Effectiveness of Traumatic Brain Injury Management Guideline Introduction in Hungary and Risk factors of External Ventricular Drain Infection

PhD thesis

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1. INTRODUCTION: Background of Theses

1.1. Traumatic Brain Injury management guideline in Hungary

Traumatic brain injury (TBI) is a major cause of death and disability in the world harbouring significant public health and socio-economic importance. TBI is estimated to be the primary cause of death and disability among young individuals. Epidemiological data on TBI from the European Union are scarce, but do indicate an incidence of hospitalized TBI of approximately 235/100 000/year, although substantial variation exists between European countries.

The disease burden of serious intracranial trauma is continuously high in Hungary especially among middle aged men representing the leading cause of death in the young, active population. The reported incidence of TBI patients in Hungary is 140/100,000/year. The proportions of mild, moderate, and severe cases are 67%, 23%, and 11%, respectively. The case fatality ratio (CFR) was extremely high in Hungary: the estimated CFR for hospitalized TBI cases was 45% in 2002. To exploit the evidence based guidelines opportunities, the Hungarian Ministry of Health introduced the guideline of TBI care in 2006, which was established on recommendation of Brain Trauma Foundation and it focused on the prehospital and clinical management of patients.

1.2. Risk factors of External Ventricular Drain infection

Ventriculostomy is frequently used in the management and monitoring of intracranial pressure (ICP) in severe TBI patients. In the US, an average of about 20,586–25,634 (24,380) patients per annum undergo ventriculostomy.

The application of external ventricular drain (EVD) is a crucial point in TBI protocols; EVD infections are among the complications for EVD application with high influence on the outcome of the underlying disease and are not well characterized. EVD infection rate ranges from 0% to 22% resulting in a significant increase in cost, hospital stay, morbidity and mortality.

In order to avoid EVD infection and reduce cost, EVD application is often avoided despite the fact that EVD application can improve the prognosis of TBI patients. Unfortunately the avoidance EVD application can be supported by the EVD infection related uncertainties. The cases where the fear of infection is justified (and the intention of saving resources and reducing cost is acceptable) cannot be differentiated from cases where the risk of EVD infection is acceptably low (and the resource saving jeopardizes the patients' prognosis).

Due to the heterogeneous knowledge on the effectiveness of EVD, uncertainties of EVD application and the infection related complications, further research is required.

1.3. Blood based Diagnostic Protein Biomarkers in Adult Mild Traumatic Brain Injuries

Mild Traumatic brain injury (mTBI) represents more than 80% of all TBIs. Clinical diagnosis remains a challenge and computed tomography (CT) is considered the diagnostic cornerstone used in the ED to rule out post-traumatic brain lesions and complement clinical assessment of patients with a possible MTBI. However, it is generally acknowledged that CT is not always available, implies patient radiation exposure, and is relatively costly in terms of ED logistical burden and

health care expenditures owing to the small proportion of subjects (~10%) diagnosed as having actual traumatic intracranial lesion.

The need to manage patients with possible mild TBI more effectively and efficiently — to reduce unnecessary CT scans and medical costs, while not compromising patient care and safety - has driven the quest for sensitive blood-based markers as objective parameters that can be easily and rapidly measured in the systemic circulation. Identification of biomarker signatures associated with distinct aspects of TBI pathophysiology may be also of clinical value for a more accurate characterization and risk stratification of TBI, thereby optimizing medical-decision making and facilitating individualized and targeted therapeutic intervention. As such, over the past decades, a focused effort has been made to identify novel blood biomarkers for TBI, and a growing number of candidates has been described and proposed, leading to the recent incorporation of S100B into the Scandinavian Neurotrauma guidelines. Nonetheless at present, the role of body fluid biomarkers in TBI is primarily relegated to research studies, and the provision of high quality evidence is paramount to meet regulatory requirements and support their adoption and routine use in clinical practice.

We focused on markers for which promising scientific evidence of analytical and clinical validity is available and, thus, are likely to be rapidly transferable to clinical practice, namely S100B, glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), ubiquitin C-terminal hydrolase-L1 (UCH-L1), and Tau and neuro-filament proteins.

2. AIMS

Traumatic Brain Injury management guideline in Hungary

1. The aim was to describe the impact of the guideline introduction on the degree of care centralization and the CFR for the Hungarian severe TBI patients, in order to describe the usefulness of guideline introduction without parallel introduction of audit system.

Risk factors of External Ventricular Drain infection

2. The aim of this review was to identify risk factors that can potentially affect the incidence of EVD infection and create a model, which can be used in future studies to determine the real risk factors with their real strengths in order to contribute to the elaborations on the guideline for EVD application among TBI patients.

Blood based Diagnostic Protein Biomarkers in Adult Mild Traumatic Brain Injuries

3. The aim of this systematic review and meta-analysis was to comprehensively summarize and critically evaluate the existing body of evidence for the use of blood protein biomarkers for diagnosis of brain injury as assessed by CT in adult patients presenting to the ED after mild head trauma.

3. MATERIALS AND METHODS

3.1. Effectiveness of Traumatic Brain Injury Management Guideline Introduction in Hungary

3.1.1. Case definition

National Health Insurance Fund (NHIF), the only institution responsible for financing the inpatient neuro-traumatology care in Hungary provided the data as hospital discharge records (HDR). Direct assessment of TBI severity was not possible in this studied dataset because the NHIF HDR does not contain the Glasgow Coma Score (GCS). Instead, the severe TBI cases (sTBI) were defined by ICD code and clinical intervention codes. Patients with S06 diagnosis of intracranial injury and with a code of external ventricular drainage application were considered as sTBI subjects. The HDR of sTBI patients admitted between 01/01/2004 and 31/12/2010 recorded in every inpatient institution of Hungary were included in the database analyzed by our investigation. The records were pseudonymized, and the pseudo-identifiers were used to link the episodes of care to patients. Severe TBI patients who died at the scene of trauma or before arrival to the hospitals were not included in the study population.

3.1.2. Study center definition

The institutions that took part in the sTBI care were described by the number of patients first admitted by them. By evaluating the pathways of sTBI patients, the TBI centers and secondary institutions were differentiated. The biggest institutions altogether treated 50% of the patients and were considered as centers while the rest of institutions as secondary.

3.1.3. Case Fatality Rate (CFR): Period, Age group, Gender and Center CFRs

The CFR was calculated for the period of one week, one month and six months after the first hospital admission of sTBI patients. Age group and gender specific CFRs for the whole country were also calculated for each studied year. The center and secondary institution specific CFRs were calculated, as well, and compared by chi-square test to check the change in time. The indicator for centralization of care (number of patients admitted in centers over number of patients admitted in secondary institutions), the center and secondary institution specific CFRs were computed for the whole study interval (2004-2010), period before (2004-2006) and after (2007-2010) guideline introduction. The period specific results were compared by chi-square test.

3.1.4. Statistical analysis

To control for the potential confounding effect of patients demographic characteristics, the determinants of CFRs were investigated by multivariate logistic regression models where the sex and age of sTBI patients, the level of first admitting institution (classified as centers or secondary institutions), and time of the admittance (distinguishing before and after guideline introduction periods) were the explanatory variables. The results of statistical tests were considered as significant if the obtained P-value was less than 0.05. All the statistical computations were carried out by PASW Statistics 18.

3.2. Risk Factors of External Ventricular Drain Infection: Proposing a Model for Future Studies

3.2.1. Search strategy

We performed a systematic search on PubMed and Google Scholar databases (from 1966 - August 2017) for relevant studies related to ventricular drain infections. Keywords used in the search strategy include:

1. Infections (ventricular drain, ventriculostomy related, external ventricular drain, ventricular catheter and extra-ventricular drain) and
2. One of the following (traumatic brain injury, Intensive care (ICU) patients', neuro-intensive care (NICU) patients, head injury, brain injury, cerebral hemorrhage, sub-arachnoid hemorrhage).

3.2.2. Study selection

The combination of keywords generated 328 and 276 references on PubMed and Google Scholar, respectively. Of 604 references, 28 were found relevant after the title and abstract screening. In addition to these, the references of these 28 relevant articles were searched manually to find more related articles, which generated 4 new articles. The 32 relevant articles were screened; those that performed a *multivariate analysis* of suspected risk factors and had a *positive culture* as a mandatory component in diagnosis were selected for data collection and analysis. Twenty articles were finally selected for our review. The cumulative sample size of the 20 studies was 5113 patients, with a median of 164.5.

3.3. Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting with Mild Head Injury to Emergency Departments: A Living Systematic Review and Meta-Analysis

3.3.1 Information sources

We searched Ovid MEDLINE® (1946 to October 2016), OVID Embase (1980 to October 2016), OVID EBM Reviews (October 2016) and Cochrane Library (October 2016) for relevant studies. For possible ongoing trials and studies we searched WHO International clinical trials registry platform (ICTRP) (searched November, 2016) and ClinicalTrials.gov registry (searched November, 2016).

3.3.2. Study selection

Two reviewers independently reviewed the title and abstract of each citation identified by the search strategy. In the second stage, the full text was reviewed and eligible studies selected. Any disagreement between the two authors was resolved through discussion, or where necessary, arbitration by a third party. Studies were included if the article met the pre-specified list of eligibility criteria: studies enrolling adult patients presenting to the ED with a history of possible brain injury complying with any authors' definition of mild TBI; report of the admission head CT

findings; at least one quantitative measurement of the circulating biomarkers of interest (S100B, GFAP, NSE, UCH-L1, tau and Neuro-filament proteins) on admission, and relevant accuracy data.

3.3.3. Data extraction and assessment of methodological quality

Two reviewers independently extracted data using a standardized data abstraction form. We abstracted relevant information related to the study design, patient characteristics and biomarker characteristics, analytical aspects of biomarker testing, and study limitations. Details regarding the definition of mild TBI and CT abnormality were also extracted.

The methodological quality of the included studies was independently assessed by two reviewers using a modified version of the tool for quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS-2), as recommended by the Cochrane Collaboration. Discrepancies were resolved through discussion or arbitration by a third reviewer.

3.3.4. Data synthesis

Data processing and statistical analyses were conducted using Review Manager version 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and STATA version 13.0 (StataCorp, Colleage Station, Texas, USA) including the user written commands METANDI and MIDAS.

3.3.5. Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality of evidence of the included biomarker tests. The results were summarized using GRADEPro software (version 3.2, 2008).

4. RESULTS

4.1 Effectiveness of Traumatic Brain Injury Management Guideline Introduction in Hungary

Throughout the study period, the CFR in one week, in one month and in 6 months remained the same for almost all age groups before and after 2006 when the guideline was introduced.

At one week, in males, the highest CFRs were in the ninth and fourth decades. While in females, the highest CFRs were observed in third and ninth decades. At one month, in males, the highest CFRs were detected in age groups 95 and 90 and in females, in age groups 95 and 90. At six months, in males, the highest CFRs have been described in age groups 95 and 90 in females in age groups 95 and 90.

A total of 57 institutions took part in the study with 8 (referred as centers) providing 50 % of the care. There was an increase in care centralization according to the ratio of the center to secondary institutions treated number of patients. (0.85 vs 1.07; $p<0.001$) (**Table 1**)

The centers together at one week, one month and six months had CFRs of 22.6 %, 38.6 % and 48.9 % respectively. The secondary institutions together at one week, one month and six months had

CFRs of 21.7 %, 35.9 % and 47.6 %. Differences were not significant for one week and for 6 months period (p=0.358, and p=0.267). The centers' CFR was significantly higher for 1 month (p=0.018). The centers and the secondary institutions specific CFR showed no change when the before and after guideline introduction periods were compared. (**Table 1**)

Table 1 Influence of guideline introduction in 2006 on care centralization and case fatality ratios.

	Whole period (2004-2010)	Before guideline (2004-2006)	After guideline (2007-2010)	P-value*
Male/Female	2.58 (5211/2019)	2.77 (2387/861)	2.44 (2824/1158)	0.015
Age, Mean ± SD	60.89±19.23	59.01±19.30	62.41±19.04	<0.001
Centers/Secondary institutions, (N/N)	0.97 (3551/3679)	0.85 (1492/1756)	1.07 (2059/1923)	<0.001
CFR in 1 week in centers, N (%)	803 (22.6%)	349 (23.4%)	454 (22.1%)	0.454
CFR in 1 week in secondary institutions, N (%)	798 (21.7%)	377 (21.5%)	421 (21.9%)	0.803
CFR in 1 month in centers, N (%)	1369 (38.6%)	563 (37.7%)	806 (39.1%)	0.570
CFR in 1 month in secondary institutions, N (%)	1322 (35.9%)	611 (34.8%)	711 (37.0%)	0.345
CFR in 6 months in centers, N (%)	1736 (48.9%)	709 (47.5%)	1027 (50.0%)	0.416
CFR in 6 months in secondary institutions, N (%)	1753 (47.6%)	813 (46.3%)	940 (48.9%)	0.351

* for comparison of 2004-2006 and 2007-2010 periods

According to the multivariate statistical evaluation, sex was not a CFR influencing prognostic factor for any survival interval, but the higher age proved to be risk factor for each CFR studied. Neither the level of first admitting institution nor the time period of care had any significant influence on CFRs.

4.2. Risk Factors of External Ventricular Drain Infection: Proposing a Model for Future Studies

4.2.1. Classification of risk factors

Out of the 20 articles selected for analysis, three studies reported no significant association between the risk factors evaluated and EVD infection after multivariate analysis. Altogether 15 risk factors (10 patient-related and 5 catheter-related) were identified by our review (**Table 2**). Risk factors found by most investigations were neurosurgical operation and duration of catheterization.

4.2.2. Patients' factors

Age was measured in years and found a 4% - 5.1% increase in risk of EVD infection per annum respectively. Females [P-value: 0.02] were three times as likely to be infected as males.

Age & sex interaction was identified as a risk factor for EVD infection. Female patients were 6 times likely to have an EVD infection than male patients (23.7% vs 3.1%, $p < 0.003$).

The EVD infection rates were higher in patients who had a *coinfection* than in patients who did not. *Diagnosis* was identified as a risk factor with a high prevalence among the patient factors with significant influence on the incidence of ventricular catheter infection. *Cerebrospinal fluid (CSF) leakage* at the site of insertion as a risk factor and that among the infected patients, most of the catheter infection was as result of the colonization at the site of catheter insertion.

Increased frequency of CSF sampling is a risk factor to EVD infection. CSF was not always sampled according to the institution's protocol that had been set which inevitably increased the frequency of catheter manipulation and consequently the risk of infection. *Intracranial pressure (ICP) above 20 mmHg* is a risk factor for ventricular catheter infection but they mention also the alternate explanation for their observation, that patients with high ICP may need ventricular catheter for longer periods which predisposes them to infection.

Patients with one or more *neurosurgical procedures* were at a significantly higher risk for infection which may be due to immunosuppression or trauma associated with surgical procedures.

There is a significant correlation between *CSF glucose levels drawn immediately after EVD placement* associating less than 50% of serum glucose and subsequent risk of infection.

Table 2 Identified risk factors of extra-ventricular drain infections according to the published results from 1984.

Risk Factors	Arabi 2005	Bari 2017	Bota 2005	Camacho 2011	Flibotte 2004	Gozal 2014	Hagel 2014	Hoefnagel 2008	Holloway 1996	Kirmani 2015	Lo 2007	Mayhall 1984	Mounier 2015	Omar 2010	Paramore 1994	Park 2004	Peter 2016	Pople 2012	Rebuck 2000	Wright 2013	**Sum sign.**
Patient factors/Sample size	84	256	638	119	311	498	218	228	584	130	199	172	101	87	161	595	100	434	215	144	
Sex		NS	NS	NS	NS		NS			NS	X			NS		NS				NS	**1**
Age		NS	NS		X		NS			NS						NS	NS	NS		X	**2**
Age & sex interaction																				X	**1**
Co-infection			X						X	X			X						NS		**4**
CSF leakage										NS			X			NS			NS		**1**
Neurosurgical operation			X				NS		X	X		X		X			X				**6**
CSF sampling frequency								X													**1**
ICP > 20mmHg												X							NS		**1**
Diagnosis			X		NS		NS		X			X				NS	NS	NS			**3**
Reduced CSF glucose						X															**1**
Catheter factors																					
Multiple catheters	X	NS							NS		X						X		NS		**3**
Catheter insertion outside the hospital	NS															X					**1**
Duration of catheterization	NS			X	X		NS	X			NS	X	NS	X	X		X	X	NS		**8**
Catheter type							NS											NS	NS	X	**1**
Irrigation												X									**1**
Number of identified risk factors	**1**	**_**	**3**	**1**	**2**	**1**	**_**	**2**	**3**	**2**	**2**	**5**	**2**	**2**	**1**	**1**	**2**	**1**	**_**	**3**	

X – Factors investigated and found to be significant

NS – Factors investigated but found to be non-significant

4.2.3. Catheter factors

In the study carried out by Wright et al, two *types of catheters* (standard and antibiotic coated) were used. They reported infection rate as 23.5% for standard catheters and as 4.3% for antibiotic coated catheters. This represents a risk ratio of 0.18 and an absolute risk reduction of 19.2% after changing from standard catheter to antibiotic coated catheter.

Catheter insertion outside the study center had a higher risk of infection than catheter insertion in the study center. On the other hand, the location of catheter insertion (OR/ICU/ED) within the study center did not significantly influence the infection rate of patient with catheters inserted in the study center.

Some authors suggest that the longer *duration of catheterization* may cause microbial infection of the catheter while there is another opinion that the longer duration of catheterization is a consequence of the catheter infection rather than the cause.

Infection rate was higher in patients who received *multiple catheters* than in patients who did not. Infected patients used almost twice the amount of ventricular catheters as their uninfected counterparts.

Irrigation was identified as a risk factor for EVD infection and that infections are likely introduced into the ventricles by retrograde movement of microbes due the manipulation of the catheter system.

4.3. Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting with Mild Head Injury to Emergency Departments: A Living Systematic Review and Meta-Analysis

4.3.1. Description of studies

Our search strategy identified a total of 7260 citations. Removal of duplicates resulted in 5567 distinct citations, of which 90 full-text articles were assessed for eligibility, and 26 articles were included in the systematic review. The total number of patients with TBI in the included studies was 8127, ranging from 50 to 1560 per study (median 170, interquartile range 104-258). Of those, 865 had positive CT scans with an average prevalence of 17% (median 13%) (range 5% to 51%).

The reported mean or median age of the included patients ranged from 32 to 83 years with ten studies including children and/or adolescents (patient age <18yrs). The total subject pool was largely male (median 63% across the studies), with the exception of the study by Thaler et al, which comprised 68.7% of females. Most of the studies defined specific timeframe from injury to blood draw as an inclusion criterion, with the majority of the samples collected within 6 hours of injury (16 studies) and with mean or median time ranging from 24.3 minutes to 5 hours.

A single marker was evaluated in most of the studies (n= 21), while 1 study simultaneously assessed 3 markers. Of the eligible studies, 22 reported data on S100B (total number of TBI patients 7754), 4 on GFAP (total number of TBI patients 783), 3 on NSE (total number of TBI patients 314), and 2 on UCH-L1 (total number of TBI patients 347). Fewer data were available for

tau (1 study which included only 50 patients), while we found no studies evaluating neuro-filament proteins that met our inclusion criteria.

4.3.2. S100 calcium binding protein B (S100 β)

The accuracy of S100B for detecting intracranial lesions on CT scan was evaluated in 22 studies (7754 patients). The individual sensitivities and the specificities were between 72% and 100% and between 5% and 77%, respectively. All but six of the included studies used the same cut-off (0.10-0.11μg/L), which represents the 95th percentile of a healthy reference population and is conventionally considered to discriminate between physiological from pathophysiological serum concentrations. Seven studies reported multiple cut-offs.

In terms of the assays/platforms used, most of the studies (13/22) used an automated electrochemiluminescence immunoassay (ECLIA) on an Elecsys® analyzer (Roche Diagnostics) while one used the Cobas 6000 analyzer (Roche Diagnostics). There were four studies conducted using an automated immunoluminometric assay (ILMA) on a Liaison® analyzer (Diasorin), and one on LIA®-mat (Sangtec® 100); one study used a radioimmunoassay (Sangtec), and one an ELISA platform (Banyan Biomarkers, Inc.). In one study, the analytical performance of the two automated immunoassays (i.e. Diasorin and Roche Diagnostics assays) was compared and, though, not interchangeable, the two methods strongly correlated and appeared usable in a similar manner.

4.3.2.1. Performance of S100 β at 0.10 – 0.11 μg/L cut-off value

To obtain clinically relevant estimates of the performance of S100B, we pooled the results from the 16 studies using the cut-off value of 0.10-0.11μg/L. The individual sensitivities and the specificities for each study included in this meta-analysis were between 72% and 100% and between 5% and 77%, respectively. The following summary estimates were obtained: sensitivity 96% (95% CI 92% to 98%), specificity 31% (95% CI 27% to 36%), positive likelihood ratio 1.4 (1.3 to 1.5) and negative likelihood ratio 0.12 (0.06 to 0.25).

4.3.3.2. Quality of evidence of S100 β

The quality of the evidence for the use of blood S100B levels to diagnose brain injury as assessed by CT scan in patients with mild TBI was moderate.

4.3.4. Glial Fibrillary Acidic Protein

The individual sensitivities were between 67% and 100% while the specificities were between 0% and 89%. Sensitivities were sufficiently homogenous while specificities were clearly heterogeneous. The thresholds used, ranging from 0 ng/ml to 0.6ng/ml, were not pre-specified and were determined from ROC analyses.

4.3.5. Neuron Specific Enolase

The accuracy of NSE for discriminating between TBI patients with intracranial lesions on CT scanning from those without lesions was evaluated in 3 studies (314 patients). The sensitivities

were between 56% and 100% while the specificities were between 7% and 77%. The studies reported a considerable variation in the threshold adopted, ranging from 9-14.7 μg/L.

4.3.6. Ubiquitin C-terminal hydrolase-L1

The accuracy of the initial circulating UCH-L1 levels for detection of intracranial lesion on CT was evaluated in two very recent studies (96 and 251 patients respectively) including both mild to moderate adult TBI patients (GCS 9-15). The 2 studies yielded the same sensitivity of 100% (95% CI 88 to 100) and specificities of 21% (95% CI 12 to 32) and 39% (95% CI 33 to 46). They reported similar thresholds (0.029 to 0.04ng/ml) and used the same assay.

4.3.7. Tau

The accuracy of circulating tau (cleaved tau [C-tau]) for diagnosis of CT abnormalities was evaluated only in one small study (50 patients). The sensitivity was 50% while the specificity was 75%. Among the 10 patients with abnormal findings on CT enrolled in this study, 5 (50%) had no detectable C-tau levels.

5. DISCUSSION

5.1. Effectiveness of Traumatic Brain Injury Management Guideline Introduction in Hungary

Our results demonstrated a steady, high case fatality in the Hungarian TBI population undergoing EVD installation, and "no effect" of the introduction of scientific evidence-based practice guidelines in 2006 was revealed. Though, the guideline introduction coincided with moderate increase of centralization. The unreduced CFR in Hungary suggested that the existence of guidelines *"per se"* will not result in outcome improvement and additional measures (audit of care, enforcement of guideline compliance) should also be introduced.

In Hungary, the combined CFRs for both sexes at six months were highest at age group 95 (with CFR of 88.5 %). A similar trend of high CFR in the elderly was reported in other European countries and the USA. The similarity between published articles and our study observed age dependence of CFR shows that our design is reliable in dealing with the time trend of CFR.

Like in Hungary, TBI guidelines were introduced in other European countries and in the U.S. many years ago but in most of these countries, there is a long term tradition of external quality management in clinical care. Further, if there is negligence in medical practice, it can result in lawsuit and also there is competition between the medical institutions. These factors establish the guideline adherence which varies in countries remarkably (between 18- 100%), but contributes to significant reduction in mortality.

5.2. Risk Factors of External Ventricular Drain Infection: Proposing a Model for Future Studies

The published measures of associations reflect both the strength of the risk factors and the confounding effects of factors that were not included in the model but were associated with the risk factors included in the studied models. Therefore, the relative importance of a risk factor cannot be evaluated by the published models. The whole set of suspected risk factors need to be included in the model which will be tested in clinical practice in order to determine the risk factors with their strength and clinical importance.

Age, sex, CSF leakage, catheter type and diagnosis were identified by more studies as not significantly associated with EVD infection than studies that did. Duration of catheterization, co-infection, and neurosurgical operation were found by more studies to be associated with EVD infection than a few studies that did not. Catheter insertion outside the hospital, multiple catheters and ICP > 20mmHg were found to be either associated with EVD infection or not by equal number of studies.

The varying results from the reviewed studies are possibly due to non-standardized research procedures (i.e. some risk factors were selectively analyzed while some risk factors were omitted, resulting in a possible causal or coincidental relationship or the lack thereof between EVD infection and these risk factors). Some of the factors presented in this review for later research may only be confounding factors without direct influence on ventricular catheter infection occurrence (e.g. the association between gender and drain infection; far more males were involved in severe injuries whereas females appeared to be a predictive factor).

5.3. Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting with Mild Head Injury to Emergency Departments: A Living Systematic Review and Meta-Analysis

S100B

Our findings demonstrate the clinical utility of S100B for the intended use of allowing physicians to be more selective in their use of CT without compromising care of patients with mild TBI. More specifically, the 16 studies applying the same pre-specified cutoff of 0.10-0.11μg/L yielded a pooled sensitivity of 96% and specificities of 31%.

Reliability and reproducibility of S100B results also requires a critical consideration of the comparability and potential variability in biomarker measurements when using assays from different manufacturers. We found the adoption of a relatively uniform and standardized approach for S100B determination, with fourteen studies using the ECLIA Elecsys® Roche and 2 studies using the ILMA LIA-mat Sangtec 100.

Our review showed that the results across S100B studies using the pre-specified cut-off were consistent in terms of sensitivities and specificities.

Investigations from multiple research groups provided evidence that a series of factors other than the brain injury may influence levels of biomarkers in the circulation and, therefore, the diagnostic accuracies. Such factors encompass biomarker characteristics such as molecular weight; injury-specific release mechanisms and clearance, patient features including presence of extracranial injuries or polytrauma, intoxication, location of the injury, and even genetic, pre-analytical and laboratory-dependent procedures including all steps from management of equipment to execution of assays manufacturing processes; and post-analytical data handling.

Clinical application of S100B implies that choosing the right assessment time point (time between injury and sampling) is an integral part of the test. Based on the results of S100B kinetics studies, guidelines have specifically indicated a time window within 3 to 6 hours post-injury for S100B to detect intracranial lesions. A recent study supported a 3-hour window for safe rule-out of acute intracranial lesion in clinical practice showing that a second blood sampling 3 hours after the first one is not informative and resulted in a non-trivial loss of sensitivity of about 6% (eight patients with positive CT would have been missed). The results of our study expand and corroborate those from previous systematic reviews and meta-analyses and confirm that the implementation of S100B might allow a reduction of the number of CT scans by approximately 30%. These considerations also have broad financial implications for healthcare costs. However, none of the studies in our review explored the cost effectiveness of the use of biomarkers, and the few economic studies and data in the literature are controversial.

GFAP

In the meta-analysis reported here, we included four studies, in which diagnostic accuracy of GFAP ranged from sensitivities of 67% to 100% and specificities from 0% to 100%. While promising, these results must be approached with caution since the studies included patients with severe and moderate TBI not representative of the target population of the test (the median prevalence of abnormal CT findings across the studies was 22%) and thresholds were not pre-specified. For diagnostic validation, it will be fundamental to establish reliable and valid thresholds. Also, GFAP needs be tested in larger clinical studies with a focus on the *intended use*.

NSE and UCH-L1

The diagnostic value of NSE remains uncertain, with studies showing remarkable variations and inconsistency. In contrast, the accuracy of UCH-L1 for detecting intracranial lesions on CT scan was evaluated in 2 studies which yielded an optimal sensitivity (100%) but modest specificities (21% to 39%). Hence, further studies are required to confirm the reproducibility of these findings and to determine clinical utility in daily bedside care.

Tau and Neurofilament Proteins

There is insufficient evidence to support the clinical validity of initial circulating c-Tau or Neurofilament protein concentrations for the management of patients with mild TBI.

6. SUMMARY OF THESES

1. Traumatic Brain Injury management guideline in Hungary

The total CFR at one week, one month and six month post injury were 21.9%, 36.8% and 48.0% respectively. The centers and the secondary institutions specific CFR showed no change when the before and after guideline introduction periods were compared. Sex was not a CFR influencing prognostic factor for any survival interval. Higher age proved to be risk factor for each CFR period studied. Neither the level of first admitting institution nor the time period of care had any significant influence on CFRs. The guideline introduction without supportive financing and external auditing cannot achieve the quality improvement in countries having similar legal environment and economic development like Hungary.

2. Risk factors of External Ventricular Drain infection

The outcome of our review is a recommendation that former approaches should be replaced by a design able to determine the clinical importance of factors related to EVD infection and able to prepare a formal quantitative meta-analysis. According to our results, the set of the parameters in the study model should be used at least – besides other factors depending on the tested hypothesis in the etiology of EVD infection. These variables are: age, sex, age & sex interactions, coinfection, catheter insertion outside the hospital, catheter type, CSF leakage, CSF sampling frequency, diagnosis, duration of catheterization, ICP > 20 mmHg, irrigation, multiple catheter, neurosurgical operation, and reduced CSF glucose at insertion of ventricular catheter.

7. BIBLIOGRAPHY

1. Articles grounding the thesis

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2. Presentation and poster grounding the thesis

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3. Article not grounding the thesis

Mondello S, **Sorinola A,** Czeiter E, Vámos Z, Amrein K, Synnot A, Donoghue E, Sándor J, Wang KKW, Diaz-Arrastia R, Steyerberg EW, Menon DK, Maas AIR, Buki A. Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting to Emergency Departments with Mild Brain Injury: A Living Systematic Review and Meta-Analysis. J Neurotrauma. 2018 Jul 2. doi: 10.1089/neu.2017.5182. *(in press)*

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Harmonization and Systemic Approach to the Sophisticated Use of Biomarkers in Field of Traumatic Brain Injury (TBI). Mondello S, **Sorinola A,** Czeiter E, Vámos Z, Amrein K, Synnot A, Donoghue EL, Sándor J, Wang KKW, Diaz-Arrastia R, Steyerberg EW, Menon D, Maas A, Buki A. 7th CNS (Pannonian Symposium on CNS Injury), 30th August – 1st of September 2017, Pécs, Hungary (Presentation)

Sum IF.:
Articles grounding the thesis: 4.283
Article not grounding the thesis: 5.002
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