Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients

By

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Abstract

Severe traumatic brain injury (TBI) is a significant cause of death and disability around the world. Management based on Brain Trauma Foundation (BTF) guidelines is widely accepted and thought to improve outcomes. The objectives of this thesis are to provide an overview of adherence to BTF guidelines as a whole and specifically for intracranial pressure (ICP) monitoring, to explore which factors influence adherence and to study the effects of guideline-based management on outcomes. Firstly, we conducted a search of relevant electronic bibliographic databases. Twenty articles met inclusion/exclusion criteria out of 666 papers screened. All were cohort studies. Wide variation of adherence to BTF guidelines was observed with a median of 60.7% (range 0-100%). The lowest median adherence was observed with surgical management (14%), while the highest was observed with oxygenation (100%), steroid (97.8%) and blood pressure recommendation (92.3%). Variability was primarily explained by the variation in strength of evidence of each recommendation. Treating patients with higher severity of injury and treatment in a level 1 trauma center positively influenced adherence. Adherence was not associated with improved crude mortality [OR: 0.82, (95% CI: 0.60-1.12) or adjusted mortality [OR: 0.95, (95% CI: 0.88-1.02). However, beneficial effects were observed in subgroup analysis through implementation of a guidelines-based protocol in terms of in-hospital crude mortality as well as adherence to specific recommendations; nutrition, Systolic Blood Pressure (SBP), oxygen (O2) and cerebral perfusion threshold, but low level of evidence and study heterogeneity limit the generalizability of the results. Secondly, We conducted a retrospective cohort study of patients with severe blunt TBI registered in Alberta Trauma Registry between 2000 to 2013. Patients who died in the emergency department and patients from provinces other than Alberta were excluded. Outcomes were adherence rate with 3rd edition

of the BTF guidelines, overall in-hospital mortality, and length of stay in hospital and intensive care unit (ICU). In this cohort, the BTF guideline adherence rate for ICP monitoring was 30%. Adherence rates increased with younger age, high ISS score, lower Glasgow Coma Score (GCS), abnormal CT head, craniotomy, admission to neurocritical care unit, and absence of alcohol intoxication or cardiac arrest. After adjusting for potential confounders adherence was associated with higher mortality (OR 2.01, 95% CI: 1.56-2.59, $p<0.001$) and increase ICU and hospital length of stay ($p<0.001$). Overall, the literature indicate that adherence to BTF guidelines is variable and further study is required to strengthen the current evidence and identify factors related to adherence with guidelines include professional prospective. Adherence to BTF guidelines for ICP monitoring in severe TBI in Alberta was low, varied across centers and was associated with higher mortality and morbidity. ICP insertion may be an indicator of TBI severity, alternatively the current BTF criteria for ICP monitoring may fail to identify patients likely to benefit. Further study is required to refine the indications of ICP monitoring in TBI patients.

Preface

This thesis is an original work by Yahya Khormi. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Compliance with brain trauma foundation guidelines for intracranial pressure monitoring in severe traumatic brain injury and its effect on outcome: A population based study", No. Pro00054084, February 5, 2015.

A version of Chapter 2 and 3 of this thesis are being submitted for publication in Journal of Neurotrauma and Neurosurgery Journal subsequently.

Yahya Khormi was responsible for study design and data analyses as well as manuscript composition for the above studies. A. Senthilselvan provided guidance to the data analyses and manuscript revision. D. Zygun and C. O'kelly provided guidance in study design and manuscript revision. I. Gosadi was the second researcher in the systematic review; he provided independently study selection and data extraction. S. Campbell provided guidance to the search strategy.

Dedication

This dissertation is dedicated to my mother Maryam Zukan, my father Hadi Khormi for the overwhelming support, whom always believes in me, encourages me and supports me throughout my studies. I would like to thank my wife Maryam Bahkali for her unlimited help and support. I also thank my daughters Layan and Lana for all the happiness they brought to me.

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List of Abbreviations

BTF: Brain Trauma Foundation

TBI: Traumatic brain injury

CINAHL: Cumulative Index to Nursing and Allied Health Literature

CENTRAL: Cochrane Central Register of Controlled Trials

RCT: Randomized controlled trial

AANS: American Association of Neurological Surgeons

CNS: Congress of Neurological Surgeons

GCS: Glasgow Coma Scale

MOOSE: Meta-analysis of observational studies in epidemiology

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

EBM: Evidence Based Medicine

ACP: American College of Physicians

NOS: Newcastle-Ottawa Scale

STROBE: Strengthening the Reporting of Observational studies in Epidemiology

TREND: Transparent Reporting of Evaluations with Nonrandomized Designs

ISS: Injury Severity Score

CT: Computer Tomography

CPR: Cardiopulmonary resuscitation

ICU: intensive care unit

SNP: specialized neurological program within ICU

LOS: Length of Stay

SBP: Systolic Blood Pressure

Chapter 1

Introduction

1.1 Background of the problem

Traumatic brain injury (TBI) is a leading cause of death and disability around the world. In the US, the prevalence of TBI is estimated to be 2% in the general population[1] and the reported mortality rate is 18.4 per 100,000 persons with an annual average of 53,014 deaths[2]. A Canadian Institute for Health Information (CIHI) report indicated that there were 16,811 hospitalizations annually for TBI with 1,368 (8%) related deaths[3]. Among residents in the Calgary Heath Region in Alberta, Canada, the annual incidence of severe TBI was 11.4 per 100,000 persons with a mortality rate of 5.1 per 100,000 persons per year[4].

Clinical practice guidelines are developed to improve quality of care, to decrease discrepancy in practice and to ensure that evidence is followed[5]. Mostly, these guidelines are developed and distributed by well-recognized organizations. A guideline consists of systematically developed recommendations to guide practitioners in choosing the appropriate health care decision for specific clinical circumstance[6]. A guideline recommendation is defined as "any statement that promotes or advocates a particular course of action in clinical care"[7]. In the treatment of TBI, guidelines are proposed to be an important aspect of patient management.

There are many published guidelines in management of TBI, released from different countries and targeting different aspects of TBI management, including but not limited to, pre-hospital,

emergency department, in-hospital, intensive care unit, surgical management and indication for computed tomography (CAT) scan of the head[8-12].

Internationally, Brain Trauma Foundation (BTF) guidelines are widely disseminated. They have been translated into over 15 different languages and applied in Europe, South America, and parts of China. The BTF maintains and revises several TBI Guidelines on an approximate 5- year cycle, including: Guidelines for Prehospital Management of Traumatic Brain Injury, Guidelines for the Management of Severe Traumatic Brain Injury, Guidelines for the Surgical Management of Traumatic Brain Injury, Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents, Guidelines for the Field Management of Combat Related Head Trauma and Early Indicators of Prognosis of Severe Traumatic Brain Injury. These guidelines are developed and maintained through a collaborative agreement with the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), and in collaboration with the AANS/CNS Joint Section on Neurotrauma and Critical Care, European Brain Injury Consortium and other stakeholders in TBI patient outcome[13].

Studies suggest that implementation and strict adherence to BTF guidelines results in improvement in neurological outcomes and reduction in mortality from severe traumatic brain injury [14,15]. However, there is still significant variability and inconsistency in management of traumatic brain injury patients[16,17].

1.2 Study objectives

The first objective is to study the practitioners' adherence to the BTF guidelines for the management of severe TBI. The second objective is to explore which factors influence adherence to the guidelines. Identification of these factors may provide valuable insight into the development of strategies to increase the adherence. The third objective is to study the outcome of guideline-based management in comparison to non-guideline based management to resolve some uncertainty about the effect of these guidelines.

1.3 Thesis submitted for partial fulfillment of MSc

This thesis begins with a systematic review and meta analysis of Adherence to BTF guidelines for management of TBI patients and its effect on outcomes (Chapter 2), which address all each of the thesis objectives outlines in section 1.2.

This is followed by a population based cohort study (Chapters 3) to study the adherence in Alberta to the BTF guidelines for the indication for ICP monitoring in severe TBI patients. The final chapter (Chapter 4) provides a summary of the entirety of the thesis and concluding remarks.

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Chapter 2

Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients and its effect on outcomes: systematic review and meta-analysis

2.1 Abstract

Traumatic brain injury (TBI) management based on Brain Trauma Foundation (BTF) guidelines is widely accepted and thought to improve outcome. The objectives of this study are to provide an overview of adherence to BTF guidelines, to explore which factors influence adherence and to study the effects of guideline-based management on outcomes. We conducted a search of relevant electronic bibliographic databases. Twenty articles met inclusion/exclusion criteria out of 666 papers screened. All were cohort studies. Wide variation of adherence to BTF guidelines was observed with a median of 60.7% (range 0-100%). The lowest median adherence was observed with surgical management (14%), while the highest was observed with oxygenation (100%), steroid (97.8%) and blood pressure recommendation (92.3%). Variability was primarily explained by the variation in strength of evidence of each recommendation. Treating patients with higher severity of injury and treatment in a level 1 trauma center positively influenced adherence. Adherence was not associated with improved crude mortality [OR: 0.82 (95% CI: 0.60-1.12)] or adjusted mortality [OR: 0.95 (95% CI: 0.88-1.02)]. However, beneficial effects were observed in subgroup analysis through implementation of a guidelines-based protocol in terms of in-hospital crude mortality as well as adherence to specific recommendations; nutrition, Systolic Blood Pressure (SBP), oxygen (O2) and cerebral perfusion threshold. Low level of evidence and study heterogeneity limit the generalizability of the results. Overall, adherence to

BTF guidelines is variable and further study is required to strengthen the current evidence and identify factors related to adherence with guidelines include professional prospective.

2.2 Background

Guidelines for Management of Severe Traumatic Brain Injury address key topics useful for in-hospital medical management of severe TBI in adult patients with a Glasgow Coma Scale (GCS) score of 3–8. These include blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, intracranial pressure monitoring, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics and sedatives, nutrition, anti-seizure prophylaxis and hyperventilation through steroids use. These guidelines were published in 1995, 2000 and 2007 [1-3] with a fourth edition released in 2017 [4]. Guidelines for the Surgical Management of Traumatic Brain Injury address important issues in acute surgical management of TBI including: acute epidural and subdural hematomas, parenchymal mass lesions, depressed skull fractures through posterior fossa lesions, with focus on indications, technique and timing of surgery. These Guidelines were published in 2006 [5].

Studies suggest that implementation and strict adherence to BTF guidelines results in improvement in neurological outcomes and reduction in mortality from severe traumatic brain injury [6, 7] . However, there is still significant variability and inconsistency in management of traumatic brain injury patients [8,9] .

2.3 Objectives

The first objective of this study is to present a systematic review of practitioners' adherence to the BTF guidelines for the management of severe TBI. The second objective is to explore which factors influence adherence to the guidelines. The third objective is to study the outcome of guideline-based management in comparison to non-guideline based management to resolve some uncertainty about the effect of these guidelines.

2.4 Methods

2.4.1 Protocol and study overview

The methods of this systematic review and meta-analysis have been developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (MOOSE guidelines) [10] and the Meta-Analysis of Observational Studies in Epidemiology (PRISMA)[11] . We assembled a comprehensive database containing all published literature that addresses adherence to BTF guidelines in management of severe TBI. The goal of this study is to comprehensively and critically analyze the world's relevant literature in order to evaluate the utilization of BTF guidelines in clinical practice, study the factors influence guideline utilization and the impact of BTF recommendation on outcomes. This protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42015017794) (Appendix 1) and published in Systemic Review Journal "Adherence to Brain Trauma

Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta-analysis[12] (Appendix 2).

2.4.2 Selection criteria

Population

The population of interest was hospitalized adult patients of ages 18 years and over with TBI.

Outcome

The outcomes included adherence rate with BTF guidelines, factors influencing the adherence, and comparison of mortality and morbidity of traumatic brain injury in patients managed according to the BTF recommendation with patients managed differently.

Study design

Randomized controlled trials, cohort study, case-control study and case series.

2.4.3 Search strategy

The primary search strategy was developed by the primary investigator (YK) in collaboration with an expert searcher/librarian (SC). We searched the following electronic bibliographic databases: PROSPERO, Medline (OVID), EMBASE (OVID), EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews – ACP Journal Club, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Cochrane Central Register of Controlled

Trials, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, CINAHL Plus with Full Text, Proquest Dissertations and Theses Full-text, SCOPUS and Google Scholar, using both controlled vocabulary (eg: EMTREE and MeSH) and keywords to retrieve concepts including: (Brain Trauma Foundation) or (brain injur* and guideline* and adhere*). Searches were limited to adult patients in non-military settings. Animal studies were excluded. No other limits were applied (Appendix 3).

2.4.4 Study selection

Two investigators (YK and IG) independently screened all titles, abstracts and articles to identify studies addressing the adherence to BTF guidelines for in-hospital management of adult civilian patients of ages more than 17 years with TBI. We included a) in-hospital guidelines regarding blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, indications for intracranial pressure monitoring, intracranial pressure monitoring technology, intracranial pressure thresholds, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics, and sedatives, nutrition, antiseizure prophylaxis, hyperventilation and steroids and b) guidelines for surgical management for acute epidural and subdural hematomas, parenchymal lesions, posterior fossa mass lesions and depress cranial fractures.

Articles were included if they met the following criteria: 1) original research 2) randomized trials, cohort and case-control studies, and case series 3) reported adherence rate, factors

influencing adherence, point estimate and 95% confidence interval for mortality or morbidity of traumatic brain injury patients treated according to the BTF management guidelines in comparison to patients treated differently. We excluded: a) animal studies, b) studies with majority of pediatric patients, c) case reports, and non-original articles, d) studies that included fewer than ten patients, 5) studies addressing adherence to pre-hospital guidelines and e) studies focused on military/combat-related TBI. Studies related to pre-hospital management were excluded because failure to achieve target recommendation might be an indicator of severe injury. Studies focused on military/combat-related TBI were excluded because the results would not be generalizable to the study population of civilian patients with TBI. Inclusion disagreements were discussed and resolved by consensus or arbitration by other researchers (CO and DZ).

2.4.5 Data extraction

Two investigators (YK and IG) independently extracted data from eligible studies using a pre-designed and pilot-tested standardized electronic data extraction form. We extracted data on a) Publication details (year and language of publication, name of the publishing journal and country in which the study was conducted), b) type of study (RCT, cohort and case-control studies, case series), c) study temporality (prospective, retrospective) d) patient characteristics (age, sex, GCS, injury severity score), e) percentage adherence to BTF guidelines, and f) demographic and injury-related characteristics (elevated blood alcohol level, normal CT scan and planned neurosurgical intervention or other factors reported in the study) and f) outcomes including mortality or morbidity if they compared between patients treated according to the BTF

guidelines and patients treated differently. Discrepancies were discussed and resolved by consensus or arbitration by other researchers (CO and DZ).

2.4.6 Quality assessment

The quality of reporting of observational studies was assessed using a checklist, which is based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. Two researchers (YK and IG) addressed quality assessment of the included studies independently. Differences of opinion were resolved by a discussion with other researchers (CO and DZ).

2.4.7 Data synthesis

Narrative synthesis and quantitative meta-analysis were used. Synthesis was based on clustering the selected studies based on type of recommendation. Adherence to BTF based protocol was extracted as a separate category if the full description of the protocol and protocol adherence rate was reported. Data synthesis included description of studies characteristics (such as design, year and language of publication, publishing journal, country (mono-center/multicenter), study period, professionals studied for adherence, number of participants, median age, GCS, injury severity score and quality assessment measure). From each article (a) adherence percentages for each recommendation were extracted. In the case of a pre- and post-intervention design for evaluation of intervention (for example, introducing a protocol or teaching program), only the post-intervention percentages were extracted because we wanted to assess the current clinical

practice. The median percentage of adherence for each recommendation was calculated. Additionally, factors influencing adherence were extracted when a statistically significant relationship between the factor and adherence was demonstrated in the article. Outcome measures were extracted if the point estimate and 95% confidence interval were reported.

Calculation of pooled estimates of mortality among TBI patients managed based on BTF guidelines and management strategy.

As the majority of the studies used odds ratio as measure of association, odds ratios were used as the common measure of association. When only relative risk was reported in a selected study, we transformed it into an odds ratio using the method described by Deeks and Altman[13]. We conducted stratified analyses of pooled estimate of mortality by type of recommendation, outcome (for example; in-hospital mortality, intensive care unit mortality, 30 days mortality or 6 months mortality) as well as the country (North America, Non-North American studies). We examined the heterogeneity among all included studies and separately among the subgroups by using the Cochrane Q and I2 statistics[14]. In the presence of heterogeneity, random effects models were used (rather than fixed effects models) to obtain pooled effect estimates across studies, to account for the expected variability beyond the chance[15]. Publication bias was assessed using funnel plot and methods described by Begg and Egger[16, 17]. Meta-analysis was performed using Comprehensive Meta Analysis software and supplemented with Stata Statistical Software version 13.1. (StataCorp LP, College Station, TX, USA).

All data was extracted by two independent investigators (YK, IG). To assess inter- rater reliability, the percent agreement was calculated on adherence percentage for number of guideline recommendations by the third investigator (AS).

2.5 Results

2.5.1 Study selection

In total, 666 studies were identified. Initial title screening identified 228 ineligible studies, which were excluded. Secondly, 438 abstracts were evaluated based on inclusion/exclusion criteria and 377 studies were excluded. The full text of the remaining 61 studies was subjected to detailed evaluation. Based on inclusion/exclusion criteria, 41studies were excluded and 20 studies were included in the analysis (Figure 2.1), authors of 24 abstracts presented in a conference were emailed; we only received one response indicating that their result has not been finalized. The overall inter-rater agreement between the two investigators was moderate (kappa statistic= 0.402).

2.5.2 Description of the studies

The studies that were included were observational (cohort studies) and are summarized in Table 1. The majority of the studies included were retrospective cohort studies. Only 3 studies collected data prospectively and one study utilized both prospective and retrospective approaches to collect the data. The majority of the studies were conducted in multi-center settings while 6 studies were based on a single center. The studies included were conducted in North America, (n=13; 12 in USA and one in Canada), Europe (n= 5) and Asia (n=2 with one from Taiwan) and Middle East (n=1, from Saudi Arabia). Table 2 summarizes the recommendations assessed, level of evidence, and the number of studies that addressed each recommendation.

2.5.3 Adherence to BTF Guidelines for management of TBI

Eighteen studies reported the adherence to the BTF guidelines. These studies mostly assessed the adherence of neurosurgeon and intensivist [18-35]. Adherence by critical care nurses to the recommendation to normothermia was assessed in one study[29] .

Agreement between investigators was high (93.8% for guideline adherence percentage). The median percentage of adherence to the BTF guidelines for management of TBI was 60.7% ranging from 0-100%. Upon investigating the adherence level according to the location of the study, there was no significant difference in adherence level between the studies conducted in North America (59.2%) and those conducted in other countries (67.1%). The adherence level in North American centers had less variability in comparison to studies conducted in other countries, ranging between 13.5% and 55.9% and 0-100% respectively. Overall adherence to BTF guidelines was 40% in 1997. An increase in the adherence to the guidelines was observed, reaching 60% in 2002. Nonetheless, it seems that no further improvement in the median adherence was observed since 2002.

2.5.3.1 Adherence to BTF guidelines for Medical Management of severe TBI

Eighteen studies reported the adherence for 10 different medical management of severe TBI as illustrated in Table 2. The most commonly studied recommendation for medical management of severe TBI was indication for intracranial pressure ICP monitoring. This was reported in 15 of

the studies included. The remaining recommendations were reported less frequently as follows: cerebral perfusion threshold, blood pressure and oxygenation, steroid use, ICP threshold, nutrition, anti-seizure prophylaxis and hyperventilation.

Overall median percentage of adherence was 66.2%, varying from 0-100%. Figure 2.2 demonstrates the median percentage adherence and interquartile range of different recommendations. Smaller median adherence percentages (31% and 40.1%) were reported in two studies for normothermia and CPT recommendations whereas higher median adherence percentages (100%, 97.8%, 92.3%) were reported in three studies with recommendations of oxygenation, steroid and blood pressure, respectively. These were followed by the adherence to nutrition, ICP threshold and hyperventilation, which were, 79% 78.4%, and 70%, respectively. Moderate adherences were reported in two studies for anti-seizure prophylaxis and indication for (ICP) recommendation, which were 58.1% and 46.4% respectively. One study reported the adherence for 6 different guidelines including the indication for ICP monitoring, BP and CPT, which was 73%. Another study reported the adherence to oxygenation and blood pressure recommendation combined, which was 79.2%.

2.5.3.2 Adherence to BTF guidelines for surgical management of severe TBI

Only one study[24] assessed the adherence to the surgical recommendation for management of acute subdural (ASD) hematoma and intraparynchemal lesion (IPL). In this study, the percentages of adherence to the recommendation for management of ASD hematoma and IPL were 13% and 14% respectively.

2.5.3.3 Adherence to BTF guidelines organized based on the level of evidence

Reported guidelines were organized based on the level of evidence in Table 2 to examine whether level of evidence could influence the adherence level to the BTF guidelines. We observed that recommendations with the higher the level of evidence were associated with the higher median percentage of adherence, 96.9%, 79%, 32% and 13.5% for level 1, 2, 3 and unclassified recommendations, respectively,

2.5.4 Mortality

2.5.4.1 Crude Mortality

Eight studies included information on crude mortality; overall, the studies were heterogeneous (I^2= 90.13 %, df = 7, p <0.001). Studies were grouped by timing of mortality: in-hospital mortality (n=4), six-month mortality (n=1), and two-week mortality (n=3). Heterogeneity was not significant when restricting to studies reporting in-hospital mortality (I^2= 25.80%, df = 3, p=0.26). Because of this heterogeneity, a random-effects model was used in all the analyses. Overall pooled OR of mortality due to TBI in guideline-based management compared to non-guideline based management was 0.82 (p = 0.21) indicating a non-significant association between implementation of BTF guideline and mortality. As shown in Figure 2.4, subgroup analysis showed the same result in 2-week and 6-months mortality (pooled OR: 0.86; 95% CI: 0.35–2.09, p =0.74) and (pooled OR: 1.60; 95% CI: 0.98–2.61; p = 0.06), respectively. However,

in-hospital mortality decreased among adherent group in comparison to the non-adherent group (pooled OR: 0.47; 95% CI: 0.30–0.73; p =0.001).

Studies were also grouped by type of recommendation with five studies assessing mortality for adherence to indication for ICP monitoring recommendation, two studies addressing crude mortality of pre and post implementation of BTF based protocol and one study assessing the anti-seizure prophylaxis. Heterogeneity was not significant when restricting to pre and post BTF guidelines based protocol implementation (I^2= 60.85%, df = 1, p=0.11). Neither adherence to indication for ICP monitoring nor anti-seizure prophylaxis recommendation was shown to have effect on mortality (pooled OR: 0.85; 95% CI: 0.44–1.62; p = 0.62) and (pooled OR: 1.16; 95% CI: 0.25–5.49; p = 0.85), respectively. As shown in Figure 2.5, implementation of BTF based protocol might decrease the mortality (pooled OR: 0.41; 95% CI 0.17–1.00; p =0.051).
Six of the studies conducted in North America showed no evidence of adherence affecting mortality, similar to the two studies conducted in other regions (Figure 2.6).

2.5.4.2 Adjusted Mortality

Seven studies included information on adjusted mortality for 13 recommendations. Overall, the studies were heterogeneous (I^2= 83.39 %, df = 7, p <0.001). Studies were grouped by timing of mortality; in-hospital mortality (n=5), six-month mortality (n=1), and two-week mortality (n=1). Heterogeneity was not eliminated by restricting the studies only to ICU or in-hospital mortality (I^2= 75.05%, df = 5, p=001 and I^2= 91.43%, df = 4, p=<001). In the analysis using a random-effects model, overall pooled OR of mortality due to TBI in guideline-based management in

comparison to non-guideline based management was 0.95 ranging (p-value = 0.15). Implementation of BTF guideline was not associated with decreased adjusted mortality. As shown in Figure 2.7, subgroup analyses showed the same result in 2-week, 6-months, ICU and in-hospital mortality, p-value 0.05, 0.84, 0,32, and 0.12, respectively.

Studies were also grouped by type of recommendation with 6 studies addressing mortality with adherence to indication for ICP monitoring recommendation and the rest of the recommendations being addressed by one study each. Heterogeneity persisted among these groups. Adherence to indication for ICP monitoring was shown to have no association with adjusted mortality (pooled OR: 1.02; 95% CI: 0.72–1.46, p = 0.90). The beneficial effect on mortality was observed with adherence to nutrition, implementation of BTF guideline based protocol, SBP and O_2 and cerebral perfusion threshold, [OR and 95% CI: 0.03 (0.01-0.13), 0.45 (0.24-0.85), 0.80 (0.72-0.89) and 0.90 (0.82-0.99), respectively]. As shown in Figure 2.8, adherence to steroid, anti-seizure prophylaxis and ICP threshold recommendation did not show any effect on adjusted mortality [OR and 95% CI: 1.04 (0.97-1.12), 0.99 (0.92-1.07) and1.04 (0.91-1.19). respectively].

Five recommendations assessed in studies conducted in North America showed no evidence that adherence affect mortality, similar to the eight recommendations that were assessed in studies conducted in other regions (Figure 2.9).

2.5.5 Morbidity

Two studies included information on ICU LOS [18,36] , three studies included information on LOS in hospital [18,24, 36] , four studies included data on favorable and unfavorable outcome based on GOS [19,28,35,37] , one study reported the incidence of tracheostomies and duration of the ventilation[36]. Since the outcome measures were heterogeneous and number of studies were small, these outcomes were not be pooled.

2.5.5.1 Pre and Post guidelines based protocol implementation

Significant improvement of outcome with implementation of BTF guidelines based protocol was observed in one study[37] with the reported estimated odds ratio of good outcome (GOS) in comparison to poor outcome being 9.13 (95% CI: 3.25 25.67), after adjusting for age, gender, Injury Severity Score, GCS. Although results were not statistically significant in another study examined the effect of guidelines-based protocol implementation on number of patients needing tracheostomies, mechanical ventilation duration, ICU and hospital length of stay, adjusted for EVD placement and concomitant injuries of other systems[36].

2.5.5.2 Indication for ICP monitoring

Conflicting findings were reported on the effect on ICU and hospital length of stay on ICP monitoring. One study reported that patients treated based on BTF guidelines for ICP monitoring were associated with statistically significant shorter mean ICU and hospital stay by 6 and 7 days

respectively, p <0.001 and p = 0.001 respectively, adjusted for age, hypotension, head AIS, extremity AIS, presence of IPH or SAH on CT, partial thromboplastin time, early nutrition, and time of craniotomy[18]. Although the results of another study were not statistically significant, the percentage change in length of stay in hospital between patients treated based on BTF guideline for ICP monitoring compared with patients treated differently was 19.59% with 95% CI (-0.62%, 43.91%), after adjusting for age, sex, race/ethnicity, insurance status, mechanism of injury, presence of injuries to the chest or abdomen, injury severity (ISS), GCS, and first SBP on arrival and need for ICU and ventilator use[24]. For the effect on GOS, one study reported an estimated odds ratio of having unfavorable outcome (Glasgow Outcome Scale Extended 1–4) of 1.81 (95% CI:0.88–3.73) for patients treated based on BTF guidelines in comparison to patients treated differently after adjusting for baseline and clinical characteristics using propensity score [19]. Similarly, another study reported no significant effect of BTF guideline adherence on GOS outcome, (the OR favorable outcome (GOS 4 or 5) was 1 (0.92-1.09), adjusted for age, ISS and GCS)[28].

2.5.5.3 ICP threshold

For the effect on GOS, one study reported the odd ratio of favorable outcome (GOS 4 or 5) 1.02 (0.88-1.17) when comparing patients treated based on BTF guidelines for ICP threshold to patients treated differently, adjusted for age, ISS and GCS, its not statistically significant[28]. Another study result also was not statistically significant the reported OR of poor outcome (GOS 1-3): 0.33 (0.09-1.25) comparing patients treated based on BTF guideline to patients treated differently, adjusted for age[35].

2.5.5.4 Nutrition

Regarding the effect on hospital length of stay, one study showed patients treated based on BTF guideline for nutrition had a higher percentage change in length of stay in comparison to patients treated differently 103.77 with 95% CI: (51.42-174.18), adjusted for age, sex, race/ethnicity, insurance status, mechanism of injury, presence of injuries to the chest or abdomen, injury severity (ISS), GCS, and first SBP on arrival and need for ICU and ventilator use[24].

2.5.5.5 Blood pressure and oxygenation

Concerning the effect on GOS, one study showed a slightly more favorable outcome (GOS 4 or 5) in patient treated based on BTF guidelines of blood pressure and oxygenation in compared to patients treated differently, odd ratio of 1.18 with 95% CI: (1.04 - 1.34), adjusted for age, ISS and GCS[28].

2.5.5.6 Cerebral perfusion thresholds, steroids and antiseizure prophylaxis recommendation

One study did not show significant effect on GOS in comparing patients treated based on this individual recommendation and patients treated differently, adjusted for age, ISS and GCS, OR and 95% CI; 1.02 (0.93 - 1.11), 1.04 (0.96 - 1.12), 1.02 (0.95 - 1.1) respectively[28].

2.5.6 Influencing factors

Six studies addressed factors influencing adherence in the context of indication for ICP monitoring, blood pressure and cerebral perfusion pressure management. These factors were clustered in relation to patient characteristics: age, sex, severity of injury, clinical and radiological neurological status, systemic injury, management, and organization factors (Table 2.3).

Adherence to the indication for ICP monitoring was higher when treating younger patients, patients with severe neurological injury, and patients who underwent surgical treatment. Adherence was lower among patient whose neurological status improved within 24 hours, patients with GCS 3 on admission and coagulopathic patients.

Patients with lower SBP were less likely to be treated based on guidelines for ICP monitoring, despite the fact that the guidelines recommend ICP monitoring for these patients.

Adherence to BP and cerebral perfusion pressure management guidelines were higher when treating younger patients and patients with higher severity of neurological injury.

Findings related to adherence to recommendations concerning papillary abnormality contradictory. Biersteker et al., 2012 reported that the presence of more pupillary abnormalities increased the adherence level [19], whereas Farahvar et al., 2012[20] reported that more pupillary abnormality decreased the adherence to ICP monitoring.

Two studies reported that more abnormality in the CT increased adherence and normal CT scans decreased the adherence[18,19]. Shafi et al., reported the opposite, with a Marshal score equal to or less than 2 associated with increase adherence[31]. These controversies are most likely the result of not incorporating specific information on CT findings, and using different classifications for CT head findings.

As for organizational factors, treatment in a level 1 trauma center and higher economic status country positively influenced adherence, while lack of health insurance negatively influenced the adherence.

2.6 Methodological Quality

2.6.1 Quality of reporting

Out of the 20 studies, 9 studies presented the key elements of study design early in the paper; 19 studies described the setting, location and relevant dates including period of recruitment; 19 studies gave the eligibility criteria, source and method of selection; 17 studies gave method of assessment for each variable; 4 studies described the plan to address the potential source of bias; 8 studies explained how study size was determined; 17 studies described the statistical methods, including those used to control for confounding and described any methods used to examine the subgroup or interaction; 8 studies presented a flow diagram for participants; 17 studies adequately described their study population (include information on exposure and potential

confounders), 13 studies reported confounder-adjusted estimate and made clear which confounders were adjusted for, subgroup analysis or sensitivity analysis; 15 studies discussed limitation of their study; 13 studies discussed the external validity of the study; 8 studies listed the sources of funding. Other Items were reported by all studies. Tables 2.4a and 2.4b provides a more details of evaluation of methodological quality of reporting.

2.6.2 Publication Bias

Visual evaluations of funnel plots for studies investigating the crude mortality reveal no publication bias (Figure 2.10), confirmed by Egger regression (intercept -2.62, SE 2.67, p=0.36), and by Begg and Mazumdar rank correlation (Kendall's z-value: JI0, p=1.00).

Visual evaluations of funnel plots for studies examining the adjusted mortality reveal no publication bias (Figure 2.11), confirmed by Egger regression (intercept -1.37, SE 1.03, p= 0.21), and by Begg and Mazumdar rank correlation (Kendall's Z-value: 1.53, p=0.13).

2.7 Discussion

This systematic review is the first one to look at the adherence to BTF guidelines for management of severe TBI. It is designed to provide an overview of professionals' adherence to BTF guidelines, to explore factors influencing adherence to these guidelines, as well as to study the effect of adherence on outcomes. Eighteen articles reported adherence to medical

management recommendations, and only one small size study reported the adherence to surgical management recommendations.

Despite the urgency and life-threating nature of severe TBI, as well as the worldwide dissemination since 1996 of BTF guidelines in management of severe TBI, results show a wide variation in adherence even among the studies conducted in North America.

The adherence to recommendations related to steroids, oxygenation, and blood pressure were above 88%. Adherence to nutrition, ICP threshold and hyperventilation ranged from 70% to 79%. Moderate adherence was reported for antiseizure prophylaxis and indication for ICP recommendation, between 46 and 58%. Lower adherence to guidelines for medical management was noted with normothermia and CPT recommendations ranging between 30 and 40%. The lowest adherence was with surgical recommendations, around 14%. However, it is difficult to draw a valid conclusions based on adherence to specific recommendations when study number and size are small. For example, the adherence to recommendations for surgical management of acute subdural hematomas and intraparynchemal lesions were conducted in different settings, with different recommendation assessed in different countries and over different periods of time.

This review was able to find that the level of adherence was proportionally associated with the strength of evidence. Level 1 evidence recommendations were associated with optimal adherence (96%), level 2 recommendations had reasonable adherence (79%), suboptimal adherence was detected with level 3 evidence recommendations (32%) and very poor adherence was associated with unclassified recommendations (13.5%). These findings explain the large variation in

adherence to BTF guideline recommendations, which might indicate a barrier specifically for individual recommendations rather than guidelines as a whole. Another explanation could be that guidelines containing large number of recommendations would interfere with appropriate level of adherence, therefore translation of guideline into more efficient, practical and feasible protocols and algorithms would enhance the adherence as shown before[38].

Factors influencing adherence were reported in 6 studies[18,19,20,22,25,33] . These factors related to the patients and organization. No professional related factors were studied. More research focusing on the perspectives of professionals would be valuable. This systematic review demonstrates that higher strength of evidence would increase the adherence for BTF guidelines as whole. Patients' characteristics were addressed mostly in the context of the indication for ICP monitoring recommendation. Generally adherence was higher when treating surviving patients with more severe TBI. Patients with lower SBP were less likely to be treated based on guidelines for ICP monitoring, although low SBP is one of the indications for insertion ICP monitoring. This was reported in two studies[18,22] , which have insufficient information to make a solid conclusion, either this is an indicator of lower adherence since this recommendation represents level III evidence or hypotension in this group of patient was a representative of devastating systemic injury (not survivable patient), which decrease the adherence.

The controversy of the effect of pupillary abnormality on adherence between two studies[19,20] , might be explained by the difference in the duration of the pupillary abnormality between the patient in the 2 studies, since neither study account for that in their analysis. It has been shown that bilateral and longer duration of pupillary abnormality has a worse outcome[39] .

It is not possible to draw a conclusion on the effect of the CT findings on adherence, since only 3 studies reported that [18,19,33] , and they each used different classifications of CT finding in their analyses.

In terms of organizational factors there are consistent patterns showing that treatment in a level 1 trauma center or being in a higher economic status country positively influences adherence [22,25] while lack of health insurance negatively influences adherence[33] .

This knowledge can be used to improve guidelines and to establish strategies to improve adherence. These strategies should also focus on individual guideline recommendations as well as the guidelines as a whole.

In this review, eight studies assessed the association between adherence and mortality. Although beneficial effects of adherence to BTF guidelines were observed in some subgroup analyses and none of the subgroup analysis showed harmful effect, the overall pooled result did not show that adherence to BTF guidelines improves mortality rates. This is most likely explained by the heterogeneity and quality of the included studies, as well as the limited number of studies reporting the association between adherence and outcome. Therefore, future research focusing on the relationship between BTF guideline adherence and patient outcomes is needed, particularly with surgical management, for which no studies were found.

The beneficial effect of guideline adherence on adjusted mortality was observed in a single study with implementation of BTF guideline based protocol and adherence to nutrition, SBP and O2 recommendation.

ICP monitoring in management of TBI were studied in 2 systematic reviews. One of them included meta-analysis, but overall did not show that ICP monitoring is superior to no ICP monitoring, in terms of the mortality of TBI patients[40,41] . However, in this systematic review we did examine whether or not ICP monitoring was beneficial for subgroups of patients who met the criteria of BTF guidelines for ICP monitoring. This did not show beneficial effect on mortality, although this finding is most likely explained by clinical heterogeneity; different outcome measures, clinical setting, adjusting for different confounding factors, as well as the small number of included studies and low quality of the included studies. Therefore, future research focused on the outcomes associated with adherence to BTF guidelines for ICP monitoring is needed to verify its beneficial effect.

Heterogeneity and small numbers of studies assessing the effect of adherence on morbidity in severe TBI prevented us from pooling the result. Again contradictory results were observed across adherence to different recommendations, very high adjusted OR of good outcome based on GOS score 9.13 and 95% CI ranging from 3.25 to 25.67 with implementation of BTF guideline based protocol was reported in one study[5] would overcome the poor outcome reported based on surrogate outcome: needs tracheostomies, mechanical ventilation duration, ICU and hospital length of stay by other study[36] .

2.7.1 Limitations of included studies

This study is limited by the fact that the included studies are observational studies and most used retrospective design and patient databases. These methods have high risk of bias. The second limitation is the variability among the included studies, as they addressed different recommendations, different study designs and settings, different patients characteristics and different time periods, thus heterogeneity made the comparison between the studies difficult. Thirdly, although some studies reported the adjusted odds ratio using different statistical analysis, the confounding factors for which the studies adjusted were different among the studies. This might make residual, unmeasured or misclassification of confounding factors a possible alternative explanation for the heterogeneity among the studies as well as for our study findings. Finally, as an example, only four studies described the plan to address the potential source of bias, indicating that the risk of bias might be high.

2.7.2 Review limitations

First, the differences in recommendations, settings, patient's characteristics, and outcome measurements made the analysis and interpretation of the results extremely challenging. Second, small numbers of studies reporting mortality and morbidity outcomes associated with adherence to BTF guideline met the inclusion criteria. Finally, although high methodological standards were followed in conducting this systematic review with good inter-rater reliability, the results of any meta-analysis are limited by the quality of the studies included.

2.7.3 Study Strength

A very comprehensive systematic search was conducted based on established guidelines for systematic reviews. Fairly good inter-rater reliability was achieved; as well as comprehensive statistical analyses were conducted, including both the crude and adjusted outcomes. Finally, the standard protocol for reporting systematic reviews was followed.

2.8 Conclusions

Adherence to Brain Trauma Foundation guidelines shows high variability in the reported literature, despite the wide dissemination of these guidelines as well as the urgency needed in treating this life-threatening disease. The most likely explanations are the weakness of evidence of some recommendations. This emphasizes the need for more well conducted research to strengthen the current evidence, to focus on the perspectives of professionals and to develop strategies to increase adherence. These could include treating severe TBI patients in level 1 trauma centers and supporting economic improvements to the health system. Adherence to BTF guidelines was not associated with improved mortality in overall pooled analysis. However, some beneficial effects were observed with implementing a guidelines-based protocol and in-hospital crude mortality as well as adherence to specific recommendations; nutrition, SBP, O2 and cerebral perfusion threshold. Low levels of evidence and study heterogeneity limit the generalizability of the results and a well-conducted study to verify these results are needed.

Figure 2.1 Study selection process

Table 2.1 Summary of included studies

Study	Language of the publication	Publishing journal	Number of centers	Country	Study type and temporality	Study period, start	Study period, end	Inclusion/Exclusion criteria	Number of patients
Talving et al., 2013. (18)	English	Journal of Neurosurgery	2 centers	USA	Prospective cohort	January 1, 2010,	December 30, 2011	**Inclusion:** GCS ≤ 8, head AIS ≥ 3, met the BTF criteria for ICP monitoring, admitted to the surgical ICU. **Exclusion:** age < 18years, moribund patients, and those who were not expected to improve prior to the decision of whether an ICP monitoring device would be placed.	216

Biersteker et al., 2012. (19)	English	Critical Care Medicine	5 (level 1 trauma center)	Netherland	Prospective cohort	June 1, 2008	May 31, 2009	**Inclusion:** patients met BTF criteria for ICP monitoring. **Exclusion:** age <16 years and hospital admission >72 hours after the injury was sustained.	265
Farahvar et al., 2012. (20)	English	Journal of Neurosurgery	22 trauma centers (20 Level I and 2 Level II)	USA	Prospective cohort	June 6, 2000	December 31, 2009	**Inclusion:** patients met BTF criteria for ICP monitoring and at least one of the following ICP treatment regimens was administered in the first 2 days following admission: mannitol, hypertonic saline, barbiturates, drainage of CSF or decompressive craniectomy. **Exclusion:** Non paralyzed patients on Day 1 or 2 following trauma, with a GCS score of 3 or 4, and with fixed and dilated pupils	1307

Shafi et al., 2008. (21)	English	The Journal of Trauma Injury, Infection, and Critical Care	Participating trauma centers nationally	The National Trauma Data Bank of the American College of Surgeons (USA)	Retrospective cohort	1994	2001	**Inclusion:** admission to a designated Level I or II trauma center, blunt mechanism, age 20 to 50 years, admission to an intensive care unit for at least 3 days, and met the BTF criteria for ICP monitoring. **Exclusion:** Patients with AIS of < 3, Patients who died within 48 hours of admission and those who were admitted to a trauma center 24 hours after sustaining the injury.	1646
Barmparas et al., 2012. (22)	English	The American Surgeon Journal	2 centers	The National Trauma Data bank research	Retrospective cohort	2007	2008	**Inclusion:** patients met the BTF criteria for placement of an ICP monitor, blunt mechanism of injury, admission to a Level I or a Level II trauma center, and age older than 14 years. **Exclusion:** AIS	15,921

				data sets (USA)				in any body region was equal to 6, had missing head AIS or GCS scores, died in the emergency	
Tang et al., 2014. (23)	English	Journal of surgical research	Monocenter	USA	Retrospective cohort	2010	2012	**Inclusion:** patients who met the BTF guidelines for placement of an ICP monitor. **Exclusion:** Patients transferred from other institutions and patients with non-salvageable brain injury were excluded.	194

Shafi et al., 2014. (24)	English	The American College of Surgeons	5 centers	USA	Retrospective observational	Center A: January 1, 2006 Centers B, C, D, and E: January 1, 2009	Center A: December 31,2008. Centers B, C, D, and E: December 31, 2010.	**Inclusion:** age>16, GCS of 8 or less, intracranial bleed on head CT and endotracheal intubation. **Exclusion:** time from injury to arrival in emergency department of >1 day; burns, poisoning, drowning, hanging, submersion, or asphyxiation; gunshot wounds to the head; and dead on arrival in emergency department.	831

Mauritz et al., 2008. (25)	English	European Journal of Public Health	13 centers	Europe (Austria, Bosnia, Croatia, Macedonia and Slovakia)	Retrospective cohort	January, 2001	June, 2005	**Inclusion:** GCS of 8 or less following resuscitation or a GCS score deteriorating to 8 or less within 48 h of injury and survived at least until admission to the intensive care unit (ICU) were enrolled into this study. Exclusion: GCS of 3.	1172
Bulger et al., 2002. (26)	English	Critical care medicine	28 (level I trauma centers) and 6 (level II trauma centers)	USA	Retrospective cohort	May 1, 1998	December 31, 1998	**Inclusion:** GCS of 8 or less and has a fracture of the tibia, fibula, or femur. **Exclusion:** burn injury, pregnancy, spinal cord injury with paralysis, and patients transferred from another institution > 24 hours after injury.	182

Gerber et, al., 2013. (27)	English	Journal of Neurosurgery	22 (20 are Level I trauma centers and 2 are Level II)	USA	Retrospective cohort	2007	2009	**Inclusion:** isolated or multitrauma TBI within 24 hours of injury, GCS < 9 with a GCS motor score < 6 for at least 6 hours after injury and resuscitation. **Exclusion:** Patients with severe TBI who died in the emergency department or admitted with the diagnosis of brain death.	1133
Rusnak et al., 2007. (28)	English	The Middle European Journal of Medicine	5 centers	Austria	Retrospective cohort	2007	2009	**Inclusion:** fulfilled the criteria for severe brain trauma. **Exclusion:** Patients who died at the scene, during transport to the hospital, or immediately after admission to the emergency room were excluded.	415

Thompson et al., 2007. (29)	English	Intensive and Critical Care Nursing	Monocenter	USA	Retrospective cohort	2000	2002	**Inclusion:** patients admitted to a level I trauma center following a primary diagnosis of severe TBI.	108
Griesdale et al., 2014. (30)	English	Journal of Critical Care	Monocenter	Canada	Retrospective cohort	2006	2012	**Inclusion:** all patients who were admitted to the ICU if they had an admission diagnosis of TBI and had an ICP monitor inserted during their stay. **Exclusion:** ICP monitor inserted for reasons other than a closed TBI or penetrating TBI.	127
Neumann et al., 2008. (31)	English	Journal of Intensive Care Medicine	22 centers	Europe	Retrospective cohort	July, 2003	June 2005	**Inclusion:** all traumatic brain injury patients with a known time of trauma and at least one record ABG.	151

Frohlich et al., 2011. (32)	English	Irish Journal of Medical Science	Monocenter	Ireland	Retrospective cohort	2005	2007	**Inclusion:** all traumatic brain injury patients	46
Shafi et al., 2014. (33)	English	Journal of Neurosurgery	11 Level I trauma centers	USA	Retrospective cohort	January 1, 2008	September 9, 2009	**Inclusion:** GCS ≤ 8. **Exclusion:** non-survivable head injuries (AIS of 6) patients and age> 99 years.	2056
Bhullar et al., 2014. (34)	English	Journal of Trauma and Acute Care Surgery	Level 1 trauma centers	National Trauma Registry of the American College of Surgeons (USA)	Retrospective cohort	January, 2008	January, 2010	**Inclusion:** age > 18 years, blunt severe TBI (positive CT scan of the head and GCS of 3-8) and remained in the hospital at least 7 days after injury. **Exclusion:** antiseizure prophylaxis with levetiracetam, seizure before possible AED loading opportunity, and death within 72 hours of hospital admission.	93

Tsai et al., 2006. (35)	English	Surgical neurology	6 medical centers	Taiwan	Retrospective cohort	January, 1, 2003	June 31, 2003	**Inclusion:** aged 18 years or older, sustained head injury with a post resuscitation GCS of 3 to 8 and required mechanical ventilation. Exclusion: lost to follow-up at 6 months after the injury.	94
Arabi et al., 2010. (36)	English	Journal of critical care	Monocenter	Saudi Arabia	Retrospective cohort	March, 1999	December, 2006	**Inclusion:** patients older than 12 years with severe TB (GCS of 8 or less). Exclusion: brain death on admission.	434
Palmer et al., 2001. (37)	English	Journal of Trauma Injury Infection and Critical Care	Monocenter	USA	Combined retrospective and prospective cohort	1994	1999	**Inclusion:** GCS 3 to 8, CT scan had findings indicative of brain injury, age >8 years, closed head injury and had to have ICP monitor. **Exclusion:** dead within 24 hours of admission.	93

Table 2.2 BTF recommendations being evaluated for adherence in included studies

Guideline	Recommendations	Number of studies (Reference)
Pre and Post guidelines based protocol implementation	Level I II and III All Guidelines	2 (36,37)

Indication for ICP monitoring	Level II ICP should be monitored in all salvageable patients with a severe traumatic brain injury (TBI; Glasgow Coma Scale [GCS] score of 3–8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns. Level III ICP monitoring is indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure (BP) < 90 mm Hg.	15 (18,19,20,21,22,23,24,25,26,27,28,32,33,34,35)
ICP thresholds	Level II Treatment should be initiated with intracranial pressure (ICP) thresholds above 20 mm Hg.	3 (23,28,35)
Blood Pressure	Level II Blood pressure should be monitored and hypotension (systolic blood pressure < 90 mm Hg) avoided.	5 (23,27,28,32,33,)

Oxygenation	Level III Oxygenation should be monitored and hypoxia (PaO2 < 60 mm Hg or O2 saturation < 90%) avoided.	2 (28,32)
Cerebral perfusion Thresholds	Level II Aggressive attempts to maintain cerebral perfusion pressure (CPP) above 70 mm Hg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome (ARDS). Level III CPP of <50 mm Hg should be avoided. The CPP value to target lies within the range of 50–70 mm Hg. Patients with intact pressure autoregulation tolerate higher CPP values. Ancillary monitoring of cerebral parameters that include blood flow, oxygenation, or metabolism facilitates CPP management.	6 (23,27,28,30,33,35)

Hyperventilation	Level II Prophylactic hyperventilation (PaCO2 of 25 mm Hg or less) is not recommended. Level III Hyperventilation is recommended as a temporizing measure for the reduction of elevated intracranial pressure (ICP). Hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation (SjO2) or brain tissue oxygen tension (PbrO2) measurements are recommended to monitor oxygen delivery.	2 (31,32)
Steroids	Level I The use of steroids is not recommended for improving outcome or reducing intracranial pressure (ICP).	4 (25,27,28,32)

Anti-seizure Prophylaxis	Level II Prophylactic use of phenytoin or valproate is not recommended for preventing late posttraumatic seizures (PTS). Level III Anticonvulsants are indicated to decrease the incidence of early PTS (within 7 days of injury). However, early PTS is not associated with worse outcomes.	3 (28,32,34)
Nutrition	Level II Patients should be fed to attain full caloric replacement by day 7 post-injury.	3 (24,27,32)
Temperature	Normothermi	1 (29)
Surgical management of acute subdural hematoma (SDH)	Acute SDH with a thickness greater than 10 mm or a midline shift greater than 5 mm on CT scan should be surgically evacuated, regardless of the patient's Glasgow Coma Scale (GCS) score. All patients with acute SDH in coma (GCS score less than 9) should undergo ICP monitoring.	1 (32)

Surgical management of traumatic parenchymal lesion	Signs of progressive neurological deterioration referable to the lesion, medically refractory intracranial hypertension, or signs of mass effect on CT scan should be treated operatively. Patients with Glasgow Coma Scale (GCS) scores of 6 to 8 with frontal or temporal contusions greater than 20 cm3 in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan, and patients with any lesion greater than 50 cm3 in volume should be treated operatively.	1 (32)

Level of recommendations based on third edition.

Figure 2.2 Median percentage adherence and interquartile range for BTF recommendations

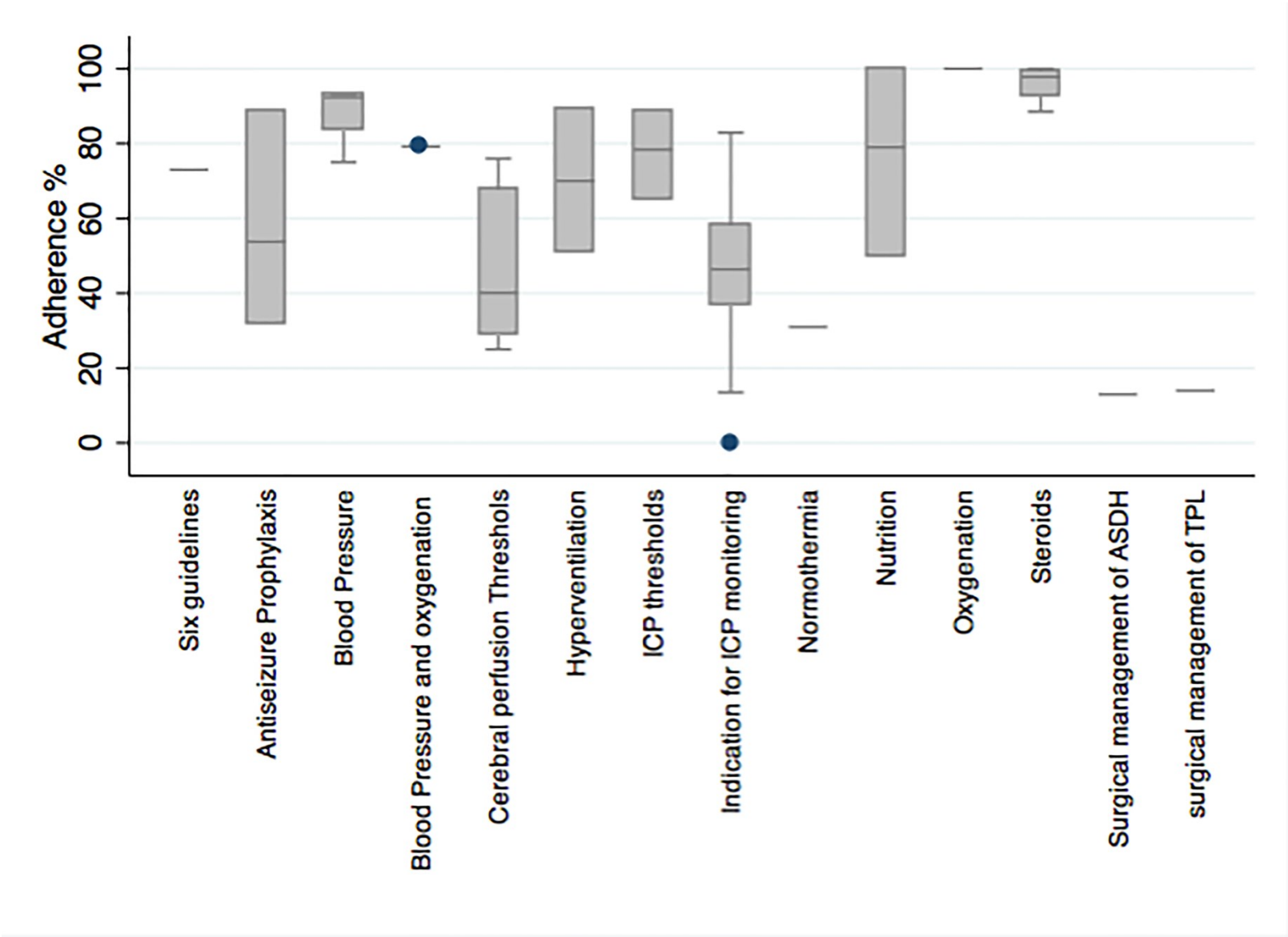


Figure 2.3 Median percentage adherence and interquartile range for BTF recommendations grouped by level of evidence

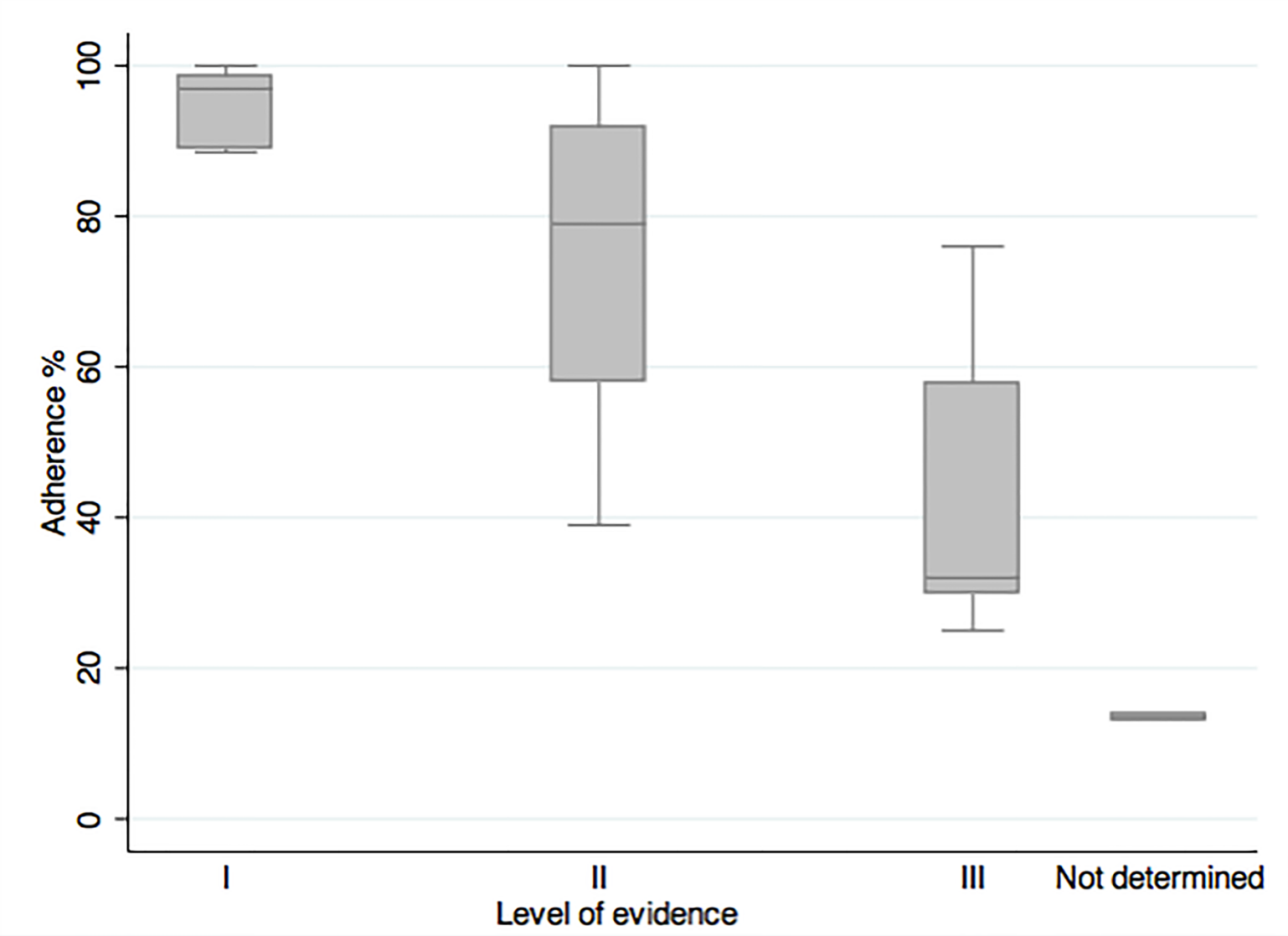


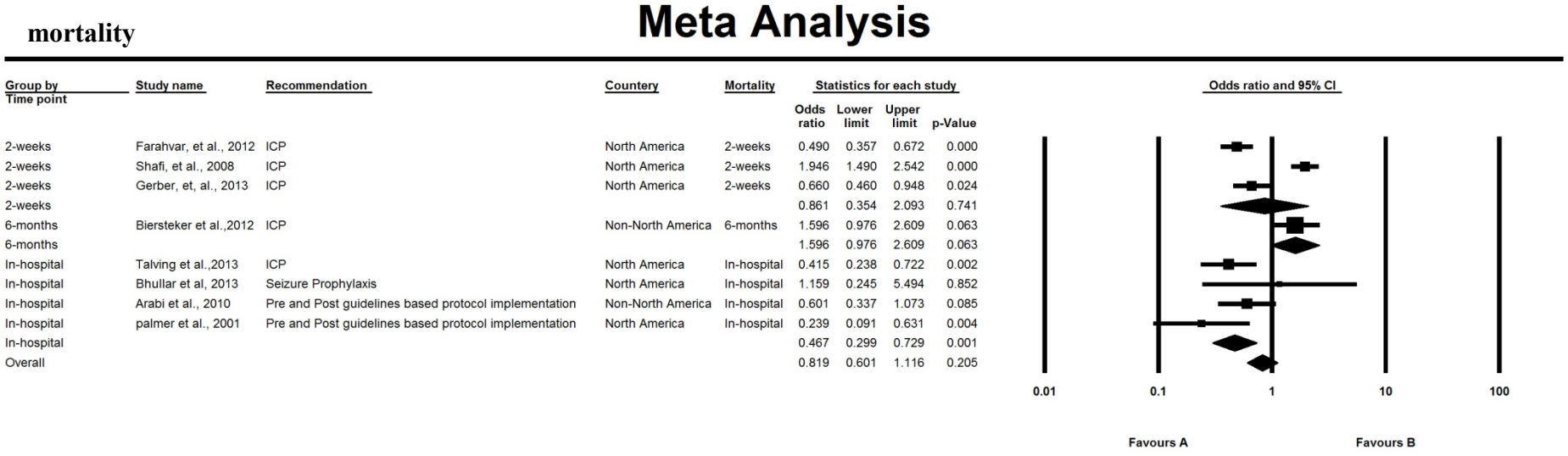
Table 2.3 Factors influencing adherence with BTF guideline

Influencing factors		**Recommend ation**	**Adherence**	
			Increase	**Decrease**
Patient characteristic	Age	ICP, BP, CPT	Younger age (19)	Older age (18,19,33)
	Sex	ICP, BP, CPT		Female sex (33)
Severity of Injury	Neurologic al status; Clinical	ICP	Lower GCS scores (19), more abnormal pupillary reactions (19), head AIS greater than 3 (22), higher head AIS score (33).	Improve neurological status within 24 hours (18). Pupillary abnormalities (20). GCS of 3 on admission (22).
		BP, CPT	Higher head AIS score (33).	

	Neurological status; Radiological	ICP	SAH and IPH (18), more lesions on the initial CT scan (19). Lower Marshall score on initial head CT scan (33).	Normal CT head (19),
		BP, CPT	Lower Marshall score on initial head CT scan (33).	
	Systemic Injury	ICP	Extremity AIS score ≥3 (18). More severe systemic injuries (19). Sever injury; ISS greater than 16 and critical injuries; ISS greater than 25 (22). Higher SBP (33)	Hypotension on admission (18,22), Coagulopathy (18)
		BP, CPT	Higher SBP (33)	
Managements		ICP	(decompressive craniectomy ≤4 hours (18). Craniotomy (22)	

Organizational factors		ICP	Admission to a Level I trauma center (22)	Lack of health insurance (33).
			Higher economic status countries (25)	
		BP, CPT		Lack of health insurance (33).
		Steroid	Higher economic status countries (25)	

Figure 2.4 association between adherence to BTF guideline and crude mortality; overall, 2 weeks, 6 weeks and in-hospital mortality



Meta Analysis

Figure 2.5 Association between adherence to BTF guideline and crude mortality, overall and stratified by recommendation

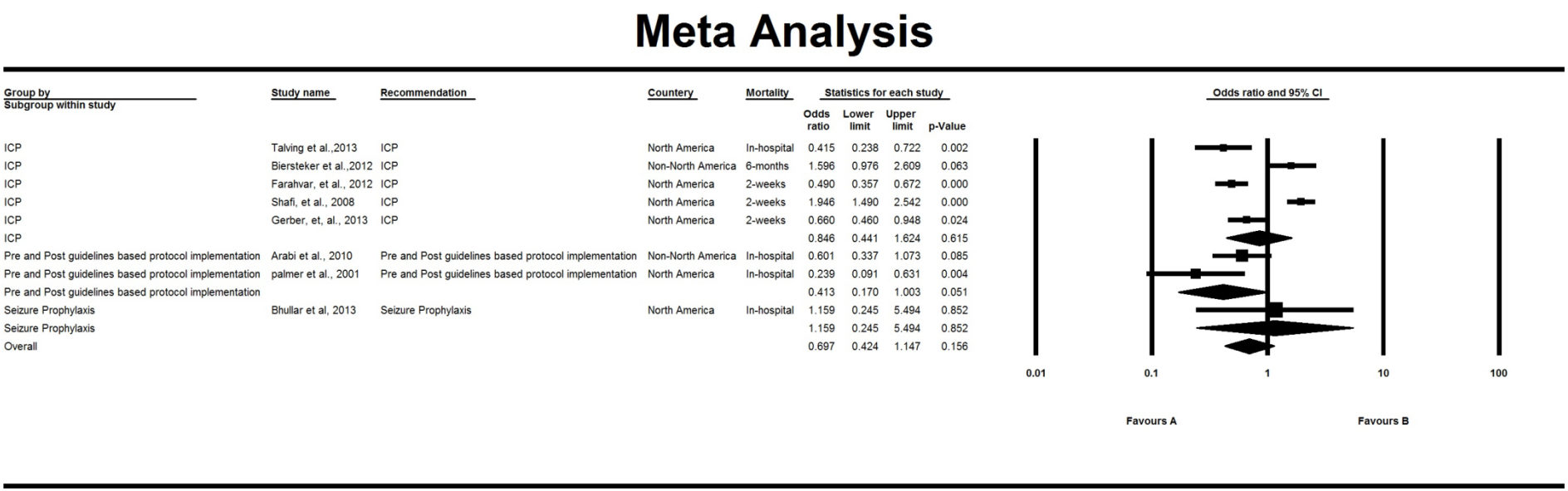
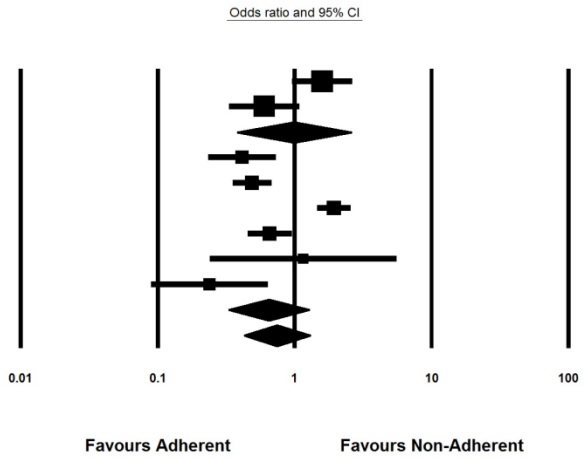


Figure 2.6 Association between adherence to BTF guideline and crude mortality, overall and stratified by country

Group by Comparison	Study name	Recommendation	Countery	Mortality	Statistics for each study			
					Odds ratio	Lower limit	Upper limit	p-Value
Non-North America	Biersteker et al.,2012	ICP	Non-North America	6-months	1.596	0.976	2.609	0.063
Non-North America	Arabi et al., 2010	Pre and Post guidelines based protocol implementation	Non-North America	In-hospital	0.601	0.337	1.073	0.085
Non-North America					0.992	0.381	2.580	0.987
North America	Talving et al.,2013	ICP	North America	In-hospital	0.415	0.238	0.722	0.002
North America	Farahvar, et al., 2012	ICP	North America	2-weeks	0.490	0.357	0.672	0.000
North America	Shafi, et al., 2008	ICP	North America	2-weeks	1.946	1.490	2.542	0.000
North America	Gerber, et, al., 2013	ICP	North America	2-weeks	0.660	0.460	0.948	0.024
North America	Bhullar et al, 2013	Seizure Prophylaxis	North America	In-hospital	1.159	0.245	5.494	0.852
North America	palmer et al., 2001	Pre and Post guidelines based protocol implementation	North America	In-hospital	0.239	0.091	0.631	0.004
North America					0.648	0.331	1.269	0.206
Overall					0.746	0.431	1.293	0.297



Meta Analysis

Figure 2.7 Association between adherence to BTF guideline and adjusted mortality, overall, 2 weeks, 6 months, ICU and in-hospital mortality

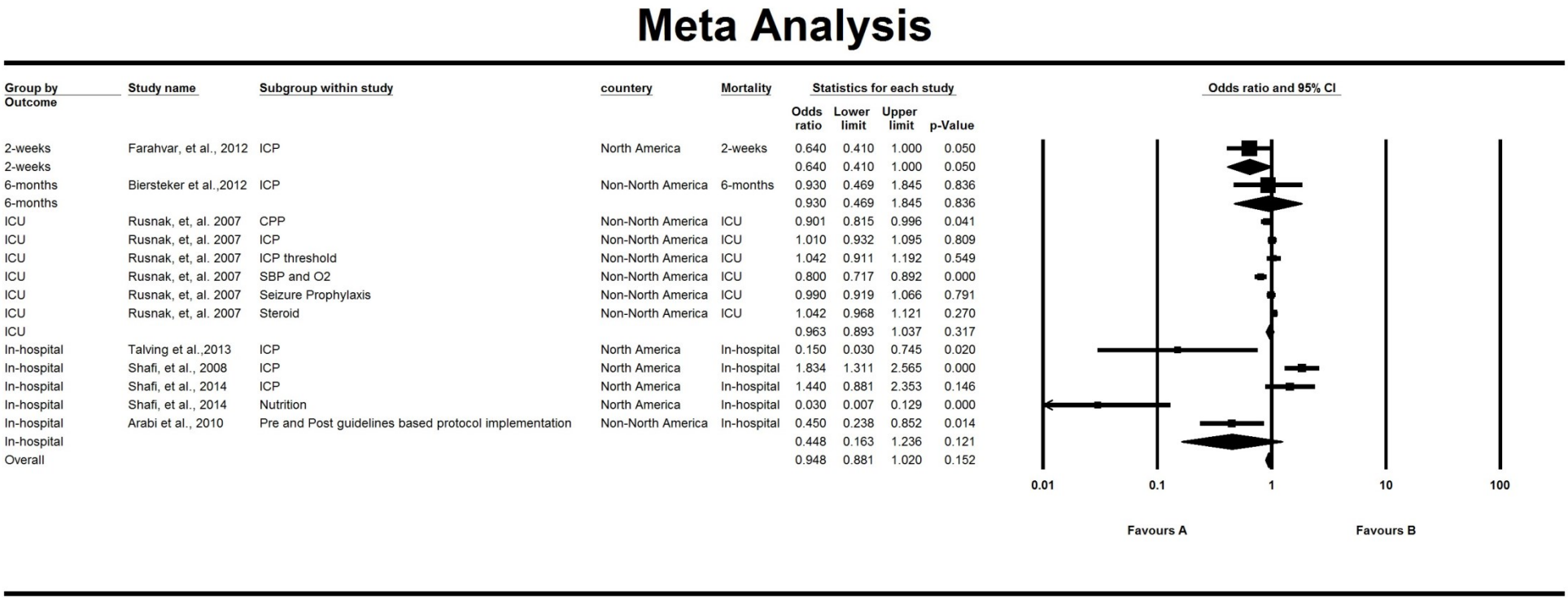


Figure 2.8 Association between adherence to BTF guideline and adjusted mortality, overall and stratified by recommendation

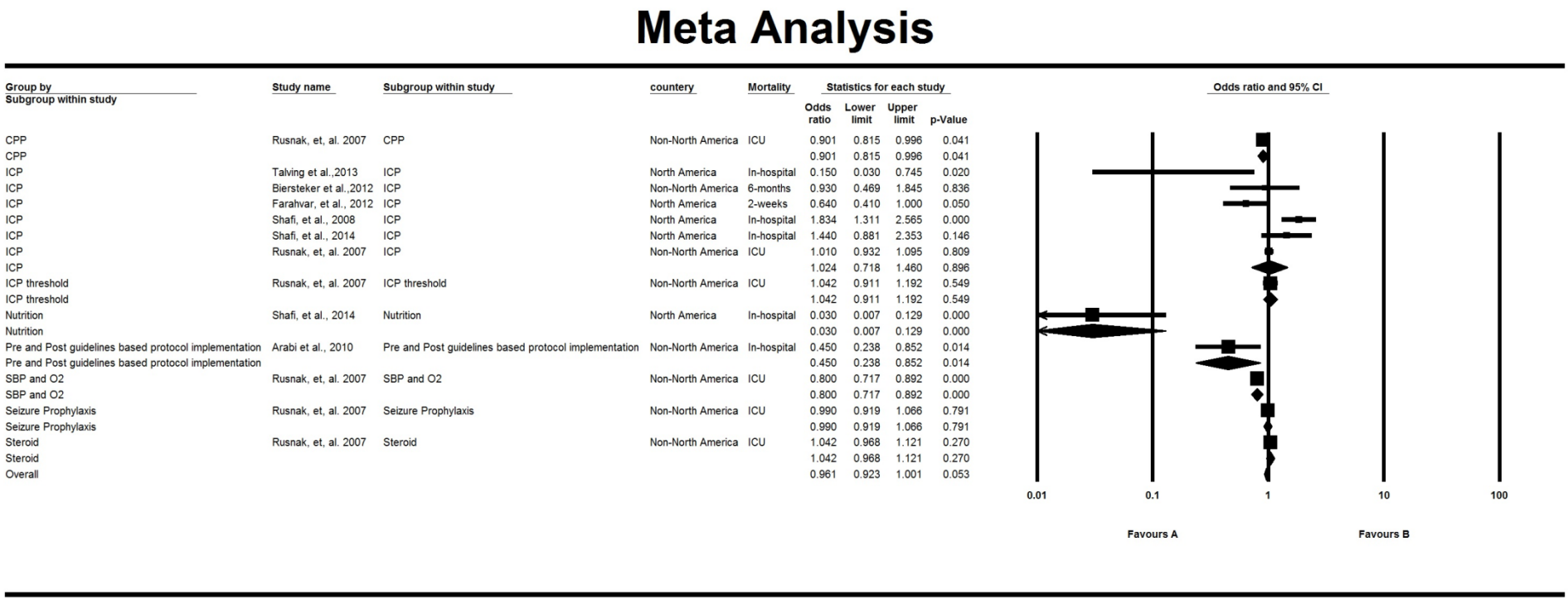


Figure 2.9 Association between adherence to BTF guideline and adjusted mortality, overall and stratified by country

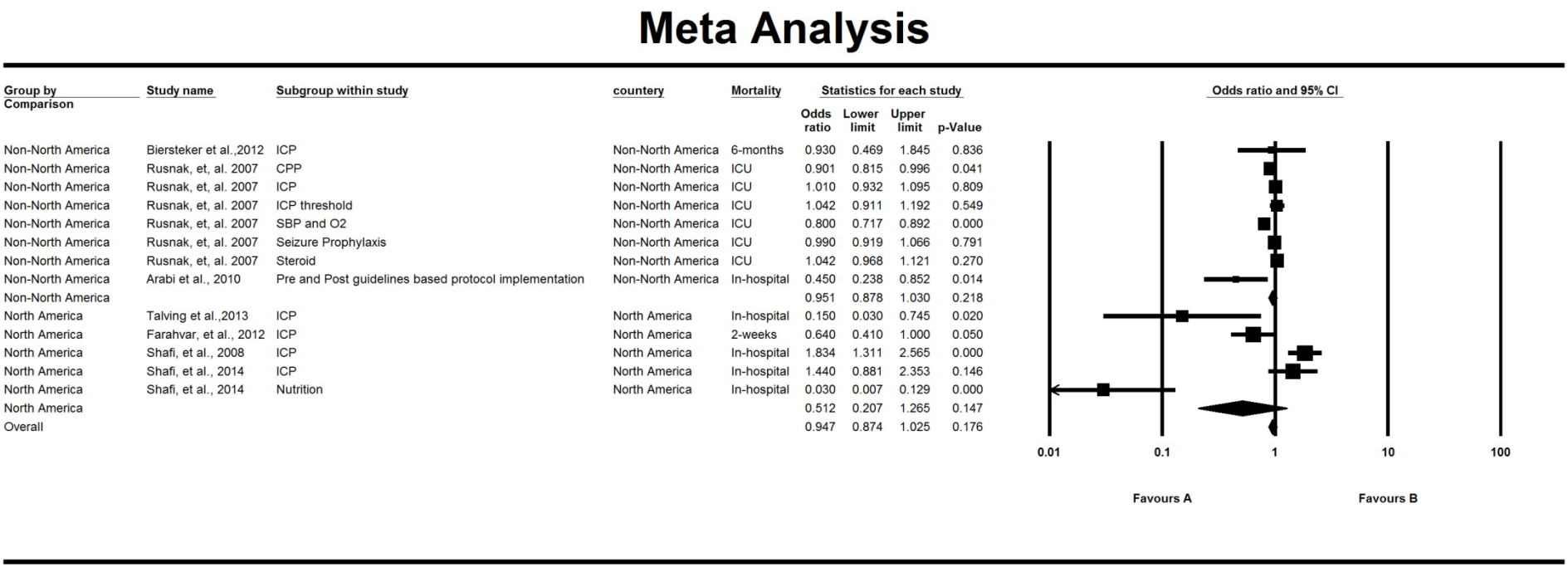


Table 2.4.1 Quality of reporting of observational studies based on STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology)

Variable	Title /abstract	Introduction	Background/rationale	Objectives	Methods	Study design	Setting	Participants	Variables	Data sources/measurement	Bias	Study size	Quantitative variables
Talving et al., 2013	.		.	.		.	.	.	.	.	.		.
Biersteker et al., 2012	.		.	.		.	.	.	.	.			.
Farahvar, et al., 2012	.		.	.		.	.	.	.	.			.
Shafi, et al., 2008	.		.	.			.	.	.	.			.

BARMPA RAS, et al., 2012	.		.	.			.	.	.	.			.
Tang, et al., 2014	.		.	.		.	.	.	.	.		.	.
Shafi, et al., 2014	.		.	.			.	.	.	.	.	.	.
Mauritz, et al., 2008	.		.	.			.	.	.	.			.
Bulger, et al., 2002	.		.	.			.	.	.	.			.
Gerber, et, al., 2013	.		.	.			.	.	.	.		.	.
Rusnak, et,	.		.	.				.	.				.

al. 2007													
Thompson, et al, 2007	.		.	.			.	.	.	.			.
Griesdale, et al, 2015	.		.	.		.	.	.		.		.	.
Neumann, et al, 2008.	.		.	.		.	.	.	.	.		.	.
Frohlich, et, al., 2011	.		.	.			.		.				.
Shafi, et al., 2014	.		.	.			.	.	.	.	.	.	.
Bhullar et al, 2013	.		.	.		.	.	.	.	.		.	.

Tsai et al, 2006	.		.	.			.	.	.			.	.
Arabi et al, 2010	.		.	.		.	.	.	.	.			.
Palmer et al, 2001	.		.	.		.	.	.	.	.	.		.

Table 2.4.2 Quality of reporting of observational studies based on STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology)

Variable	Statistical methods	Results	Participants	Descriptive data	Outcome data	Main results	Other analyses	Discussion	Key results	Limitations	Interpretation	Generalizability	Funding information
Talving et al., 2013	.			.	.	.	.		.	.	.	.	
Biersteker et al., 2012	.		.	.	.	.	.		.	.	.	.	.
Farahvar, et al., 2012	.		.	.	.	.	.		.	.	.		.
Shafi, et al., 2008	.			.	.	.	.		.	.	.	.	
Barmparas, et al., 2012	.			.	.	.	.		.	.	.		
Tang, et al., 2014	.		.	.	.	.	.		.	.	.		

Shafi, et al., 2014	.		.	.	.	.	.		.	.	.	.	
Mauritz, et al., 2008	.			.	.	.	.		.		.	.	.
Bulger, et al., 2002	.			.	.	.	.		.	.	.	.	
Gerber, et, al., 2013	.			.	.	.	.		.		.	.	.
Rusnak, et, al. 2007	.				.	.	.		.	.	.		.
Thompson, et al, 2007				.	.	.			.	.	.	.	
Griesdale, et al, 2015	.		.	.	.	.			.	.	.		.
Neumann, et al, 2008.	.		.		.	.			.	.	.		
Frohlich, et, al., 2011	.				.	.			.		.	.	
Shafi, et al., 2014	.		.	.	.	.	.		.	.	.	.	.

Bhullar et al, 2013			.	.	.				.	.	.	.	
Tsai et al, 2006				.	.	.			.		.		.
Arabi et al, 2010	.			.	.	.			.	.	.	.	
Palmer et al, 2001	.			.	.	.	.		.		.	.	

Figure 2.10 Funnel plot for all studies reported crude mortality included in the meta-analysis

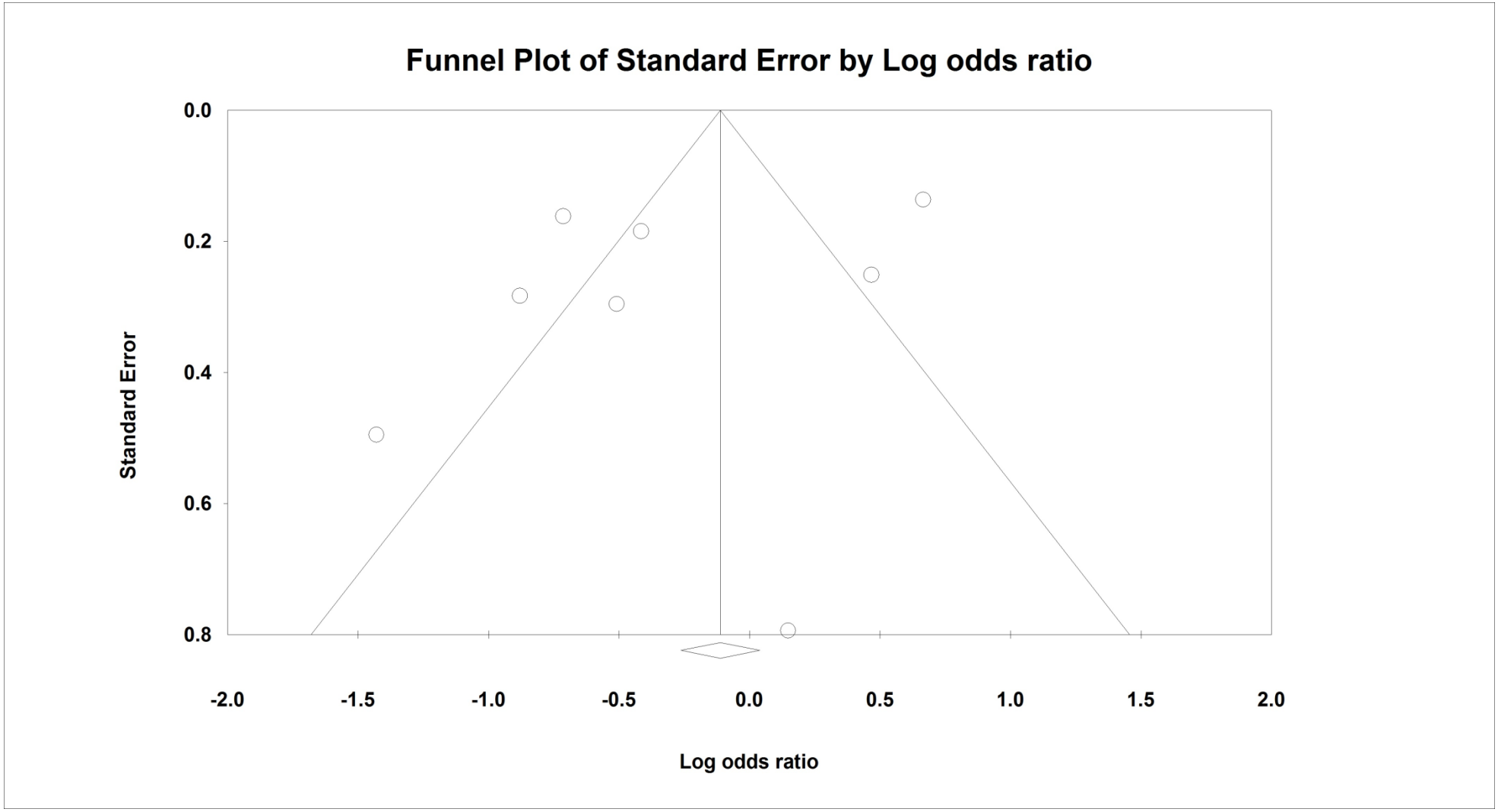
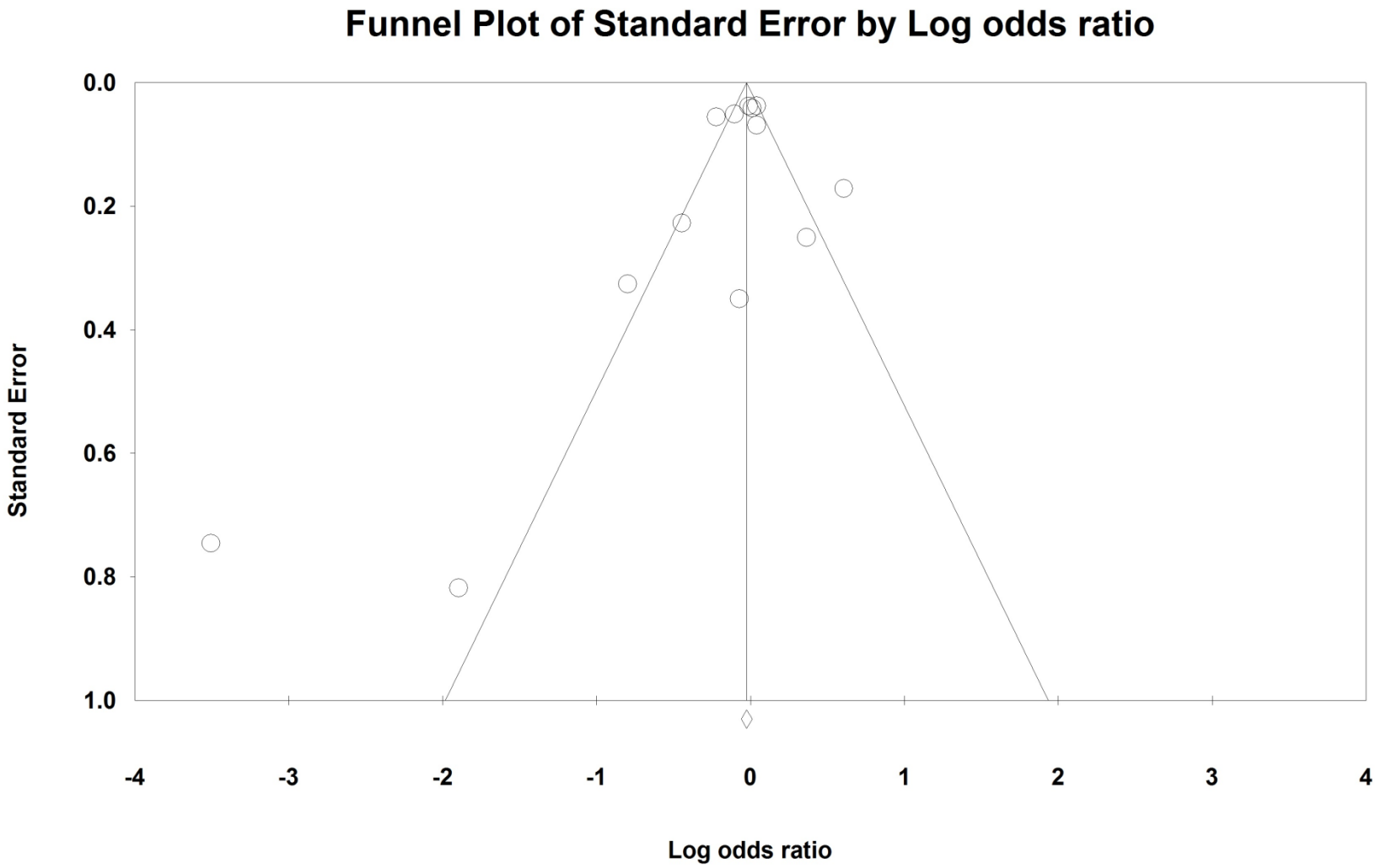


Figure 2.11 Funnel plot for all studies reported adjusted mortality included in the meta-analysis



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Chapter 3

Adherence to brain trauma foundation guidelines for intracranial pressure monitoring in severe traumatic brain injury and the effect on outcome: A population based study

3.1 Abstract

Severe traumatic brain injury (TBI) is a significant cause of death and disability around the world. Management based on Brain Trauma Foundation (BTF) guidelines is widely accepted and thought to improve outcomes. The objectives of this study to provide an overview of adherence to BTF guidelines for intracranial pressure **(**ICP) monitoring, explore which factors influence adherence and study the effects of adherence on outcomes. We conducted a retrospective cohort study of patients with severe blunt TBI registered in Alberta Trauma Registry between 2000 to 2013. Patients who died in the emergency department and patients from provinces other than Alberta were excluded. Outcomes were adherence rate with 3rd edition of the BTF guidelines, overall in-hospital mortality, and length of stay in hospital and intensive care unit (ICU). In our cohort, the BTF guideline adherence rate for ICP monitoring was 30%. Adherence rates increased with younger age, high ISS score, lower Glasgow Coma Score (GCS), abnormal CT head, craniotomy, admission to neurocritical care unit, and absence of alcohol intoxication or cardiac arrest. After adjusting for potential confounders adherence was associated with higher mortality (OR 2.01, 95% CI: 1.56-2.59, $p<0.001$) and increase ICU and hospital length of stay ($p<0.001$). In conclusion, Adherence to BTF guidelines for ICP monitoring in severe TBI was low, varied across centers and was associated with higher mortality and morbidity. ICP insertion may be an indicator of TBI severity, alternatively the current BTF criteria for ICP monitoring

may fail to identify patients likely to benefit. Further study is required to refine the indications of ICP monitoring in TBI patients.

3.2 Background

The Brain Trauma Foundation (BTF) guidelines are thoroughly constructed and widely disseminated guidelines for the management of TBI. The 3rd edition BTF recommended continuous ICP monitoring in all salvageable severe TBI patients (Glasgow Coma Score (GCS) ≤ 8) with a computed tomography (CT) scan revealing intracranial pathology (level II recommendation), or in severe TBI patients with a normal CT scan, but with two or more of the following risk factors: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure <90 mm Hg (level III recommendation)[1]. The current evidence for these recommendations failed to meet the inclusion criteria in the recent update[2].

It has been suggested that implementation and adherence to BTF guidelines results in improvement in neurological outcome and reduction in mortality of severe traumatic brain injury. However, there is significant variability in the use of ICP monitors and inconsistency in adherence to BTF guidelines across neurosurgical centres[3-5]. This may reflect uncertainty about the strength of evidence supporting the benefit of ICP monitoring in severe TBI[6]. In particular, a recent randomized controlled trial by Chesnut et al.[7] found that rigorous control of ICP was not associated with increased benefit, though the trial suffered from several methodological shortcomings.

Adherence to BTF guidelines for ICP monitoring in severe TBI has been investigated in few studies. In a cohort study from Netherlands [8], authors reported an adherence of 46 % to BTF guidelines and found that non-adherence was most prominent in patients with minor or very

large computed tomography abnormalities. However, there was no significant association between adherence and mortality. The presence of multiple baseline differences between monitored and unmonitored patients, and small sample size might have contributed to non-significant relationship between ICP monitoring and mortality. Another cohort study conducted in the USA [9], reported similar adherence rate, but the overall in hospital mortality was significantly higher in non-monitored group in comparison to the monitored group (53.9% vs. 32.7%). These studies suffered from several limitations including small sample size, non-population based, short follow-up and lack of consideration of functional outcomes. In addition, there is no consensus on traumatic brain injury management across countries, which limits the external validity of these studies.

3.3 Objectives

The primary goal in this study is to determine the adherence to BTF guidelines for continuous ICP monitoring in severe TBI patients and investigate the impact of adherence on mortality, hospital and ICU length of stay and discharge disposition, The study will seek to identify demographic and injury-related characteristics, which may influence adherence to the BTF guidelines. Specifically, the hypothesis of the study is that increasing age, elevated blood alcohol level and a normal CT scan on admission would decrease adherence, while a planned neurosurgical intervention would increase adherence

3.4 Methods

3.4.1 Design and Setting

After obtaining the approval from the University of Alberta Health Research Ethics Board (Appendix 4), a population-based retrospective cohort study of trauma patients with severe blunt brain injury who were admitted to all specialized Level 1 and 2 trauma centers in Alberta was conducted.

3.4.2 Patient selection

Patients admitted between January 1, 2000 to December 31, 2013 to one of the three trauma centers and registered in Alberta Trauma Registry were considered for the study. The inclusion criteria included patients who are 18 years or older, had an Injury Severity Score (ISS) $\geq$ 12 and TBI defined by ICD-9 code, Abbreviated Injury Score (AIS) score of head and neck > 3 and, GCS $\leq$ 8 or ICP monitoring. Patients who died in the emergency department (ED) were excluded, as guideline adherence cannot be determined. The patients who were not residents of Alberta and patients with a penetrating brain injury were excluded.

3.4.3 Data Collection and Definitions

Demographic and clinical variables collected included date of admission, admitting hospital, age, sex, GCS, systolic blood pressure, trauma severity score including: ISS and AIS for each body

region (head, chest, abdomen, and extremity), alcohol level, craniotomy and other surgical procedures, ICU stay, hospital stay, discharge disposition and over-all in hospital mortality. The study population was stratified into two-study arms based on adherence to BTF guidelines for insertion of ICP monitoring.

Two selection criteria were defined based on BTF guidelines for insertion of ICP monitoring: 1) patients with severe TBI (GCS $\leq$ 8) and an abnormal CT scan, 2) patients with severe TBI without CT abnormalities, but with at least two of the following criteria: age >40 years, unilateral or bilateral motor posturing (GCS motor score $\leq$3), or a systolic blood pressure <90 mm Hg.

Primary outcomes for the two-study arms included adherence to BTF guidelines and overall in-hospital mortality. Secondary outcomes were surrogate outcomes indicting the morbidity: ICU and hospital length of stay (LOS) and discharge disposition. Factors that might have an influence on adherence to the guidelines were included: age, CT abnormality, coagulopathy, alcohol level and the model of post resuscitation care, which included neurocritical care, general intensive care unit (ICU) and specialized neurological program within a general ICU).

3.4.4 Statistical Analysis

Percentages of adherence to the two selection criteria for ICP monitoring were calculated. To identify the independent predictors of adherence a purposeful selection method was deployed using variables after univariate analysis. Only the statistically significant variables are reported

as well as using variable we hypothesized to be associated with adherence. Subsequent univariate logistic regression for in-hospital mortality as well as a multiple logistic regression was performed using the purposeful selection method, which allowed for testing the well-known confounders cited in the literature. To assess the effect of adherence on mortality we used adherence as an independent variable. The hospital and ICU length of stay (LOS) and discharge disposition were assessed using multiple linear regressions adjusting for possible confounders in the same way as the mortality.

To assess the robustness of the assumption that all patients admitted to ICU are treatable we did sensitivity analysis to assess the influence of this assumption on the overall conclusions of the study by excluding patients who died within 48 hours after admission to ICU.

All statistical analyses were performed using STATA version 13.1. A p-value of less than 0.05 was considered statistically significant.

3.5 Results

3.5.1 Patient Demographics and Injury Characteristics

In total, 3,997 patients met the inclusion/ exclusion criteria. The patients were predominantly males (77.36%) with a median age of 40 years.

3.5.2 Adherence rate to BTF guidelines

2,149 patients did not meet BTF guidelines for ICP monitoring. Of the 1, 848 patients who met the BTF guidelines for ICP monitoring, 556 patients received an ICP monitor, reflecting an adherence rate of 30.09%. The majority of patients meeting criteria for ICP monitoring had an abnormal CT scan (1,606 patients). The adherence rate was highest among these patients (33.31%) in comparison with patients with normal CT head findings (8.68% of 242 patients) (Figure 3.1).

3.5.3 Predicting ICP Monitoring adherence

Baseline demographics, injury characteristics and model of care system of the ICP adhered and non-adhered groups are reported in Table 3.1. The association between the characteristics and adherence is shown in Table 3.2. The following variables were significant predictors of guideline adherence: younger age, higher ISS score, lower GCS, the absence of alcohol intoxication, CT scan abnormality, the absence of cardiac arrest, craniotomy, and using neurocritical or general ICU model. In the sensitivity analysis, which excluded patients who died within in 48 hours of admission, adherence rates and predictors of adherence were unchanged.

3.5.4 Mortality

In-hospital mortality was 42% in the adherent group and 32% in non-adherent group (Table 3.3), (crude OR: 1.54; p=0.0001) (Table 3.4). Adherence to BTF of ICP monitoring was associated with greater mortality even after adjusting for age, ISS score, GCS, CT abnormality, cardiac arrest, and craniotomy (OR: 2.01; p=0.0001). In the sensitivity analysis from excluding patients who died within 48 hours of admission, the association between adherence to BTF of ICP monitoring and mortality was greater (OR: 4.59; p =0.0001). Increased age, higher ISS score, lower GCS, and cardiac arrest were associated with increased mortality. CT abnormality and craniotomy were not associated with increased mortality (Table 3.4).

3.5.5 Morbidity

The adherent group had greater length of stay at hospital and ICU and ventilation days in comparison to the non-adhered group. Only 5% of patients from the adherent group were discharged home in comparison to 18% in non-adherent group (Table 3.3). As shown in Tables 3.5 and 3.6 adherence to ICP monitoring of BTF guidelines was associated with higher length of stay in the ICU and hospital with an average ICU length of stay being greater by 7 days with adherence (p-value = 0.0001) and hospital length of stay being greater by 14 days with adherence (p = 0.0001) even after adjusting for age, SBP, ISS score, GCS, CT abnormality, cardiac arrest, and craniotomy. Administration of CPR, greater ISS, lower GCS, and lower SBP (< 90 mm) were associated with longer ventilation and ICU stay. Older age group, administration of CPR, greater ISS and lower GCS are associated with longer hospital stay.

3.6 Discussion

ICP monitoring has been included in evidence-based practice guidelines, in particular in BTF guidelines for last two decades. Our study confirmed that ICP monitoring is performed in a minority of patients with severe traumatic brain injuries patients who meet the 3ed BTF criteria for monitoring (30.1%), even lower than those reported in the studies conducted in UK (43% and 46%) and Austria (56%)[10-12].

There are several possible reasons that could explain the lower adherence to BTF recommandations for ICP monitoring. Firstly, ICP monitoring has not been validated by level one-evidence studies. Secondly, clinicians might prefer to rely on their clinical judgment based on frequent CT scan and clinical exams that followed closely even in intubated patients. A Canadian survey among 103 neurosurgeons reported that only 20% had a high level of confidence that ICP monitoring improves outcome[13]. Finally, patient's premorbid level of functioning and comorbidities as well as personal expectations of the treating clinicians, for example, use craniectomy instead of craniotomy may decrease the ICP insertion.

Adherence rate was significantly different across different critical care units within the same province (Alberta), which confirms variability in the management severe TBI patients. Higher ISS and low GCS indicate the severity of TBI, thus a subgroup of patients was subjected to more monitoring.

Adherence was lower in patients with a normal CT scan and two or more risk factors; age, BP, and motor GCS (9%) compared to patients with abnormal intracranial finding (33%), suggesting that clinicians are likely not convinced that ICP monitoring in this subgroup of severe TBI patients is necessary since the reason for low GCS is the diffuse axonal injury; therefore, monitoring in these patients needs further investigation. Clinician judgment likely explains the lower rate of adherence among older patients, alcohol intoxicated patients, and patients with cardiac arrest (Table 3.2). Older age patients usually have a brain atrophy and less likely to have high ICP, thus subgroup of patient should be studied separately. Alcohol intoxication and cardiac arrest could explain patient low level of consciousness.

In this study, ICP monitoring is associated with higher mortality and morbidity despite controlling multiple confounders. This finding is in agreement with one study[14]. Conversely, three studies reported that monitoring associated with lower mortality[15-17] and two studies reported no effect on mortality[18-19]. The findings of the current study may have several potential explanations. Firstly, BTF criteria for ICP monitoring do not identify patients who are likely to benefit from it, since GCS score and abnormal CT are not quantitative measures, and clinical management decisions should not be based solely on them. Secondly, neurosurgeons may have intended to insert monitors in patients who were at greater risk for mortality and worse outcome, although multiple potential confounders were controlled, still the nature of the study design might have failed to identify other potential confounders, for example; pupils abnormality and sign of increase ICP on CT scan. Thirdly, measures to reduce ICP may be associated with harm. For example, overuse of hyperventilation could cause brain ischemia and overuse of mannitol could cause harmful hypotension. In addition targeting the recommended CPP threshold, which

could cause fluid overload and subsequently increasing the mortality. Hence, ICP monitoring does not imply it was effectively treated, monitoring and high ICP management measure should be assessed as combined intervention. Finally, ICP might be a predictor of the severity of brain injury and the difficulty to control ICP reflecting the extensive of injury.

This is a large population-based study to address the adherence to BTF guidelines in severe TBI, with adequate sample size to detect small effect size and adjust for potential confounders. Despite these strengths, multiple limitations must be considered. Firstly, our data were collected retrospectively, which raises the concern of data completeness and correctness. Secondly, early pupillary reaction and detailed CT head finding, which are not reported in our database, which may confound our result. Additionally, it is likely that some of those patients in the group not receiving ICP monitoring were being treated differently that may confound the outcome assessment based on the ICP insertion. This is specifically relevant with respect to patient/family decisions with respect to aggressiveness of care. A well conducted randomized controlled trial would be the study design of choice to prove an effect of ICP monitoring on outcome, however, it is unlikely such a trial will be performed in North America given ethical concerns regarding withholding ICP monitoring after TBI. An additional limitation of our study was the lack of long-term follow-up and functional outcome measures, Finally, cause of death was not specified in our database As such; patients may have died of causes other than their brain injuries. Given the size of the sample and methodologies used to control for injury severity and mortality risk, this is unlikely to invalidate the finding of increased mortality risk in monitored patients.

3.7 Conclusion

In a sample of Canadian TBI patients, adherence to BTF guidelines for ICP monitoring is low and varies across centers, particularly in patients with normal imaging. Further studies to address the role of monitoring in older patients and in patients with no intracranial pathology are warranted. In the current analysis, ICP monitoring is associated with higher mortality and ICU and hospital length of stay when used in patients with severe TBI who meet the BTF criteria for ICP monitoring. This may be due to harmful effects of ICP monitoring or, more likely, the association is spurious due to an confounded relationship between ICP monitoring and TBI severity or failure of the BTF criteria to identify patients likely to benefit from monitoring. Regardless, further studies are required to determine the utility of ICP monitoring and to refine the criteria for its use.

Figure 3.1 Flow chart

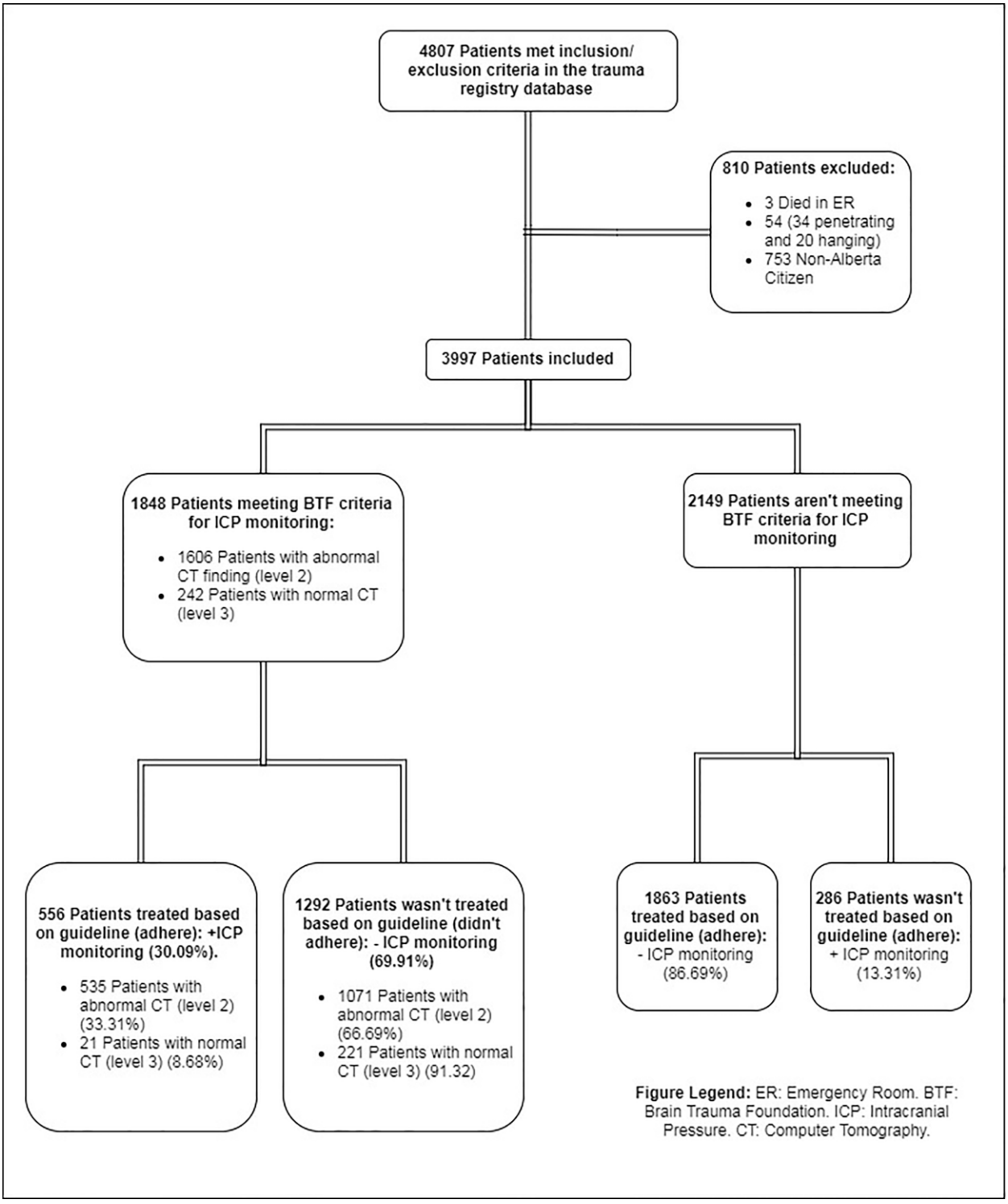

Table 3.1 Patient characteristics in adherent and non-adherent group

		Adhere % (n=556)	Not-Adhere % (n=1292)	P-value
Age (year)	18- 37	55.58	42.41	0.0001
	38-56	32.73	33.98	
	57-75	10.97	17.18	
	76-94	0.72	6.42	
Sex	Male	76.98	75.00	
	Female	23.02	25.00	0.364
Extraction	No	63.24	66.50	
	Yes	36.76	33.50	0.321
SBP<90	No	92.61	88.21	
	Yes	7.39	11.79	0.005
ISS	13-23	5.40	13.47	0.0001
	24-33	39.93	42.41	
	34-43	32.55	26.93	
	44-53	16.91	12.77	
	54-75	5.22	4.41	

		Adhere % (n=556)	Not-Adhere % (n=1292)	P-value
GCS	7-8	15.34	23.79	0.0001
	5-6	21.78	20.55	
Alcohol intoxication	3-4	62.88	55.67	
	No	53.78	49.30	
	Yes (>17)	46.22	50.70	0.078
CT finding	Normal	3.78	17.11	
	Abnormal	96.22	82.89	0.0001
CPR	No	97.84	89.55	
	Yes	2.16	10.45	0.0001
Craniotomy	No	66.01	84.83	
Intensive care unit model	Yes	33.99	15.17	0.0001
	SNP within ICU	33.63	43.11	0.001
	ICU	23.56	20.05	
	Neurocritical care	42.81	36.84	

Table 3.2 Predictors of adherence*

		Univariate		Multivariate	
		OR	**P-value (95% CI)**	**OR**	**P-value (95% CI)**
Age (year)	18- 37	1		1	
	38-56	0.74	0.007 (0.59 - 0.92)	0.94	0.625 (0.73 - 1.21)
	57-75	0.49	0.0001 (0.36 - 0.67)	0.51	0.0001 (0.35 - 0.73)
ISS	76-94	0.09	0.0001 (0.03 - 0.24)	0.13	0.0001 (0.04 - 0.36)
	13-23	1		1	
	24-33	2.35	0.0001 (1.55 - 3.57)	2.07	0.003 (1.29 - 3.33)
	34-43	3.02	0.0001 (1.97 - 4.62)	2.71	0.0001 (1.67 - 4.39)
	44-53	3.30	0.0001 (2.08 - 5.25)	3.19	0.0001 (1.89 - 5.40)
	54-75	2.95	0.0001 (1.63 - 5.33)	2.83	0.002 (1.44 - 5.57)
GCS	7-8	1		1	
	5-6	1.64	0.003 (1.18 - 2.29)	1.59	0.01 (1.12 - 2.27)
	3-4	1.75	0.0001 (1.32 - 2.32)	2.08	0.0001 (1.53 - 2.82)
Alcohol intoxication	No	1		1	
	Yes (>17)	0.84	0.078 (0.68 - 1.02)	0.76	0.018 (0.60 - 0.95)
CT finding	Normal	1		1	

		Univariate		Multivariate	
		OR	**P-value (95% CI)**	**OR**	**P-value (95% CI)**
	Abnormal	5.26	0.0001 (3.32 - 8.32)	4.67	0.0001 (2.81 - 7.75)
CPR	No	1		1	
	Yes	0.19	0.0001 (0.10 - 0.34)	0.28	0.0001 (0.15 - 0.53)
Craniotomy	No	1		1	
	Yes	2.88	0.0001 (2.28 - 3.63)	3.19	0.0001 (2.43 - 4.18)
Intensive care unite model	SNP within ICU	1		1	
	ICU	1.51	0.003 (1.15 - 1.97)	1.59	0.0001 (1.32 - 2.42)
	Neurocritical care	1.49	0.001 (1.19 - 1.87)	2.08	0.0001 (1.36 - 2.27)

* Purposeful selection method was used for selecting variables in the model. Overall fit of the model was assessed using Hosmer-Lemeshow statistc which not statistically significant (Chi-square statistics =14.98, df=8, p=0.06) indicating that the model provided a good-fit for the data.

Table 3.3 Percentage of in hospital death, discharge disposition, hospital and ICU length of stay and ventilation days in adhere and not-adhere group

		Adhere	Not-Adhere	P.value
In-hospital mortality	Survive	57.73%	67.8%	
	Died	42.27%	32.2%	0.0001
Discharge disposition	Home	5.58	18.67%	0.0001
	Acute care facility	14.21%	17.82%	
	Rehabilitation facility	37.95%	31.29%	
	Chronic care facility	42.27%	32.22%	
Hospital LOS	Mean (SE) (days)	34.32 (1.76)	24.41 (1.30)	0.0001
ICU LOS	Mean (SE) (days)	13. 40 (0.46)	8.06 (0.33))	0.0001
Ventilation days	Mean (SE) (days)	11.24 (0.42)	5.83 (0.25)	0.0001

Table 3.4 Crude and adjusted Odd Ratio (OR) of the mortality*

		Univariate		Multivariate	
		OR	**P-value (95% CI)**	**OR**	**P-value (95% CI)**
Adhere	No	1		1	
	Yes	1.54	0.0001 (1.26 - 1.89)	2.01	0.0001 (1.56 - 2.59)
Age (year)	18- 37	1		1	
	38-56	1.32	0.002 (1.11 - 1.57)	1.59	0.001 (1.22 - 2.09)
	57-75	2.13	0.0001 (1.75 - 2.59)	3.45	0.0001 (2.45 - 4.85)
	76-94	3.24	0.0001 (2.49 - 4.20)	10.53	0.0001 (5.78 - 19.17)
SBP	>=90	1		1	
	<90	3.03	0.0001 (2.39 - 3.85)	2.12	0.0001 (1.43 - 3.14)
ISS	13-23	1		1	
	24-33	3.91	0.0001 (2.97 - 5.15)	4.34	0.0001 (2.59 - 7.27)
	34-43	2.67	0.0001 (1.99 - 3.57)	3.19	0.0001 (1.87 - 5.46)
	44-53	4.27	0.0001 (3.09 - 5.91)	3.93	0.0001 (2.21 - 6.99)
	54-75	4.90	0.0001 (3.17 - 7.58)	2.46	0.016 (1.18 - 5.10)
GCS	7-8	1		1	

		Univariate		Multivariate	
		OR	**P-value (95% CI)**	**OR**	**P-value (95% CI)**
	5-6	1.61	0.006 (1.15 - 2.26)	1.30	0.286 (0.80 - 2.10)
	3-4	5.03	0.0001 (3.81 - 6.64)	4.71	0.0001 (3.16 - 7.04)
CT finding	Normal	1		1	
	Abnormal	1.21	0.014 (1.04 - 1.42)	1.12	0.561 (0.77 - 1.64)
CPR	No	1		1	
	Yes	12.06	0.0001 (8.78 - 16.56)	8.34	0.0001 (4.84 - 14.36)
Craniotomy	No	1		1	
	Yes	1.02	0.826 (0.86 - 1.20)	1.65	0.120 (0.88 - 3.09)

* Purposeful selection method was used for selecting variables in the model. Overall fit of the model was assessed using Hosmer-Lemeshow statistc which not statistically significant (Chi-square statistics =11.56, df=8, p=0.17) indicating that the model provided a good-fit for the data.

Table 3.5 Crude and adjusted Length of stay in hospital

		Univariate		Multivariate	
		B	**P-value (95% CI)**	**B**	**P-value (95% CI)**
Adhere	No				
	Yes	18.10	0.0001 (11.60 - 24.60)	14.4	0.0001 (7.15 - 21.66)
Age (year)	18- 37				
	38-56	5.10	0.003 (1.71 - 8.49)	11.89	0.001 (4.80 - 18.97)
	57-75	6.61	0.003 (2.20 - 11.02)	12.96	0.012 (2.87 - 23.06)
	76-94	4.26	0.219 (-2.54 - 11.06)	22.65	0.039 (1.10 - 44.20)
SBP	>=90				
	<90	17.46	0.0001 (10.82 - 24.09)	10.67	0.099 (-2.02 - 23.36)
ISS	13-23				
	24-33	5.73	0.005 (1.72 - 9.74)	-0.12	0.98 (-9.93 - 9.68)
	34-43	17.11	0.0001 (12.82 - 21.40)	11.15	0.033 (0.90- 21.40)
	44-53	23.63	0.0001 (17.95 - 29.30)	19.82	0.001 (7.64 - 32.00)
	54-75	33.24	0.0001 (24.10 - 42.38)	20.9	0.018 (3.65- 38.15)
GCS	7-8				
	5-6	10.94	0.003 (3.77 - 18.11)	9.68	0.026 (1.15 - 18.21)

		Univariate		Multivariate	
		B	**P-value (95% CI)**	**B**	**P-value (95% CI)**
	3-4	12.85	0.0001 (6.64 -19.06)	10.52	0.007 (2.88 - 18.15)
CT finding	Normal				
	Abnormal	7.99	0.0001 (4.85 - 11.13)	10.4	0.073 (-0.98 - 21.78)
CPR	No				
	Yes	12.94	0.025 (1.64 - 24.24)	23.04	0.049 (0.12 - 45.96)
Craniotomy	No				
	Yes	1.16	0.516 (-2.35 - 4.67)	6.3	0.122 (-1.68 - 14.27)

Table 3.6 Crude and adjusted length of stay in Intensive Care Unit

		Univariate			Multivariate
		B	**P-value (95% CI)**	**B**	**P-value (95% CI)**
Adhere	No				
	Yes	8.05	0.0001 (6.53 - 9.58)	6.55	0.0001 (4.95 - 8.15)
Age (year)	18- 37				
	38-56	-0.20	0.669 (-1.13 - 0.72)	0.66	0.404 (-0.90 - 2.22)
	57-75	-0.65	0.288 (-1.85 - 0.55)	0.61	0.590 (-1.61 - 2.83)
SBP	76-94	-0.47	0.621 (-2.32 - 1.39)	2.60	0.282 (-2.14- 7.34)
	>=90				
	<90	6.88	0.0001 (5.07 - 8.68)	4.56	0.001 (1.76 - 7.35)
ISS	13-23				
	24-33	2.39	0.0001 (1.33 - 3.44)	1.68	0.128 (-0.48 - 3.83)
	34-43	7.14	0.0001 (6.02 - 8.27)	5.74	0.0001 (3.48 - 8.00)
	44-53	10.71	0.0001 (9.22 - 12.20)	9.94	0.0001 (7.26 - 12.62)
	54-75	13.20	0.0001 (10.80 - 15.60)	8.26	0.0001 (4.46 - 12.06)

		Univariate			Multivariate
		B	**P-value (95% CI)**	**B**	**P-value (95% CI)**
GCS	7-8				
	5-6	2.08	0.019 (0.34 - 3.83)	1.21	0.206 (-0.67 - 3.09)
	3-4	4.50	0.0001 (2.99 - 6.01)	2.80	0.001 (1.12 - 4.48)
CT finding	Normal				
	Abnormal	3.01	0.0001 (2.16 - 3.86)	1.68	0.187 (-0.82 - 4.19)
CPR	No				
	Yes	7.39	0.0001 (4.32 - 10.46)	10.52	0.0001 (5.48 - 15.57)
Craniotomy	No				
	Yes	-0.95	0.050 (-1.91 - 0.0003)	1.49	0.097 (-0.27 - 3.24)

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Chapter 4 Discussion and Conclusions

4.1 Summary of the findings

First, The systematic review and meta analysis included twenty observational studies based on inclusion inclusion/exclusion criteria. The median percentage of adherence to the BTF guidelines for management of TBI was 60.7% ranging from 0-100%. The adherence level in North American centers had less variability in comparison to studies conducted in other countries, ranging between 13.5% and 55.9%. Overall median adherence to BTF guidelines increased and reached 60% in 2002 with no further improvement since then. The lowest percentages of adherence to the recommendation for management of ASD hematoma and IPL were 13% and 14%, the percentages adherence were 31% and 40.1% for normothermia and CPT recommendations whereas higher median adherence percentages 100%, 97.8% and 92.3% were for recommendations of oxygenation, steroid and blood pressure, the adherence to nutrition, ICP threshold and hyperventilation were, 79% 78.4%, and 70%, Moderate adherences were reported for anti-seizure prophylaxis and indication for (ICP) recommendation, which were 58.1% and 46.4%. Recommendations with the higher the level of evidence were associated with the higher median percentage of adherence, 96.9%, 79%, 32% and 13.5% for level 1, 2, 3 and unclassified recommendations.

Adherence was not associated with improved crude mortality [OR: 0.82, (95% CI: 0.60-1.12) or adjusted mortality [OR: 0.95, (95% CI: 0.88-1.02). However, beneficial effects were observed in subgroup analysis through implementation of a guidelines-based protocol in terms of in-hospital

crude mortality as well as adherence to specific recommendations; nutrition, Systolic Blood Pressure (SBP), oxygen (O2) and cerebral perfusion threshold.

Overall, Treating patients with higher severity of injury, treatment in a level 1 trauma center and higher economic status country positively influenced adherence, while lack of health insurance negatively influenced the adherence. Adherence to the indication for ICP monitoring was higher when treating younger patients, patients with severe neurological injury, and patients who underwent surgical treatment. Adherence was lower among patient whose neurological status improved within 24 hours, patients with GCS 3 on admission and coagulopathic patients.

Second, The cohort study included 1, 848 patients who met the BTF guidelines for ICP monitoring treated in Alberta, the adherence rate was 30.09%, it was highest among patients with abnormal CT head findings. Younger age, higher ISS score, lower GCS, the absence of alcohol intoxication, CT scan abnormality, the absence of cardiac arrest, craniotomy, and using neurocritical or general ICU model were significant predictors of guideline adherence.

In-hospital mortality was 42% in the adherent group and 32% in non-adherent group (crude OR: 1.54 p=0.0001). After adjusting for potential confounders adherence was associated with higher mortality (OR 2.01, 95% CI: 1.56-2.59, $p<0.001$). Increased age, higher ISS score, lower GCS, and cardiac arrest were associated with increased mortality. CT abnormality and craniotomy were not associated with increased mortality. The adherent group had greater length of stay at hospital and ICU and ventilation days in comparison to the non-adhered group ($p<0.001$) and

Only 5% of patients from the adherent group were discharged home in comparison to 18% in non-adherent group.

4.2 Discussion

This thesis is the first one to look at the adherence to BTF guidelines for management of severe TBI. Both included studies in this thesis are designed to provide an overview of professionals' adherence to BTF guidelines as a whole and specifically for intracranial pressure (ICP) monitoring, to explore factors influencing adherence to these guidelines, as well as to study the effect of adherence on outcomes.

Despite the urgency and life-threating nature of severe TBI, as well as the worldwide dissemination since 1996 of BTF guidelines in management of severe TBI, results show a low and wide variation in adherence even among the studies conducted in North America, adherence rate was significantly different across different critical care units within the same province (Alberta), which confirms variability in the management severe TBI patients.

The systematic review was able to find that the level of adherence was proportionally associated with the strength of evidence. Level 1 evidence recommendations were associated with optimal adherence (96%), level 2 evidence recommendations had reasonable adherence (79%), suboptimal adherence was detected with level 3 evidence recommendations (32%) and very poor adherence was associated with unclassified recommendations (13.5%). The cohort study confirmed that ICP monitoring is performed in a minority of patients with severe traumatic brain

injuries patients who meet the current BTF criteria for monitoring (30.1%) in Alberta, even lower than those reported in the studies conducted in UK (43% and 46%) and Austria (56%)[1-3] These findings explain the large variation in adherence to BTF guideline recommendations, which indicate barrier specifically for individual recommendations with low evidence rather than guidelines as a whole. Another explanation could be that guidelines containing large number of recommendations would interfere with appropriate level of adherence, therefore translation of guideline into more efficient, practical and feasible protocols and algorithms would enhance the adherence as shown before[4]. Finally, patient's premorbid level of functioning and comorbidities as well as personal expectations of the treating clinicians, for example, use craniectomy instead of craniotomy may decrease the adherence specifically for ICP insertion.

Factors influencing adherence were reported in related to the patients and organization. No professional related factors were studied. More research focusing on the perspectives of professionals would be valuable. In terms of organizational factors there are consistent patterns showing that treatment in a level 1 trauma center or being in a higher economic status country positively influences adherence [5,6] while lack of health insurance negatively influences adherence[7] .

Patients' characteristics were addressed mostly in the context of the indication for ICP monitoring recommendation. Generally adherence was higher when treating surviving patients with more severe TBI. The cohort study showed that adherence was lower in patients with a normal CT scan compared to patients with abnormal intracranial finding, suggesting that clinicians are likely not convinced that ICP monitoring in this subgroup of severe TBI patients is

necessary since the reason for low GCS is the diffuse axonal injury; therefore, monitoring in these patients needs further investigation. Clinician judgment likely explains the lower rate of adherence among older patients, alcohol intoxicated patients, and patients with cardiac arrest. Older age patients usually have a brain atrophy and less likely to have ICP, thus subgroup of patient should be studied separately. Alcohol intoxication and cardiac arrest could explain patient low level of consciousness.

This knowledge can be used to improve guidelines and to establish strategies to improve adherence. These strategies should also focus on individual guideline recommendations as well as the guidelines as a whole.

In the review, although beneficial effects of adherence to BTF guidelines were observed in some subgroup analyses and none of the subgroup analysis showed harmful effect, the overall pooled result did not show that adherence to BTF guidelines improves mortality rates. This is most likely explained by the heterogeneity and quality of the included studies, as well as the limited number of studies reporting the association between adherence and outcome. Therefore, future research focusing on the relationship between BTF guideline adherence and patient outcomes is needed, particularly with surgical management, for which no studies were found.

ICP monitoring in management of TBI were studied in 2 systematic reviews. One of them included meta-analysis, but overall did not show that ICP monitoring is superior to no ICP monitoring, in terms of the mortality of TBI patients[8,9] . However, in this systematic review we did examine whether or not ICP monitoring was beneficial for subgroups of patients who met the criteria of BTF guidelines for ICP monitoring. This did not show beneficial effect on mortality,

although this finding is could be explained by clinical heterogeneity; different outcome measures, clinical setting, adjusting for different confounding factors, as well as the small number of included studies and low quality of the included studies. Therefore, future research focused on the outcomes associated with adherence to BTF guidelines for ICP monitoring is needed to verify its beneficial effect.

In the cohort study, ICP monitoring is associated with higher mortality and morbidity despite controlling multiple confounders. This finding is in agreement with one study[10]. Conversely, three studies reported that monitoring associated with lower mortality[11-13] and two studies reported no effect on mortality[14-15]. The findings of the current study may have several potential explanations. Firstly, BTF criteria for ICP monitoring do not identify patients who are likely to benefit from it, since GCS score and abnormal CT are not quantitative measures, and clinical management decisions should not be based solely on them. Secondly, neurosurgeons may have intended to insert monitors in patients who were at greater risk for mortality and worse outcome, although multiple potential confounders were controlled, still the nature of the study design might have failed to identify other potential confounders. Thirdly, measures to reduce ICP may be associated with harm. Furthermore, hence ICP monitoring does not imply it was effectively treated; monitoring and high ICP management measure should be assessed as combined intervention. Finally, ICP might be a predictor of the severity of brain injury and the difficulty to control ICP reflecting the extensive of injury.

4.3 Limitation

This thesis included a very comprehensive systematic search, which was conducted based on established guidelines for systematic reviews. Fairly good inter-rater reliability was achieved; as well as comprehensive statistical analyses were conducted, including both the crude and adjusted outcomes. Finally, the standard protocol for reporting systematic reviews was followed. This thesis also included a large population-based study to address the adherence to BTF guidelines in severe TBI, with adequate sample size to detect small effect size and adjust for potential confounders

This Thesis is limited by the fact that the included studies in the systematic review are observational studies and most used retrospective design and patient databases. These methods have high risk of bias. The second limitation is the heterogeneity among the included studies, which made the comparison between the studies difficult with potential residual, unmeasured or misclassification of confounding factors a possible alternative explanation for the study findings. Third, the results of any meta-analysis are limited by the quality of the studies included. Fourth, some data were missing early pupillary reaction and detailed CT head finding which may confound our result. An additional limitation was the lack of long-term follow-up and accurate functional outcome measures, Finally, cause of death was not specified in some studies, although given the size of the sample and methodologies used to control for injury severity and mortality risk, this is unlikely to invalidate the finding of increased mortality risk in monitored patients.

4.4 Conclusion

Adherence to Brain Trauma Foundation guidelines shows high variability in the reported literature, despite the wide dissemination of these guidelines as well as the urgency needed in treating this life-threatening disease. The most likely explanations are the weakness of evidence of some recommendations. This emphasizes the need for well-conducted research to strengthen the current evidence, to focus on the perspectives of professionals and to develop strategies to increase adherence. These could include treating severe TBI patients in level 1 trauma centers and supporting economic improvements to the health system.

In a sample of Canadian TBI patients, adherence to BTF guidelines for ICP monitoring was low and varies across centers, particularly in patients with normal imaging. Further studies to address the role of monitoring in older patients and in patients with no intracranial pathology are warranted.

Adherence to BTF guidelines was not associated with improved mortality in overall pooled analysis. However, some beneficial effects were observed with implementing a guidelines-based protocol and in-hospital crude mortality as well as adherence to specific recommendations; nutrition, SBP, O2 and cerebral perfusion threshold. Low levels of evidence and study heterogeneity limit the generalizability of the results and a well-conducted study to verify these results are needed.

In a sample of Canadian TBI patients, ICP monitoring is associated with higher mortality and ICU and hospital length of stay when used in patients with severe TBI who meet the BTF criteria for ICP monitoring. This may be due to harmful effects of ICP monitoring or, more likely, the association is spurious due to an confounded relationship between ICP monitoring and TBI severity or failure of the BTF criteria to identify patients likely to benefit from monitoring. Regardless, further studies are required to determine the utility of ICP monitoring and to refine the criteria for its use.

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Appendix 1 PROSOERO International prospective register of systematic review

Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta-analysis

Yahya Khormi, Ibrahim Qosadi, Sandy Campbell, A. (Sentil) Senthilselvan, Cian O'Kelly, David Zygun

Citation
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Review question(s)
1. Present a systematic review of practitioners adherence to the BTF guidelines in management of TBI.

2. Explore which factors influencing adherence to the guidelines. Knowing these factors provide valuable insight into the development of strategies to increase the adherence.

3. Study the outcome of guideline-based management in comparison to non-guideline based management to support the existing literature of the beneficial effect of the these guidelines to resolve some uncertainty about the strength of some recommendation.

Searches
We will search the following electronic bibliographic databases: PROSPERO, MEDLINE (OVID), EMBASE (OVID), EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 2014>, EBM Reviews - ACP Journal Club <1991 to November 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials (CENTRAL) <November 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2014>, CINAHL Plus with Full Text, Proquest Dissertations and Theses Full-text, SCOPUS and Google Scholar using both controlled vocabulary (eg: EMTREE and MeSH) and keywords to retrieve concepts including: (Brain Trauma Foundation) or (brain injur* and guideline* and adhere*).

Searches will be limited to adult patients. No other limits will be applied.

Types of study to be included
Randomized trials, cohort, case-control and case series.

Condition or domain being studied
Traumatic brain injury (TBI).

Participants/ population
Adult (>17 years old) hospitalized patients with TBI.

Intervention(s), exposure(s)
Two investigators (YK and IG) will independently screen all titles, abstracts and articles to identify studies addressing the adherence to BTF guidelines for in-hospital management of adult civilian patients of ages more than 17 years with TBI. We will include a) in-hospital guidelines regarding blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, indications for intracranial pressure monitoring, intracranial pressure monitoring technology, intracranial pressure thresholds, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics, and sedatives, nutrition, antiseizure prophylaxis, hyperventilation and steroids. b) guidelines for surgical management for acute Epidural and subdural

Hematomas, Parenchymal Lesions, Posterior Fossa Mass Lesions and Depress Cranial Fractures.

Articles will be included if they meet the following criteria:

1) original research

2) randomized trials, cohort, case-control and case series to study the outcome and factors influence the adherence to guidelines, and supplement these with cross-sectional studies to asses adherence rate with guidelines

3) reported adherence rate, factors influencing adherence, point estimate and 95% confidence interval for mortality or morbidity of traumatic brain injury patients treated according to the BTF guidelines in comparison to patients treated differently.

We will exclude:

1) animal studies

2) pediatric studies

3) case reports, and non-original articles

4) studies that included fewer than ten patients

5) studies addressed adherence to pre- hospital guidelines (pre-hospital management is challenging and the results may not reflect the adherence because failure to achieve target recommendation may be an indicator of severe injury)

6) studies focused on military/combat-related TBI, because the results would not be generalizable to the source population of civilian patients with TBI. Inclusion disagreement will be discussed and resolved by consensus or arbitration by other researcher (CO and DZ).

Comparator(s)/ control
Adult patients hospitalized with traumatic brain injury who were not managed based on BTF guidelines.

Outcome(s)
Primary outcomes
Adherence rate with BTF guidelines for management of TBI patients.

Secondary outcomes
Identify factors influencing adherence.

Mortality and morbidity of traumatic brain injury in patients managed according to the BTF recommendation versus mortality and morbidity in patients managed differently

Data extraction, (selection and coding)
Two investigators (YK and IG) will independently extract data from eligible studies using a pre-designed and pilot-tested standardized electronic data entry form. We will extract data on:

1) Publication details (year and language of publication, name of the publishing journal and country in which the study was conducted)

2) design: type of study (RCT, cohort, case-control, case series), study temporality (prospective, retrospective)

3) study participant details: patient characteristics (age, sex, GCS, Injury severity score)

4) data for percentage adherence to BTF guidelines

5) demographic and injury-related characteristics, which may influence adherence to the BTF guidelines: increase

age, elevated blood alcohol level, normal CT scan and planned neurosurgical intervention or other factors reported in the study. 6) outcomes including mortality or morbidity if they compared between patients treated according to the BTF guidelines and patients treated differently. Discrepancies will be discussed and resolved by consensus or arbitration by other researchers (CO and DZ).

Risk of bias (quality) assessment

The quality of observational studies will be assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, which evaluates studies based on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. For quality assessment of the randomized studies, we will use the Cochrane Handbook ' Risk of Bias ' assessment tool.

For this assessment we will develop a checklist, which will be based on the STROBE statement to assess the reporting of observational studies and the TREND statement to assess the reporting of interventional studies.

Two researchers (YK and IQ) will address quality assessment of the included studies independently. Differences of opinion will be resolved by a discussion with other researchers (CO and DZ).

Publication bias will also be assessed using funnel plot and methods described by Begg and Egger.

All data will be extracted by two independent investigators (YK, IQ). To assess inter-rater reliability, the percent agreement will be calculated on adherence percentage for number of guideline recommendations by third investigator (AS).

Strategy for data synthesis

Narrative synthesis and, where appropriate, quantitative meta-analysis will be used. Synthesis will be based on clustering the selected studies based on type of recommendation. Adherence to BTF based protocol will be extracted as a separate category if the full description of the protocol is reported and adherent to the BTF guidelines. Data synthesis will include description of studies characteristics (such as design, year and language of publication, publishing journal, country (monocenter/multicenter), study period, professionals studied for adherence, number of participants, Median age, GCS, Injury severity score and quality assessment measure).

From each article (a) adherence percentages for each recommendation will be extracted. In case of multiple designs for measurements of adherence regarding one recommendation, multiple adherence percentages will be extracted and clustered based on the study design. In case of a pre and post intervention design for evaluation of intervention for example; introducing a protocol or teaching program, only the post-intervention percentages will be extracted as we want to know the current clinical practice. The median adherence for each recommendation will be calculated. Additionally, factors influencing adherence will be extracted when a statistically significant relationship between the factor and adherence is demonstrated in the article. Outcome measures will be extracted if adjusted point estimate and 95% confidence interval are reported.

Calculation of pooled estimates of mortality among TBI patients managed based on BTF guidelines and patients managed differently.

In preliminary search, we found most studies used odd ratio as measure of association, for that reason odd ratio will be used as the common measure of association. When only relative risk is reported in selected study, we will transform it into odd ratio using the method described by Deeks and Altman. The cohort studies and RCTs will be pooled separately. We will conduct stratified analyses of pooled estimate of mortality by type of recommendation and outcome (for example; in-hospital mortality, intensive care unit mortality, 30 days mortality or 6 months mortality). We will examine heterogeneity separately in the pooled estimates by study design (RCT, observational) using the Cochran Q and I-squared statistics. In the presence of heterogeneity, random effects models will be used (rather than fixed effects models) to obtain pooled effect estimates across studies, to account for the expected variability beyond the chance. The pooled estimates obtained from these calculations will then be compared to determine if experimental versus cohort study design is associated with a different overall result. If studies vary in the degree of adjustment for confounding variable, analysis will be stratified into two models; highly adjusted model, adjust for age, GCS, injury severity score, pupillary response and CT head finding. Minimally adjusted model if did miss one of the confounding

variables mentioned earlier.

Analysis of subgroups or subsets
If an adequate number of studies are chosen for the meta-analysis, we will conduct meta-regression considering the following covariates: year of publication, country of origin, study period and sample size.

Meta-analysis will be performed using Review Manager software (RevMan5.3.5, Cochrane Collaboration) and supplement that with Stata Statistical Software version 13.1. (StataCorp LP, College Station, TX, USA) to perform regression analysis.

Dissemination plans
Conference venues will be sought for poster and oral presentations. The review will be published on completion.

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Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Appendix 2 Adherence to BTF guidelines for management of TBI patients: study protocol for a systematic review and meta analysis

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SYSTEMATIC REVIEWS

PROTOCOL Open Access

Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta-analysis

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Abstract

Background: Traumatic brain injury (TBI) is a leading cause of death and disability around the world. Management based on Brain Trauma Foundation (BTF) guidelines is widely accepted and thought to improve outcome. The objectives of this systematic review are to give an overview of adherence to the BTF guidelines, describe factors influencing adherence, and study the effect of guideline-based management on outcome.

Methods/design: We will search electronic bibliographic databases: PROSPERO, Medline, EMBASE, SCOPUS, NHS, CINAHL, Cochrane Database, and ProQuest Dissertations and Theses Global. Two investigators will independently screen all titles, abstracts, and articles and select Randomized Controlled Trial (RCT), cohort studies, case-control studies, and case series reporting the adherence rate, factors influencing adherence, and mortality or morbidity. These investigators will also independently extract data using a pre-designed and pilot-tested standardized electronic data extraction form and assess the risk of bias. We will exclude pediatric and military-related TBI studies, studies that included fewer than ten patients or addressed adherence to pre-hospital guidelines. Narrative synthesis and if appropriate, quantitative meta-analysis clustered by type of recommendation will be reported.

Discussion: This study is expected to demonstrate the current level of professionals' adherence to BTF guidelines in patients with severe traumatic brain injury, it will describe the factors influencing adherence, which may provide valuable input for development of strategies to successfully increase adherence. In addition, if the studies are sufficiently homogenous, it will describe the effect of these guidelines on patient outcome.

Systematic review registration: PROSPERO CRD42015017794

Keywords: Traumatic brain injuries, TBI, Brain injury guidelines, Brain Trauma Foundation guidelines

Background

Traumatic brain injury (TBI) is a leading cause of death and disability around the world [1, 2]. In the USA, the prevalence of TBI is estimated to be 2 % in the general population [3]. The mortality rate was reported to be 18.4 per 100,000 persons with annual average of 53,014 deaths [4]. A report from the Canadian Institute for Health Information (CIHI) report indicated that there were 16,811 hospitalizations annually for TBI with 1368 (8 %) related deaths [5]. Among residents in a large Canadian health region, the annual incidence of severe TBI was 11.4 per 100,000 persons with a mortality rate of 5.1 per 100,000 persons per year [6].

Clinical practice guidelines are developed to improve quality of care decrease discrepancy in practice and ensure that evidence is followed [7]. Mostly, these guidelines are developed and distributed by well-recognized organizations. A guideline consists of systematically developed recommendations to guide practitioners in choosing

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the appropriate health care decision for specific clinical circumstances [8]. A guideline recommendation is defined as "any statement that promotes or advocates a particular course of action in clinical care" [9]. In the treatment of TBI, guidelines are proposed to be an important aspect of patient management.

There are several published guidelines in the management of TBI from different countries. These guidelines target different aspects of TBI management including management during pre-hospital at the emergency department, in-hospital and intensive care unit, indications for surgical management, and computed tomography (CAT) scan of the head [10–14].

Internationally, Brain Trauma Foundation (BTF) guidelines are widely disseminated. They have been translated into over 15 different languages and applied in Europe, South America, and some parts of China [12]. The BTF maintains and revises several TBI guidelines on an approximate 5-year cycles, including *Guidelines for Prehospital Management of Traumatic Brain Injury*, *Guidelines for the Management of Severe Traumatic Brain Injury*, *Guidelines for the Surgical Management of Traumatic Brain Injury*, *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents*, and *Guidelines for the Field Management of Combat Related Head Trauma and Early Indicators of Prognosis of Severe Traumatic Brain Injury*. These guidelines are developed and maintained through a collaborative agreement with the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), and in collaboration with the AANS/CNS Joint Section on Neurotrauma and Critical Care, European Brain Injury Consortium, and other stakeholders in TBI patient outcome [12].

Guidelines for Management of Severe Traumatic Brain Injury addresses key topics useful for in-hospital medical management of severe TBI in adult patients with a Glasgow Coma Scale (GCS) score of 3–8. These include blood pressure and oxygenation hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, intracranial pressure monitoring, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics and sedatives, nutrition, antiseizure prophylaxis, and hyperventilation through steroids use. In 2007, the third edition of these *Guidelines* was released following the first and second editions in 1995 and 2000. [12, 15, 16].

Guidelines for the Surgical Management of Traumatic Brain Injury addresses acute surgical management of TBI including acute epidural and subdural hematomas, parenchymal mass lesions, depressed skull fractures through posterior fossa lesions with focus on indications, technique, and timing of surgery. These *Guidelines* were published in 2006 [13].

Studies suggest that implementation and strict adherence to BTF guidelines results in improvement in the neurological outcomes and reduction in mortality from severe traumatic brain injury [17, 18]. However, there is still significant variability and inconsistency in the management of traumatic brain injury patients [19, 20]. This review will be the first systematic review assessing the adherence to BTF guidelines and its effect on outcome.

Objectives

The first objective of this study is to present a systematic review of adherence by practitioners to the BTF guidelines for the management of severe TBI. The second objective is to explore the factors influencing adherence to the guidelines. Identification of these factors may provide valuable insight into the development of strategies to increase the adherence. The third objective is to study the outcome of guideline-based management in comparison to non-guideline based management to determine the effectiveness of these guidelines.

Methods/design

Protocol and study overview

Methods of this systematic review and meta-analysis have been developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [22]. We will begin by developing a comprehensive database containing all published literature that addresses adherence to BTF guidelines in the management of severe TBI. This protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42015017794).

Selection criteria

Population

The population of interest will include adult (≥18 years old) hospitalized patients with blunt TBI. Whenever outcome measures are available, the patients who were treated based on the BTF guideline will be compared to the patients who were not treated based on the BTF guideline. Additionally, the population of this study will include the practitioners, mainly the neurosurgeons and critical care physicians, who will be assessed for adherences to guidelines. The assessed guidelines will be (a) in-hospital guidelines regarding blood pressure and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, indications for intracranial pressure monitoring, intracranial pressure monitoring technology, intracranial pressure thresholds, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics, sedatives, nutrition, antiseizure prophylaxis, hyperventilation,

and steroids. (b) Guidelines for surgical management for acute epidural and subdural hematomas, parenchymal lesions, posterior fossa mass lesions, and depress cranial fractures. We will exclude (1) studies addressed adherence to pre-hospital guidelines (the result from studies on pre-hospital management may not reflect the adherence because failure to achieve target recommendation may be an indicator of severe injury), (2) studies focused on military/combat-related TBI, because the results would not be generalizable to the source population of civilian patients with TBI, and (3) studies with majority of pediatric patients.

Outcome

The main outcome will be the adherence rate with BTF guidelines. In addition, we will identify factors influencing the adherence to the BTF guidelines. The effectiveness of adherence with the BTF guidelines on several clinical outcomes will be assessed. The measured clinical outcomes will include mortality (ICU, in-hospital mortality) and morbidity (Glasgow Outcome Scale (GOS), Modified Rankin Scale (MRS), ventilation days, ICU stay, and hospital stay).

Study design

Original searches will include RCT cohort, case-control, and case series. We will exclude studies that included fewer than ten patients.

Search strategy

The primary search strategy was developed by the primary investigator (YK) and in collaboration with an expert searcher/librarian (SC). We will search the following electronic bibliographic databases: PROSPERO Medline (OVID), EMBASE (OVID), EBM Reviews—Cochrane Database of Systematic Reviews, EBM Reviews—ACP Journal Club, EBM Reviews—Database of Abstracts of Reviews of Effects, EBM Reviews—Cochrane Central Register of Controlled Trials, EBM Reviews—Cochrane Methodology Register, EBM Reviews—Health Technology Assessment, EBM Reviews—NHS Economic Evaluation Database, CINAHL Plus with Full Text, ProQuest Dissertations and Theses Full-text, SCOPUS, and Google Scholar using both controlled vocabulary (e.g., EMTREE and MeSH) and keywords to retrieve concepts including Brain Trauma Foundation or brain injur* and guideline* and adhere*. Searches will be limited to adult patients in non-military settings. Animal studies will be excluded. This systematic review will include searching gray literature, reviewing references lists, and contacting experts in the field. (See appendix in Additional file 1 for the final proposed MEDLINE, EMBASE, and EBM Reviews—Cochrane Database of Systematic Reviews search strategy).

Study selection

Two investigators (YK and IG) will independently screen all title abstracts and articles to identify study meeting inclusion/exclusion criteria. Inclusion disagreement will be discussed and resolved by consensus or arbitration by other researchers (CO and DZ).

Data extraction

Two investigators (YK and IG) will independently extract data from eligible studies using a pre-designed and pilot-tested standardized electronic data extraction form. We will extract data on (1) publication details (year and language of publication name of the publishing journal and country in which the study was conducted). (2) Design: type of study (RCT, cohort, case-control, case series), study temporality (prospective, retrospective). (3) Study participant details: patient characteristics (age, sex, GCS, Injury severity score). (4) Data for percentage adherence to BTF guidelines. From each article, adherence percentages for each recommendation will be extracted. In case of a pre- and post-intervention design for evaluation of intervention (for example introducing a protocol or teaching program), only the post-intervention percentages will be extracted because our interest is in the current clinical practice. (5) Demographic and injury-related characteristics, which may influence adherence to the BTF guidelines: increase age, elevated blood alcohol level, normal CT scan, and planned neurosurgical intervention or other factors reported in the study will be extracted when a statistically significant relationship between these factors and adherence is demonstrated. (6) Outcomes including mortality or morbidity if they compared between patients treated according to the BTF guidelines and patients treated differently and 95% confidence interval are reported. Discrepancies will be discussed and resolved by consensus or arbitration by other researchers (CO and DZ).

Quality assessment

Randomized Controlled Trials (RCT)

The quality will be assessed using the Cochrane Handbook "Risk of Bias" assessment tool [23]. Additionally, we will assess the quality of reporting using a checklist, which will be based on the CONSORT (Consolidated Standards of Reporting Trials).

Observational studies

The quality will be assessed using the Cochrane Risk Of Bias Assessment Tool: for Non- Randomized Studies of Interventions (ACROBAT-NRSI) [24] which evaluates the observational studies based on three domains: (1) Pre-intervention; evaluation of bias due to confounding and bias in selection of participants into the study. (2) At intervention: evaluation of bias in measurement of

interventions. (3) Post-intervention: evaluation of biases due to departures from intended interventions bias due to missing data, bias in measurement of outcomes and bias in selection of the reported results. We will assess the quality of reporting of observational studies using a checklist, which will be based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Two researchers (YK and IG) will address quality assessment of the included studies independently. Differences of opinion will be resolved by a discussion with other researchers (CO and DZ).

Data synthesis

Narrative synthesis and where appropriate, quantitative meta-analysis will be used. Synthesis will be based on clustering the selected studies based on type of recommendation. Adherence to BTF-based protocol will be extracted as a separate category if the full description of the protocol and protocol adherence rate was reported. Data synthesis will include description of included studies.

The median adherence and interquartile range for each recommendation will be calculated as well as for overall adherence. Additionally, factors influencing adherence will be examined based on the type of recommendation.

Calculation of pooled estimates of mortality among TBI patients managed based on BTF guidelines and patients managed differently

In preliminary search, odds ratio was used as measure of association in several studies, and we will also use the odds ratio as the summary measure of association in our study. If only the relative risk is reported in a selected study, we will transform the relative risk into an odds ratio using the method described by Deeks and Altman [25]. The cohort studies and RCTs will be pooled separately. We will conduct stratified analyses of pooled estimate of mortality by type of recommendation and outcome (for example in-hospital mortality intensive care unit mortality, 30 days mortality or 6 months mortality). We will examine heterogeneity separately in the pooled estimates by study design (RCT, observational) using the Cochran Q and I^2 statistics [24]. In the presence of heterogeneity, random effects models will be used instead of fixed effects models to account for the expected variability beyond the chance and obtain pooled effect estimates across studies [26]. The pooled estimates obtained from these calculations will then be compared to determine if the results are different between experimental and cohort study designs. If the adjustment for confounding variables varies between studies, analysis will be stratified into two parts, one for studies adjusting for several confounding variables (e.g., age, GCS, injury severity score, pupillary response, and CAT scan head finding) and the other one for studies adjusting for a few confounding variables.

If an adequate number of studies are chosen for the meta-analysis, we will conduct meta-regression considering the following covariates: year of publication, country of origin, and study period.

Publication bias will also be assessed using funnel plot and the methods described by Begg and Egger [27, 28]. Meta-analysis will be performed using Review Manager software (RevMan5.3.5 Cochrane Collaboration) and regression analysis will be conducted using Stata Statistical Software version 13.1. (StataCorp LP, College Station, TX, USA).

All data will be extracted by two independent investigators (YK IG). To assess inter-rater reliability, the percent agreement will be calculated on adherence percentage for number of guideline recommendations by third investigator (AS).

Discussion

This systematic review and meta-analysis will be the first systematic review summarizing relevant literature on guidelines for management of severe traumatic brain injury. In this review, we will demonstrate the current level of professionals' adherence to BTF guidelines in patients with severe traumatic brain injury. In addition, we will describe the factors influencing adherence, which may provide valuable input for development of strategies to successfully increase adherence. Finally, we will describe the effect of these guidelines on patient outcome if data is sufficiently homogenous. Results of this review are expected to be available near the end of 2015.

The major strength of this systematic review will be the use of several electronic databases and other relevant sources based on established guideline for systematic review. An additional strength of the review will be the use of inter-rater reliability, standard protocol for reporting systematic reviews as well as quality assessment of the included studies. However, there are some limitations in this review. We may not be able to find the non-observational studies due to the nature of the measured effect. Furthermore, this review will be examining adherences with different recommendations at several locations using different clinical determinants. Therefore, a high level of heterogeneity will be expected and may limit our ability to perform meta-analysis.

Additional file

Additional file 1: Appendix 1. Proposed Medline search strategy; **Appendix 2.** Proposed Embase search strategy; **Appendix 3.** Proposed EBM Reviews—Cochrane Database of Systematic Reviews search strategy. (DOCX 24 kb)

Abbreviations
BTF: Brain Trauma Foundation; TBI: traumatic brain injury; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CENTRAL: Cochrane Central Register of Controlled Trials; RCT: Randomized Controlled Trial; AANS: American Association of Neurological Surgeons; CNS: Congress of Neurological Surgeons; GCS: Glasgow Coma Scale; MOOSE: Meta-analysis of Observational Studies in Epidemiology; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EBM: evidence-based medicine; ACP: American College of Physicians; NOS: Newcastle-Ottawa Scale; STROBE: Strengthening the Reporting of Observational studies in Epidemiology.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
YK and DZ formulated the research question. YK, DZ, and CO designed the study. YK developed the preliminary search strategy and drafted the manuscript. SC refined and executed the search strategy and exported the results. YK, IG, and AS designed the statistical analysis plan. YK, DZ, CO, AS, IG, and SC critically reviewed the manuscript for content. All authors have approved the final version of the manuscript.

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Appendix 3; Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> (Searched December 10, 2014)

Search Strategy:

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1 Brain Trauma Foundation.mp. (118)

2 Guidelines for the Management of Severe Traumatic Brain Injury.mp. (37)

3 Guidelines for the Surgical Management of Traumatic Brain Injury.mp. (1)

4 Guidelines for Prehosptial Management of Traumatic Brain Injury.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)

5 (Prehosptial Management of Traumatic Brain Injury and guideline*).mp. [mp=title, abstract, original title, name ofsubstance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)

6 Prehosptial Management of Traumatic Brain Injury.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)

7 Guideline* for the Surgical Management of Traumatic Brain Injury.mp. (1)

8 (guideline* or protocol*).mp. and (complian* or comply* or adhere*).ti,ab. [mp=title, abstract, original title,

name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (31676)

9 ((craniocerebral or head or cranium or skull or skulls or cerebrocranial or cranial) adj1 (injur* or trauma* or

wound*)).ti,ab. (30718)

10 8 and 9 (108)

11 exp Guideline Adherence/ and 9 (93)

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10 or 11 (308)

13 exp child/ or exp congenital/ or exp infant/ or exp adolescence/ or exp infant, newborn/ or exp child, preschool/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or premature birth or NICU or preschool* or pre-school* or kindergarten* or elementary school$ or nursery school$ or schoolchild* or toddler$ or boy or boys or girl* or middle school* pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. (3696478)

14 12 and 13 (122)

15 12 not 14 (186)

16 limit 14 to "all adult (19 plus years)" (68)

17 15 or 16 (254)

18 remove duplicates from 17 (243)

Database: Embase <1974 to 2014 December 10>

Search Strategy:

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1 Brain Trauma Foundation.mp. (176)

2 Guidelines for the Management of Severe Traumatic Brain Injury.mp. (46)

3 Guidelines for the Surgical Management of Traumatic Brain Injury.mp. (1)

4 Guidelines for Prehosptial Management of Traumatic Brain Injury.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)

5 (Prehosptial Management of Traumatic Brain Injury and guideline*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)

6 Prehosptial Management of Traumatic Brain Injury.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)

7 Guideline* for the Surgical Management of Traumatic Brain Injury.mp. (1)

8 ((guideline* or protocol*) and (complian* or comply* or adhere*)).ti,ab. (38698)

9 exp *practice guideline/ (47101)

10 exp physician/ (428015)

11 exp *protocol compliance/ (360)

12 9 or 11 (47379)

13 10 and 12 (3662)

14 8 or 13 (41821)

15 brain injury/ or acquired brain injury/ or brain concussion/ or brain stem injury/ or cerebellum injury/ or

traumatic brain injury/ (106543)

16 head injury/ (40657)

17 ((craniocerebral or head or cranium or skull or skulls cerebrocranial or cranial) adj1 (injur* or trauma* or

wound*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (57467)

18 15 or 16 or 17 (149550)

19 14 and 18 (354)

20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 19 (541)

21 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or exp

adolescence/ or exp infant, newborn/ or exp child, preschool/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or premature birth or NICU or preschool* or pre-school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. (4076492)

22 20 not 21 (377)

23 20 and 21 (164)

24 limit 23 to (adult <18 to 64 years> or aged <65+ years>) (61)

25 22 or 24 (438)

26 remove duplicates from 25 (430)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 2014>, EBM Reviews - ACP Journal Club <1991 to November 2014>, EBM Reviews - Database of

Abstracts of Reviews of Effects <4th Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <November 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2014>

Search Strategy:

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1 Brain Trauma Foundation.mp. (23)

2 Guidelines for the Management of Severe Traumatic Brain Injury.mp. (3)

3 Guidelines for the Surgical Management of Traumatic Brain Injury.mp. (0)

4 Guidelines for Prehosptial Management of Traumatic Brain Injury.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (0)

5 (Prehosptial Management of Traumatic Brain Injury and guideline*).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (0)

6 Prehosptial Management of Traumatic Brain Injury.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (0)

7 Guideline* for the Surgical Management of Traumatic Brain Injury.mp. (0)

8 (guideline* or protocol*).mp. and (complian* or comply* or adhere*).ti,ab. [mp=ti, ab, tx, kw, ct, ot, sh, hw]

(3815)

9 ((craniocerebral or head or cranium or skull or skulls or cerebrocranial or cranial) adj1 (injur* or trauma* or

wound*)).ti,ab. (998)

10 8 and 9 (10)

11 exp Guideline Adherence/ and 9 (1)

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10 or 11 (35)

13 exp child/ or exp congenital/ or exp infant/ or exp adolescence/ or exp infant, newborn/ or exp child, preschool/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or premature birth or NICU or preschool* or pre-school* or kindergarten* or elementary school$ or nursery school$ or schoolchild* or toddler$ or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. (172181)

14 12 and 13 (17)

15 12 not 14 (18)

16 limit 14 to "all adult (19 plus years)" [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were

retained] (17)

17 15 or 16 (35)

18 remove duplicates from 17 (35)

CINAHL Searched December 11, 2014

Search ID#	Search Terms	Search Options	Actions
S19	S16 OR S18	**Search modes** - Find all my search terms	View Results (106)
S18	S12 AND S15	**Narrow by SubjectAge:** - all adult **Search modes** - Find all my search terms	View Results (18)
S17	S12 AND S15	**Search modes** - Find all my search terms	View Results (59)
S16	s12 not s15	**Search modes** - Find all my search terms	View Results (88)
S15	S13 OR S14	**Search modes** - Find all my search terms	View Results (750,206)
S14	pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or "premature birth" or NICU or preschool* or "pre-school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild* or toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or "pre-pubesc*"	**Search modes** - Boolean/Phrase	View Results (750,135)
S13	(MH "Adolescence+") OR (MH "Child+") OR (MH "Infant+") OR (MH "Minors (Legal)")	**Search modes** - Boolean/Phrase	View Results (601,468)
S12	S3 AND S11	**Search modes** - Find all my search terms	View Results (147)
S11	S4 OR S5 OR S8 OR S10	**Search modes** - Find all my search terms	View Results (18,766)
S10	S7 AND S9	**Search modes** - Find all my search terms	View Results (1,420)
S9	(MH "Protocols+")	**Search modes** - Find all my search terms	View Results (24,641)
S8	S6 AND S7	**Search modes** - Find all my search terms	View Results (5,023)
S7	complian* or comply* or adhere*	**Search modes** - Find all my search terms	View Results (70,443)
S6	(MH "Practice Guidelines")	**Search modes** - Find all my search terms	View Results (46,677)
S5	(MH "Professional Compliance") OR (MH "Guideline Adherence")	**Search modes** - Find all my search terms	View Results (11,459)
S4	(guideline* or protocol*) and (complian* or comply* or adhere*)	**Search modes** - Find all my search terms	View Results (15,601)
S3	S1 OR S2	**Search modes** - Find all my search terms	View Results (25,736)
S2	((craniocerebral or head or cranium or skull or skulls or cerebrocranial or cranial) w1 (injur* or trauma* or wound*))	**Search modes** - Find all my search terms	View Results (8,134)
S1	(MH "Brain Injuries+") OR (MH "Skull Fractures+")	**Search modes** - Find all my search terms	View Results (19,543)

SCOPUS Searched December 12, 2014

(((TITLE-ABS-KEY(guideline* or protocol*) AND TITLE-ABS-KEY(complian* or comply* or adhere*) AND TITLE-ABS-KEY(((craniocerebral or head or cranium or skull or skulls or cerebrocranial or cranial) w/1 (injur* or trauma* or wound*))))) AND NOT ((TITLE-ABS-KEY(pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre-term" or "premature birth*" or NICU or preschool* or "pre-school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild*) OR TITLE-ABS-

KEY(toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or "pre-pubesc*" or "child day care*")))) or ((((TITLE-ABS-KEY(guideline* or protocol*) AND TITLE-ABS-KEY(complian* or comply* or adhere*) AND TITLE-ABS-KEY(((craniocerebral or head or cranium or skull or skulls or cerebrocranial or cranial) w/1 (injur* or trauma* or wound*))))) and ((TITLE-ABS-KEY(pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or "pre-term" or "premature birth*" or NICU or preschool* or "pre-school*" or kindergarten* or "elementary school*" or "nursery school*" or schoolchild*) OR TITLE-ABS-KEY(toddler* or boy or boys or girl* or "middle school*" or pubescen* or juvenile* or teen* or youth* or "high school*" or adolesc* or "pre-pubesc*" or "child day care*")))) and (TITLE-ABS-KEY(adult* or man or men or woman or women or "fully grown" or mature or "full grown"))) = 189 References

Proquest Dissertations and Theses Full Text Searched December 12, 2014

all((craniocerebral OR head OR cranium OR skull OR skulls OR cerebrocranial OR cranial) NEAR/1 (wound* OR trauma* OR injur*)) AND all(guideline* OR protocol*) AND all(complia* OR comply* OR adher*) NOT all(pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR "pre-term" OR "premature birth*" OR NICU OR preschool* OR "pre-school*" OR kindergarten* OR "elementary school*" OR "nursery school*" OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR "pre-pubesc*" OR "child day care*")

Google Scholar Searched December 12, 2014

"Brain Trauma Foundation" and (complia* or adhere* or comply*) First 20 pages were reviewed and 148 references selected.

Appendix 4 Ethics approval form

Approval Form

Date:	February 5, 2015
Study ID:	Pro00054084
Principal Investigator:	David Zygun
Study Title:	**Compliance with brain trauma foundation guidelines for intracranial pressure monitoring in severe traumatic brain injury and its effect on outcome: A population based study**
Approval Expiry Date:	February-04-16

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application, including revisions received January 30 & February 5, 2015, has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a retrospective chart review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (February-04-16), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health approvals should be directed to (780) 407-6041. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Anthony S. Joyce, Ph.D.
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).