in the acute stage of TBI is to control and lower intracranial hypertension.

In this framework, it is crucial to better characterize the progression of hemorrhagic lesions and cerebral edema and to increase our knowledge on the factors that can influence them. The substantial variability of these two phenomena among subjects not fully accounted for by the initial lesion severity suggests that an individual genetic predisposition can play a role in their magnitude and, consequently, in the final patient outcome.

We will study the evolution of the focal lesion volume (hemorrhagic and/or perilesional edema) through the analysis of serial computed tomography (CT) images, circulating and cerebrospinal fluid (CSF) biomarkers, and possible underlying genetic predisposition. There is an increasing volume of evidence that highlights the association between outcome and CT imaging, biomarkers, and genetic polymorphisms. But these three important aspects have always been analyzed independently from each other, and never been collected together in the same population.

We will implement centralized repositories of detailed clinical data, biological samples (Bio-bank), and repeated clinical imaging, on the same large sample of adult patients (up to 2,000). This will provide a unique opportunity for the integrated analysis of secondary injury following TBI.

Starting from the automated analysis of imaging data, we will evaluate the variability in the progression of both the hemorrhagic lesion and the perilesional edema, also assessing their association with the outcome. We will then concentrate the analysis on circulating and CSF biomarkers and genetic predisposition to the most promising mechanism: either trauma-induced coagulopathy underlying hemorrhagic progression, or regulation of both blood-brain barrier permeability behind vasogenic edema and ischemic events underlying cytotoxic edema.

Given the complexity of the entire picture and the expected new knowledge that may be available when the samples are ready for analysis, an ad hoc, independent, scientific advisory board (SAB) will finalize the protocol of the various determinations. Depending on the results of the imaging analysis and the new available evidence, the SAB will jointly identify which already recognized circulating and CSF biomarkers, and which other innovative ones will be tested, in addition to the most promising genetic analysis to be performed.
Building a prognostic model

Of all the CREACTIVE project aims, the most important is definitely to build an accurate prognostic model for TBI patients. Indeed, the other aims can only be achieved if such a model becomes available.

In the critical care medicine field, several “severity of illness” scoring systems have been proposed, but they have inevitably proved to lack generalizability. This is particularly true for TBI, where in 2006 prognostic models were still inadequate, as reported by a systematic review, and a more recent model still proved to calibrate poorly when applied to an external cohort. At present, a number of problems hamper the development of a reliable global prognostic model. First, a scoring system developed in a specific geographic, economic and social context, produces biased estimates when applied to other areas. This is because unmeasured context-specific variables influence the weight of the prognostic factors included in the model. Second, the development of prognostic models is so complicated that once built, they are unlikely to be updated for many years. At present, severity scores constructed many years ago, such as SAPS II, APACHE II, PIM2 and PRISM2, to cite just the general ones, are still commonly used. This generates a temporal bias related to the improvement of health care quality and changes in case mix over time that the model cannot account for. Finally, the internal validity of currently used severity scores has never been adequately tested in important subgroups and so miscalibration of the model cannot be ruled out. Consequently, when severity scores are applied to populations from the developmental sample with different case mixes, their predictive power deteriorates.

The aim of the CREACTIVE consortium is to overcome these problems. In essence, a large number of ICUs will be collecting data on a regular basis, providing enough statistical power for prognostic modeling; a prognostic model will be developed every year to avoid the temporal bias; a second yearly model will take into account the context-specific variables, together with the patients’ characteristics, to increase generalizability; the uniformity of fit of the models will be assured through the GIVITI Calibration Belt in subsets identified by a high number of prognostic variables, to assure internal validity.

Comparative effectiveness of clinical interventions

The main goals in managing patients with moderate to severe TBI are (a) to maintain life in spite of the primary tissue injury, (b) to protect the brain from secondary neuronal injury, and (c) to prevent secondary injury in other organs resulting in multi-organ dysfunction syndrome. Some of the pathophysiological mechanisms that affect the outcome of these patients include brain edema, increased intracranial pressure, hyper- and hypotension, hypoxia, brain ischemia, hyperventilation, temperature regulation, hyper and hypoglycemia (peripheral or regional), hyper- and hyponatremia, seizures, sepsis, etc. A number of interventions designed to manage these derangements have been a topic of controversy, mainly due to the lack of high quality randomized-controlled trials.

Firstly, ad hoc analyses (e.g., cluster analysis) will be performed to identify the most frequently used bundles of interventions (including individual treatments). For each bundle, a propensity score (i.e., the probability of bundle assignment according to observed baseline characteristics) will be developed through a logistic regression model. Comparative effectiveness analysis will be performed through both covariate adjustment and stratification, using the propensity score.

Identification of excellence in treating TBI patients

In the literature on quality of care assessment, one of the most widely used indicators is the standardized mortality ratio (SMR), which is the ratio between observed and expected mortality in a subgroup, according to the benchmark. When a prognostic model is used as benchmark for the centers forming its development sample, the SMRs of the individual centers will be distributed around one. However, some centers will exhibit a statistically significant deviation from one. This means that their better- or worse-than-benchmark outcome is not due to chance variation but to potentially different performance. Moreover, SMRs that do not deviate significantly from 1 may hide statistically significant differences from benchmark in specific classes of risk (say, patients at low risk of death), or in specific subgroups (say, patients with severe infection).

The GIVITI calibration belt does instead provide this detailed information. The use of such a tool will thus allow identification, on
the one hand, of centers with the highest performance in TBI treatment and, on the other, of those with poor results. In short, the GiViTI Calibration Belt is the confidence band that compares the observed with the expected probability of a dichotomous outcome (according to a given model). A statistically significant deviation from the null hypothesis of perfect calibration, i.e. when the model predicts what is actually observed, occurs when the 95% confidence boundary of the GiViTI Calibration Belt does not encompass the bisector (i.e. the ideal line of perfect calibration). Once a model has been demonstrated to calibrate well in all subsets of patients defined by the covariates considered, any deviation from the bisector by the Calibration Belt of an individual ICU means that the outcome observed in that ICU is not in line with the average performance (see Figure 1).

This approach will furnish ICUs with appropriate tools to self-evaluate weaknesses and strengths in their care performance and to enable identification of ICUs of excellence, permitting good exchange of practices and ultimately quality improvement.

Discussion

The CREATIVE project’s partners, fully embracing the InTBIR Initiative objectives, envisage the formation of an ever growing, open access, true international database that will include thousands of patients from the whole spectrum of Traumatic Brain Injury and hundreds of clinical, radiological, biochemical, hormonal, genetic, cognitive parameters/derived parameters, providing the research community with a valuable tool for TBI research. Limitations of the project’s epidemiological approach would possibly include: a) failure to recruit a valid and representative number of patients with moderate to severe TBI from each country, thus limiting their interpretation, b) failure to achieve high-level of compliance in follow up studies, rendering research based on outcome indices and construction of a reliable predictive model, difficult to pursue. Regarding collection of clinical, physiological, biological and radiological data, this attempt constitutes a serious world-leading step towards the establishment of a BIG DATA facility, dedicated to Traumatic Brain Injury. Entering the daunting era of BIG data, offers unique opportunities but also creates an unprecedented bulk of null hypotheses! Running diverse experiments on this huge testing bed and checking for pathophysiological interrelations, many research lines in basic, translational as well as industrial research shall be abandoned and new will emerge.

InTBIR will soon face the ultimate challenge to deploy the most appropriate IT infrastructure and service architecture(s) required to link, share or combine disparate datasets, as well as the correct data structure(s) to enable natural language processing, trend analysis and outcome prediction. It will also be called to face the diverse ethical and legal frameworks for the international/transatlantic transfer of medical-clinical data. At the same time, the research community across the scientific disciplines dealing with Traumatic Brain Injury, should identify areas of greatest need that would benefit most from or are most amenable to big data cognitive analytical approaches and specific projects should be designed.

REFERENCES


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