

The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: Evidentiary Tables

A Statement for Healthcare Professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine

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Abstract A variety of technologies have been developed to assist decision-making during the management of patients with acute brain injury who require intensive care.

The Neurocritical Care Society affirms the value of this consensus statement as an educational tool for clinicians.

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A large body of research has been generated describing these various technologies. The Neurocritical Care Society (NCS) in collaboration with the European Society of Intensive Care Medicine (ESICM), the Society for Critical Care Medicine (SCCM), and the Latin America Brain

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Injury Consortium (LABIC) organized an international, multidisciplinary consensus conference to perform a systematic review of the published literature to help develop evidence-based practice recommendations on bedside physiologic monitoring. This supplement contains a Consensus Summary Statement with recommendations and individual topic reviews on physiologic processes important in the care of acute brain injury. In this article we provide the evidentiary tables for select topics including systemic hemodynamics, intracranial pressure, brain and systemic oxygenation, EEG, brain metabolism, biomarkers, processes of care and monitoring in emerging economies to provide the clinician ready access to evidence that supports recommendations about neuromonitoring.

Keywords Consensus development conference · Grading of Recommendations Assessment Development and Evaluation (GRADE) · Brain metabolism · Brain oxygen · Clinical trials · Intracranial pressure · Microdialysis · Multimodal monitoring · Neuromonitoring · Traumatic brain injury · Brain physiology · Bio-informatics · Biomarkers · Neurocritical care · Clinical guidelines

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Introduction

The management of patients admitted to the Neurocritical Care Unit is centered on the early identification and removal of mass lesions and on the detection, prevention, and management of secondary brain injury. This requires careful and repeated assessment and monitoring of clinical and laboratory findings, imaging studies, and bedside physiologic data to target care. The field of neurocritical care has expanded rapidly in the last decade and there is a large and expanding body of literature that describes various bedside techniques used to monitor patients with acute brain injury. Therefore, the Neurocritical Care Society (NCS) in collaboration with the European Society of Intensive Care Medicine (ESICM), the Society for Critical Care Medicine (SCCM), and the Latin America Brain Injury Consortium (LABIC) organized a consensus conference to develop evidence-based recommendations on bedside physiological neuromonitoring. This process required the development of evidentiary tables after a systematic literature review. In this article we provide the evidentiary tables on select topics to assist clinicians in bedside decision making.

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Process

This Supplement contains a consensus summary statement that describes the process used to develop recommendations in detail [1]. Seventeen individual topics were chosen for review and two authors assigned to each topic performed a critical literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [2] with the help of a medical librarian. Evidentiary tables were prepared. These tables were used to then facilitate discussion at an international multidisciplinary conference and develop

recommendations using the GRADE system [3–5]. In this article we provide the initial evidentiary tables used to help develop recommendations for select topics including: systemic hemodynamics, intracranial pressure, brain and systemic oxygenation, EEG, brain metabolism, biomarkers, processes of care and monitoring in emerging economies.

Evidentiary Tables

Please refer to individual topic chapters in this supplement for abbreviations and cited literature.

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Systemic Hemodynamics

Studies that evaluate cardiac function in acute brain injury patients

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Incidence of altered cardiac function							
Sandvei et al. [21]	18	P	SAH	Echography	To assess the incidence of LV dysfunction	Systolic function and SV were higher in patients than in controls Diastolic function was altered in the early phase when compared to controls	Very low
Banki et al. [14]	173	P	SAH	Echography	To assess the incidence and time-course of LV dysfunction	15 % had low LVEF 13 % of patients had RWMA with normal LVEF Recovery of LV function observed in 66 % of patients	Low
Mayer et al. [16]	57	P	SAH	Echography	To assess the incidence of LV dysfunction	8 % of RWMA, which were associated with hypotension and PE	Low
Jung et al. [15]	42	P	SAH	Echography	To assess the incidence of LV dysfunction	Only 1/42 patients had LV dysfunction	Low
Lee et al. [85]	24	P	SAH	Echography	To assess the incidence of Tako-Tsubo cardiopathy among patients with SAH-induced LV dysfunction	8/24 patients had Tako-Tsubo pattern All patients recovered LVEF >40 %	Very low
Khush et al. [19]	225	P	SAH	Echography	To assess the incidence and predictors of SAH-induced LV dysfunction	RWMA were found in 27 % of patients Apical sparing pattern was found in 49 % of patients Younger age and anterior aneurysm position were independent predictors of this AS pattern	Low
Jacobshagen et al. [86]	200	R	CA	Echography	To assess the incidence of LV dysfunction	Significant reduction of LVEF (32 ± 6 %) on admission	Very low
Ruiz-Bailen et al. [87]	29	P	CA	Echography	To assess the incidence and time-course of LV dysfunction	LV dysfunction occurred in 20/29 patients in the early phase after CA LVEF slowly improved among survivors	Very low
Role of cardiac function monitoring to explain the mechanisms of brain injury-related cardiopulmonary complications							
Miss et al. [88]	172	P	SAH	Echography	To evaluate the correlation of LV dysfunction with the type of aneurysm therapy	No difference in the occurrence of RWMA or LV dysfunction with regard of coiling or clipping	Low
Frangiskakis et al. [57]	117	P	SAH	Echography	To evaluate the correlation of LV dysfunction with ECG abnormalities	Low LVEF associated with VA	Low
Pollick et al. [17]	13	P	SAH	Echography	To evaluate the correlation of LV dysfunction with ECG abnormalities	RWMA in 4/13 patients RWMA was associated with inverted T waves	Very low
Kono et al. [89]	12	P	SAH	Echography	To evaluate the correlation of LV dysfunction with ECG and coronary angiography abnormalities	Apical LV hypokinesia was not associated with coronary stenosis despite ST elevation on ECG	Low
Davies et al. [18]	41	P	SAH	Echography	To evaluate the correlation of LV dysfunction with ECG abnormalities	RWMA in 10 % of patients RWMA not associated with ECG alterations	Low

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Bulsara et al. [13]	350	R	SAH	Echography	To evaluate the correlation of LV dysfunction with ECG abnormalities and markers of heart injury	LVEF < 40 % in 3 % of patients No association of LV dysfunction with ECG abnormalities Peak of cTnI in SAH patients was lower than matched patients with MI	Very low
Deibert et al. [90]	43	P	SAH	Echography	To assess the relationship between LV dysfunction and markers of heart injury	RWMA associated with high cTnI RWMA resolved over time in all patients	Low
Hravnak et al. [91]	125	P	SAH	Echography	To assess the relationship between LV dysfunction and markers of heart injury	High cTnI was associated with RWMA and lower LVEF Only 26 % of patients returned to normal cardiac function over time	Low
Naidech et al. [29]	253	R	SAH	Echography	To assess the relationship between LV dysfunction and markers of heart injury	High cTnI was associated with RWMA and low LVEF	Very low
Parekh et al. [30]	41	P	SAH	Echography	To assess the relationship between LV dysfunction and markers of heart injury	High cTnI was associated with low LVEF	Low
Tung et al. [31]	223	P	SAH	Echography	To assess the relationship between LV dysfunction and markers of heart injury	Low LVEF predicted high cTnI	Low
Kothavale et al. [92]	300	P	SAH	Echography	To assess the relationship between LV dysfunction and markers of heart injury	RWMA in 18 % patients RWMA associated with poor neurological status and high cTnI levels	Low
Apak et al. [93]	62	P	Stroke	Echography	To assess the relationship between LV dysfunction and markers of heart injury	Serum levels of cTnT were inversely correlated with LVEF	Low
Zaroff et al. [94]	30	P	SAH	Echography	To assess the relationship between RWMA and patterns of coronary artery disease	RWMA did not correlate with typical patterns of coronary artery disease RWMA resolved in all patients	Very low
Banki et al. [33]	42	P	SAH	Echography	To assess the relationship between LV dysfunction of myocardial perfusion and innervation	LV systolic dysfunction was associated with normal myocardial perfusion and abnormal sympathetic innervation	Low
Abdelmoneim et al. [32]	10	P	SAH	RTP-CE	To assess microvascular perfusion and echographic abnormalities after SAH	RWMA was not associated with altered myocardial perfusion	Very low
Sugimoto et al. [28]	77	R	SAH	Echography	To assess the relationship between LV dysfunction and estradiol (ES) or norepinephrine (NE)	The incidence of RWMA in the high-NE/low-ES group was significantly higher than the low-NE/high-ES group	Very low
Sugimoto et al. [27]	48	R	SAH	Echography	To assess the relationship between LV dysfunction and norepinephrine (NE) levels	Plasma NE levels were significantly higher in patients with RWMA and inversely correlated with LVEF	Very low
Tanabe et al. [22]	103	P	SAH	Echography	To assess the relationship between LV dysfunction and PE	Higher incidence of systolic or diastolic dysfunction in patients with elevated cTnI	Low
Kopelnik et al. [23]	207	P	SAH	Echography	To assess the incidence of diastolic dysfunction and its relationship with PE	Diastolic dysfunction was observed in 71 % of subjects Diastolic dysfunction was an independent predictor of PE	Low

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Tung et al. [95]	57	R	SAH	Echography	To assess the relationship between LV dysfunction and elevated BNP	High BNP in patients with systolic or diastolic dysfunction	Very low
Meaudre et al. [96]	31	P	SAH	Echography	To assess the relationship between LV dysfunction and elevated BNP	No correlation between diastolic dysfunction and BNP	Very low
Naidech et al. [35]	171	P	SAH	Echography	To assess the relationship between LV dysfunction and PE	No association of LV dysfunction and PE	Low
McLaughlin et al. [97]	178	R	SAH	Echography	To assess the relationship between LV systolic or diastolic dysfunction and PE	Occurrence of PE was associated with both systolic or diastolic dysfunction	Very low
Sato et al. [37]	49	P	SAH	TT	To assess variables related to the development of PE	Patients with PE had lower cardiac function than others	Low
Junttila et al. [36]	108	P	ICH	Echography	To evaluate the predictive value of echographic abnormalities for NPE	LVEF < 50 % and E/A > 2 more frequent in NPE patients No predictive value of such abnormalities for NPE	Low
Kuwagata et al. [62]	8	P	TBI	Echography	To assess the effects of TH on cardiac function	TH did not affect stroke volume and diastolic function	Very low
Cardiac function monitoring findings and outcome							
Yousef et al. [47]	149	P	SAH	Echography	To evaluate which hemodynamic variable was associated with DCI	No influence of LVEF or RWMA on DCI	Low
Jyotsna et al. [98]	56	P	SAH	Echography	To evaluate the prognostic value of myocardial dysfunction after SAH	LV dysfunction was associated with poor outcome	Low
Sugimoto et al. [60]	47	P	SAH	Echography	To evaluate the prognostic value of myocardial dysfunction after SAH	RWMA independent risk factor of mortality	Low
Papanikolaou et al. [99]	37	P	SAH	Echography	To evaluate the prognostic value of myocardial dysfunction after SAH	LV dysfunction associated with DCI and poor outcome	Low
Temes et al. [3]	119	P	SAH	Echography	To assess the impact of LV dysfunction on cerebral infarction and neurological outcome	LV dysfunction independent predictor of DCI but not of neurologic outcome	Low
Vannemreddy et al. [59]	42	P	SAH	Echography	To evaluate the prognostic value of myocardial dysfunction after SAH	RWMA was associated with poor GCS on admission and increased hospital stay but not with increased mortality	Low
Urbaniak et al. [63]	266	P	SAH	Echography	To evaluate the prognostic value of myocardial dysfunction after SAH	LV dysfunction not associated with outcome	Low
Yarlagadda et al. [64]	300	P	SAH	Echography	To evaluate the prognostic value of myocardial dysfunction after SAH	LVEF not associated with outcome	Low
Front et al. [100]	64	R	Stroke	Radionuclide	To evaluate the prognostic value of LVEF after stroke	Non-survivors had low LVEF (52 ± 18 %) than survivors (64 ± 10 %)	Very low
Chang et al. [61]	165	P	CA	Echography	To assess the LV function and its relationship with outcome	Lower LVEF associated with previous cardiac disease and epinephrine doses LVEF < 40 % had higher mortality than normal LVEF	Low

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Khan et al. [101]	138	P	CA	Echography	To assess the LV function and its relationship with outcome	LVEF < 40 % had higher mortality than normal LVEF	Low

P prospective, *R* retrospective, *SAH* subarachnoid haemorrhage, *TBI* traumatic brain injury, *TT* transpulmonary thermodilution, *PE* pulmonary edema, *CO* cardiac output, *PCWA* pulse contour wave analysis, *LVEF* left ventricular ejection fraction, *NPE* neurogenic pulmonary edema, *CV* cerebral vasospasm, *CI* cardiac index, *PE* pulmonary edema, *IABP* intra-aortic balloon counterpulsation, *LVEF* low ventricular ejection fraction, *cTnl* troponin I, *GEDVI* global end-diastolic volume index, *GEF* global ejection fraction, *DCI* delayed cerebral infarction, *BNP* brain natriuretic peptide, *SV* stroke volume, *ECG* electrocardiogram, *VA* ventricular arrhythmias, *NPE* neurogenic pulmonary edema, *RTP-CE* real-time contrast echocardiography

Studies evaluating cardiac output (CO) in acute brain injury patients

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
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Incidence of altered CO

Mutoh et al. [24]	46	P	SAH	TT	To evaluate the time course of cardiac function	High CI on admission which diminished on day 5 Higher CI in patients with poor neurological status	Low
Trieb et al. [25]	30	P	Stroke	PAC	To evaluate CO after ischemic stroke	Patients with stroke had significantly higher CO than comparable controls	Low
Laurent et al. [26]	165	R	CA	PAC	To evaluate hemodynamics after CA	Low CI is common in the early phase after CA, which normalizes thereafter, except in those dying with cardiogenic shock and MOF	Very low
Rzheutskaya et al. [102]	13	P	TBI	TT	To assess hemodynamic alterations after TBI	Four different hemodynamic response according to CI, SVR, SVV and response to fluid administration	Very low
Schulte Esch et al. [40]	12	P	TBI	PAC	To assess hemodynamic alterations after TBI	Elevated CI with high PAOP and low SVRI were reported	Very low

Role of CO monitoring to explain the mechanisms of brain injury-related cardiopulmonary complications

Sato et al. [37]	49	P	SAH	TT	To assess variables related to the development of PE	Patients with PE had lower CI than others	Low
Deehan et al. [38]	24	R	SAH	PAC	To evaluate hemodynamics in patients with PE To assess effects of dobutamine	Variable hemodynamic variables Increased CI and decreased PAOP in patients with PE	Very low
Vespa et al. [39]	56	R	SAH	PAC	To evaluate the mechanisms of poor oxygenation after SAH	Similar hemodynamics between patients with and without poor oxygenation	Very low
Tamaki et al. [103]	15	P	TBI	PAC	To assess hemodynamic alterations after TBI	All patients had high PAOP and PVR Hypotensive patients had low CI and elevated SVRI Normotensive patients had high SVRI	Very low
Nicholls et al. [104]	60	P	TBI		To assess hemodynamic alterations after TBI	High CI and MAO with reduced tissue oxygenation were found Survivors had higher CI and tissue oxygenation than non-survivors	Low
Bergman et al. [41]	50	P	OHCA	PAC	To evaluate the effects of TH on hemodynamics	TH lowered heart rate, filling pressures, CO and MAP without deleterious effects on SvO ₂	Low
Zobel et al. [42]	40	P	CA	PAC	To evaluate the effects of TH on hemodynamics during cardiogenic shock	TH improved hemodynamics during cardiogenic shock following CA	Low

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Sato et al. [43]	60	P	SAH	PAC	To evaluate the effects of TH on systemic and cerebral hemodynamics during surgery	TH was associated with decreased CI and increased arterio-jugular difference in oxygen	Low
Association between CO and brain perfusion, neurological complications or outcome							
Tone et al. [48]	42	P	SAH	PAC	To evaluate the correlation between hemodynamic variables and CBF	CBF was correlated with CI	Very low
Hashimoto et al. [105]	20	P	BS	TT	To evaluate the correlation between hemodynamic variables and CBF	CBF was not correlated with CI after BAVM resection	Very low
Watanabe et al. [34]	34	P	SAH	TT	To evaluate which hemodynamic variable was associated with the occurrence of DCI	DCI was associated with lower CI	Low
Mayer et al. [45]	72	R	SAH	Echography	To evaluate which hemodynamic variable was associated with the occurrence of DCI	DCI was associated with lower CI	Very low
Yousef et al. [47]	149	P	SAH	Echography	To evaluate which hemodynamic variable was associated with the occurrence of DCI	DCI was associated with lower CI	Low
Torgesen et al. [106]	153	R	CA	PAC	To evaluate the impact of hemodynamic variables on outcome during NT	No association of hemodynamic variables with outcome	Very low
Torgesen et al. [107]	134	R	CA	PAC	To evaluate the impact of hemodynamic variables on outcome during TH	Elevated CI was associated with poor outcome	Very low
Yamada et al. [108]	34	P	TBI	Dye Dilution	To evaluate the impact of hemodynamic variables on outcome after severe TBI	Low CI was associated with poor outcome	Very low
Effects of therapies modifying CO on neurological status							
Chatterjee et al. [109]	15	P	BS	Echography	To evaluate the effects of mannitol on systemic hemodynamics	Mannitol increased CI during 15 min after administration	Low
Stoll et al. [110]	20	P	Stroke	BioImp	To evaluate the effects of HES on systemic hemodynamics	HES administration avoided nocturnal decrease in CO and MAP No effects on neurological status were reported	Very low
Finn et al. [52]	32	P	SAH	PAC	To evaluate the effects of hemodynamic optimization on neurological status	Maintaining PAOP between 14 and 16 mmHg reversed neurological deficit; all patients had CI > 4.5 L/min m ²	Very low
Mori et al. [53]	98	P	SAH	PAC HHH	To evaluate the effects of HHH therapy on CBF and neurological status	HHH increased PAOP and CI Increased MAP and CI was associated with increased CBF	Low
Otsubo et al. [51]	41	P	SAH	PAC NV-HT	To evaluate the effects of NV-HT on neurological status	NV-HT increased also CI and improved neurological status in 71 % of symptomatic vasospasm	Low
Muench et al. [54]	47	P	SAH	PAC HHH (NE)	To evaluate the effects of different component of HHH therapy on brain perfusion and oxygenation	Increased MAP but unchanged CI Increase in rCBF/PbO ₂ only with HTN	Low

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Mutoh et al. [111]	7	P	SAH	TT	To evaluate the effects of hyperdynamic therapy on brain oxygenation during symptomatic vasospasm	TT-guided therapy Increased rSO ₂ during VSP	Very low
Levy et al. [55]	23	P	SAH	PAC Dobu	To evaluate the effects of dobutamine on neurological status	Increased CI improved neurological status during CV in 78 % of patients who failed to respond to NE	Low
Tanabe et al. [50]	10	R	SAH	PAC	To evaluate the effects of IV albumin on systemic hemodynamics	Increased CI improved neurological status during CV	Very low
Hadeishi et al. [49]	8	R	SAH	PAC Dobu	To evaluate the effects of dobutamine on neurological status	Increased CI improved neurological status during CV	Very low
Kim et al. [112]	16	P	SAH	PAC Dobu/ Phenyl	To evaluate the effects of dobutamine and phenylephrine on neurological status	Both drugs increased CBF in patients with vasospasm	Very low
Miller et al. [113]	24	P	SAH	PAC Phenylephr	To evaluate the effects of phenylephrine on neurological status	Increased MAP did not result in CI changes—88 % of patients improved neurological status	Low
Naidech et al. [114]	11	R	SAH	PACDobu/ Milri	To evaluate the effects of different inotropes on systemic hemodynamics	Milrinone was more effective to increase CI but was also associated with lower MAP	Very low
Impact of specific therapies dealing with optimization of CO on outcomes							
Tagami et al. [65]	1,482	R (b/a)	OHCA	TT-guided therapy	To assess the impact of TT-guided therapy on outcome of CA patients	Improved good neurological outcome	Low
Kim et al. [67]	453	P (b/a)	SAH	PAC	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	Reduced incidence of sepsis and pulmonary edema Reduced mortality (29 vs. 34 %, <i>p</i> = 0.04)	Moderate
Mutoh et al. [78]	45	P	SAH	TT	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	4/8 DCI in patients with VSP No pulmonary edema or heart failure	Low
Vermeij et al. [115]	348	R (b/a)	SAH	PAC (VSP) HHH	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	Reduced mortality among patients with DCI	Low
Medlock et al. [69]	47	P	SAH	PAC Proph. HHH	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	Proph HHH did not prevent DNID 26 % incidence of PE	Low
Rondeau et al. [66]	41	RCT	SAH	TT	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	Dobu versus NE: similar VSP and DCI but lower MV duration and ICU stay	Moderate
Mutoh et al. [68]	116	RCT	SAH	PAC (late) TT	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	Reduced VSP, DCI, VSP-related infarctions, CV complications—improved mRS	Moderate

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Lennihan et al. [116]	82	RCT	SAH	PAC HV versus NV	To evaluate the effects of hemodynamic monitoring on the occurrence of complications	HV did not increase CBF but raised filling pressures No differences in occurrence of VSP and DCI	Moderate

P prospective, *R* retrospective, *SAH* subarachnoid haemorrhage, *TBI* traumatic brain injury, *TT* transpulmonary thermodilution, *PE* pulmonary edema, *CO* cardiac output, *PCWA* pulse contour wave analysis, *LVEF* left ventricular ejection fraction, *NPE* neurogenic pulmonary edema, *NR* not reported, *CV* cerebral vasospasm, *CI* cardiac index, *PE* pulmonary edema, *IABP* intra-aortic balloon counterpulsation, *LVEF* low ventricular ejection fraction, *cTnI* troponin I, *GEDVI* global end-diastolic volume index, *GEF* global ejection fraction, *DCI* delayed cerebral infarction, *BNP* brain natriuretic peptide, *SV* stroke volume, *ECG* electrocardiogram, *VA* ventricular arrhythmias

Studies evaluating preload in acute brain injury patients

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Role of preload monitoring to explain the mechanisms of brain injury-related cardiopulmonary complications							
Deehan et al. [38]	24	R	SAH	PAC	To assess effects of dobutamine	High variable PAOP in patients with PE	Very low
Watanabe et al. [34]	34	P	SAH	TT	To evaluate which hemodynamic variable was associated with the occurrence of PE	PE was associated with higher GEDVI DCI was associated with lower GEDVI	Very low
Mayer et al. [45]	72	R	SAH	Echography	To evaluate the impact of hemodynamic alterations on cerebral complications	PAOP was not associated with the development of DCI	Very low
Vespa et al. [39]	56	R	SAH	PAC	To evaluate the mechanisms of poor oxygenation after SAH	Increased ELVWI in patients with poor oxygenation	Very low
Touho et al. [44]	25	R	SAH	TT	To evaluate the mechanisms of poor oxygenation after SAH	Increased intrapulmonary shunt and ELWI were found in patients with poor oxygenation	Very low
Sato et al. [37]	49	P	SAH	TT	To assess variables related to the development of PE	Patients with PE had higher ELWI than others	Low
Verein et al. [117]	17	P	Stroke	TT	To assess the relationship between ELVWI and ICP or brainstem function	ELVWI was correlated with latency of auditory potentials	Very low
Role of preload monitoring to optimize therapy							
Bulters et al. [56]	71	RCT	SAH	PAC	To assess hemodynamic changes with IABP	PAOP-guided therapy resulted in increased CBF and CPP during IABP	Moderate
Mutoh et al. [111]	7	P	SAH	TT	To assess the effects of hyperdynamic therapy on cerebral oxygenation during s-VSP	Increased CO was associated with improved cerebral oxygenation	Very low
Preload monitoring findings and outcome							
Mutoh et al. [78]	45	P	SAH	TT	To evaluate the effects of TT-guided therapy on DCI occurrence during VSP	4/8 DCI in patients with VSP No pulmonary edema or heart failure	Low

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Kim et al. [67]	453	P (b/a)	SAH	PAC HHH versus HD	To compare the effects of two therapeutic strategies on neurological outcomes	Reduced incidence of sepsis and pulmonary edema Reduced mortality	Moderate
Mutoh et al. [68]	116	RCT	SAH	PAC (late) TT	To compare the effects of two therapeutic strategies on neurological outcomes	Reduced VSP, DCI, VSP-related infarctions, CV complications—improved mRS	Moderate

P prospective, *R* retrospective, *SAH* subarachnoid haemorrhage, *TT* transpulmonary thermomodulation, *PE* pulmonary edema, *LVEF* NPE neurogenic pulmonary edema, *NR* not reported, *HHH* triple-H therapy, *PAC* pulmonary artery catheter, *HD* hyperdynamic therapy, *CI* cardiac index, *GEDV* global end-diastolic volume, *ELVWI* extravascular lung water index, *DCI* delayed cerebral ischemia, *VSP* vasospasm, *s-VSP* symptomatic vasospasm, *CV* cardiovascular, *PAOP* pulmonary artery occlusive pressure, *IABP* intra-aortic balloon counterpulsation

TT-guided therapy consisted in optimizing CI, GEDV, and reducing EVLWI

Studies evaluating afterload in acute brain injury patients

Reference	Patient number	Study design	Group	Technique assessment	End-point	Findings	Quality of evidence
Hadeishi et al. [49]	8	R	SAH	PAC	To assess the effects of dobutamine to treat CV	Decreased SVR	Very low
Bulters et al. [56]	71	RCT	SAH	PAC	To assess hemodynamic changes with IABP	Higher SVR during IABP	Moderate
Watanabe et al. [34]	34	P	SAH	TT	To evaluate which hemodynamic variable was associated with the occurrence of DCI	DCI was associated with increased SVR	Low
Rzheutskaya et al. [102]	13	P	TBI	TT	To evaluate hemodynamic alterations after TBI	SVRI were used to identify four different patterns of hemodynamic status	Very low
Mayer et al. [45]	72	R	SAH	Echography	To assess the impact of cardiac injury on hemodynamic and cerebral complications after SAH	Higher SVRI were found in patients developing s-VSP	Very low

P prospective, *SAH* subarachnoid haemorrhage, *TT* transpulmonary thermomodulation, *IABP* intra-aortic balloon counterpulsation, *DCI* delayed cerebral infarction, *SVR* systemic vascular resistances, *s-VSP* symptomatic vasospasm, *PAC* pulmonary artery catheter

Studies evaluating fluid responsiveness (FR) in acute brain injury patients

Reference	Patient number	Study design	Group	Preload assessment	End-point	Findings	Quality of evidence
Berkenstadt et al. [20]	15	P	BS	SVV	To assess the accuracy of SVV to predict FR	SVV was a strong predictor of FR	Low
Li et al. [76]	48	P	BS	SVV	To assess the accuracy of SVV when compared to commonly used variables to predict FR	SVV was a strong predictor of FR	Low
Mutoh et al. [79]	16	P	SAH	SVV	To compare SVV with GEDVI to predict FR	SVV was a better predictor than GEDVI for FR	Moderate
Mutoh et al. [68]	116	RCT	SAH	GEDVI changes	To evaluate the changes in GEDVI versus PAOP/CVP to predict FR	Only changes in GEDVI after fluid loading was associated with SV changes	Moderate

Reference	Patient number	Study design	Group	Preload assessment	End-point	Findings	Quality of evidence
Moretti et al. [77]	29	P	SAH	dICV	To evaluate the changes in SVV versus dICV to predict FR	SVV and dICV were both strong predictor of FR	Moderate
Deflandre et al. [84]	26	P	BS	Δ PP	To evaluate the changes in Δ PP versus DD to predict FR	Δ PP and DD were both strong predictor of FR	Moderate

P prospective, *RCT* randomized clinical trial, *BS* brain surgery, *SAH* subarachnoid haemorrhage, *SVV* stroke volume variation, *GEDVI* global end-diastolic volume index, *dICV* distensibility of inferior vena cava, *Δ PP* pulse pressure variation

Studies evaluating parameters of global perfusion in acute brain injury patients

Reference	Patient number	Study design	Group	GP Assessment	End-point	Findings	Quality of evidence
Venous saturation							
Di Filippo et al. [70]	121	P	TBI	ScvO ₂	To assess the prognostic value of ScvO ₂ after TBI	ScvO ₂ values were lower in non-survivors than in survivors ($p = 0.04$) but not independently predictor of mortality	Very low
Gaieski et al. [71]	38	R (b/a)	CA	ScvO ₂ CTRL	To assess the impact of ScvO ₂ -guided therapy on outcome after CA	ScvO ₂ -guided therapy tended to a reduction in mortality	Low
Walters et al. [72]	55	P (b/a)	CA	ScvO ₂ CTRL	To assess the impact of ScvO ₂ -guided therapy on outcome after CA	ScvO ₂ -guided therapy tended to an improved neurological outcome	Moderate
Lactate							
Donnino et al. [75]	79	R	CA	Lactate	To assess the prognostic value of lactate clearance after CA	Higher lactate clearance at 6-, 12- and 24- in survivors than non-survivors	Very low
Karagiannis et al. [118]	28	R	IHCA	Lactate	To assess the prognostic value of lactate clearance after CA	Lactate clearance was significantly lower in survivors than non-survivors	Very low
Kliegel et al. [74]	394	R	CA	Lactate	To assess the prognostic value of lactate levels and lactate clearance after CA	Lactate levels at 48 h were independently associated with poor neurological outcome	Very low
Lemiale et al. [46]	1,152	R	OHCA	Lactate	To assess the prognostic value of lactate after CA	Admission lactate was an independent predictor of ICU mortality	Very low
Starodub et al. [73]	199	R	OHCA IHCA	Lactate	To assess the prognostic value of lactate levels and lactate clearance after CA	Initial serum lactate and lactate clearance were not predictive of survival	Very low
Cocchi et al. [119]	128	R	OHCA	Lactate	To assess the prognostic value of lactate levels and vasopressors after CA	Vasopressor need and lactate levels could predict mortality	Very low
Oddo et al. [120]	88	P	CA	Lactate	To assess the prognostic value of several hospital variables after CA	Lactate on admission was an independent predictor of poor outcome	Low
Shinozaki et al. [121]	98	P	OHCA	Lactate	To assess the prognostic value of lactate after CA	Initial lactate level was independently associated with poor outcome Level > 12 mmol/L predicted poor outcome (Sens. 90 % and Sp. 52 %)	Low

Reference	Patient number	Study design	Group	GP Assessment	End-point	Findings	Quality of evidence
Mullner et al. [122]	167	R	OHCA	Lactate	To assess the prognostic value of lactate after CA	Initial lactate values were correlated with the duration of arrest and associated with poor outcome	Very low
Adrie et al. [123]	130	P	OHCA	Lactate	To identify clinical and laboratory variables that predict outcome after CA	Lactate on admission was an independent predictor of poor outcome	Low
Zhao et al. [124]	81	P	TBI	Lactate	To assess the effect of TH on lactate and glucose levels after TBI	TH reduced more rapidly lactate levels than normothermia	Low
Yatsushige et al. [125]	12	P	TBI	Lactate	To assess predictors of poor outcome after decompressive craniectomy	Lactate levels were independently associated with poor outcome	Very low
Meierhans et al. [126]	20	R	TBI	Lactate	To assess the effects of arterial lactate on brain metabolism	Blood lactate > 2 mmol/L increased brain lactate and decreased brain glucose	Very low
Cureton et al. [127]	555	R	TBI	Lactate	The impact of lactate on neurological outcome	Increased lactate was associated with more severe head injury Patients with lactate > 5 mmol/L had better outcome	Very low
Brouns et al. [128]	182	P	Stroke	Lactate	The impact of lactate on neurological outcome	Blood lactate was not associated with outcome	Low
Jo et al. [129]	292	R	Stroke	Lactate	The impact of initial lactate on neurological outcome	Initial lactate levels > 2 mmol/L associated with poor outcome	Very low
ΔCO_2							
Tsaousi et al. [130]	51	P	BS	ΔCO_2	To assess the relationship between CI and ΔCO_2	Good correlation ($R^2 = 0.830$) between the two variables	Very low

P prospective, *R* retrospective, *CA* cardiac arrest, *OHCA* out-of-hospital CA, *IHCA* in-hospital CA, *ScvO₂* central venous saturation, ΔCO_2 veno-arterial CO₂ difference, *BS* brain surgery, *CI* cardiac index, *TBI* traumatic brain injury, *TH* therapeutic hypothermia, *Sens.* sensitivity, *Spec.* specificity, *CTRL* control group

Available techniques used for hemodynamic monitoring in patients with acute brain injury and their potential advantages and disadvantages

Techniques	Cardiac output	LV function	Preload	Fluid responsiveness	Afterload	Advantages	Disadvantages
PAC	+	–(LV) +(RV)	+	–	+	Measure of PAP, PAOP Measure of SvO ₂	Invasiveness Not beat-by-beat analysis
Trans-pulmonary Thermodilution ^a	+	+	+	+	+	Less invasive No need for PAC positioning	Requires a specific femoral arterial catheter Not beat-by-beat analysis
External + internal calibrated PCM ^a	+	+	–	+	+	Continuous CO monitoring Continuous ScvO ₂ (optional)	Recalibration every 4–6 h Requires a specific femoral arterial catheter
Internal-calibrated PCM ^b	+	–	–	+	+	Continuous CO monitoring Continuous ScvO ₂ (optional) Mini-invasive	Less accuracy for CO Sensitive to SVR Requires specific catheter
Non-calibrated PCM ^c	+	+	–	+	+	Continuous CO monitoring No need for dedicated catheter Mini-invasive	Few data available Less accuracy for CO (?) Requires optimal arterial pressure tracing

Techniques	Cardiac output	LV function	Preload	Fluid responsiveness	Afterload	Advantages	Disadvantages
Echocardiography	+	+	+	+	–	Visualization of the heart Estimate for filling pressure	Intermittent use Requires adequate training

PAC pulmonary artery catheter, *PCM* pulse contour method, *ScvO₂* central venous oxygen saturation, *SvO₂* mixed venous oxygen saturation, *SVR* systemic vascular resistances, *CO* cardiac output, *PAP* pulmonary artery pressure, *PAOP* pulmonary artery occlusive pressure, *LV* left ventricle, *RV* right ventricle

+ possible; – not feasible

^a PiCCO device (Pulsion Medical Systems, Irving, TX, USA)

^b FloTrac Vigileo device (Edwards, Irvine, CA, USA)

^c MostCare-PRAM device (Vygon, Padova, Italy)

Differences among different monitoring techniques for cardiac output (CO) in acute brain injury patients

Reference	Patient number	Study design	Group	Technique assessment	Findings	Quality of evidence
Franchi et al. [131]	121	P	TBI	PCA PCWA	CO: correlation 0.94; bias 0.06 L/min; PE 18 %	Moderate
Mutoh et al. [78]	45	P	SAH	PCWA TT	CI: correlation 0.77; bias 0.33 L/min m ² ; PE 15 %	Moderate
Mutoh et al. [68]	116	RCT	SAH	PAC TT	CI: correlation 0.78; bias 0.05 L/min m ² ; PE 14 %	High
Mutoh et al. [79]	16	P	SAH	PCWA TT	CI: correlation 0.82; bias was 0.57 L/min m ² ; PE 25 % and higher during MV	Moderate
Junttila et al. [80]	16	P	BS	PCWA PAC	CO: bias 1.7 L/min; PE 45 %. Larger bias during NE and NIMO therapy Significant correlation SVR/bias	Moderate
Haenggi et al. [82]	8	P	OHCA	PCWA PAC	CO: bias 0.23 L/min, PE 34 % No differences between TH and NT	Moderate
Tagami et al. [83]	88	P	CA	TT	Coefficient of error < 10 % (3 injections)	Moderate
Mayer et al. [81]	48	P	SAH	Echography PAC	CO: correlation 0.67; bias 0.75 L/min; precision 1.34 L/min; echography underestimated PAC-derived CO	Moderate

P prospective, *R* retrospective, *RCT* randomized clinical trial, *TBI* traumatic brain injury, *SAH* subarachnoid hemorrhage, *OHCA* out-of-hospital cardiac arrest, *TT* transpulmonary thermodilution, *PCWA* pulse contour wave analysis, *PAC* pulmonary artery catheter, *CO* cardiac output, *CI* cardiac index, *PE* percentage of error, *NE* norepinephrine, *NIMO* nimodipine, *SVR* systemic vascular resistances, *TH* therapeutic hypothermia, *NT* normothermia

Intracranial Pressure and Cerebral Perfusion Pressure: Fundamental Considerations and Rationale for Monitoring

Indications for ICP monitoring. Are there clinical or CT findings that predict the development of intracranial hypertension and so can guide decision making about ICP monitor placement?

Reference	# of patients	Design	Grade crit.	Results	Caveats
Hukkelhoven et al. [105]	134 monitored patients	Single-centre, retrospective observational analysis of admission clinical predictors of ICP elevation	Low	No univariate predictors with $p < 0.05$. Model discrimination (AUC) = 0.50 (95 % CI 0.41–0.58) and calibration (Hosmer–Lemeshow goodness of fit) = 0.18	No admission CT data. No control for decision to monitor. Subjective classification of intracranial hypertension. Used only hourly ICP data
Toutant et al. [6]	218	Single-centre, retrospective analysis of prospective observational data on correlation of cisterns on admission CT and ICP	Low	74 % of monitored patients with absent cisterns had ICP > 30 mmHg	Lack of rigorous definition and standardization of cisternal compression

Reference	# of patients	Design	Grade crit.	Results	Caveats
Mizutani et al. [7]	100	Single-centre, retrospective analysis of correlation of admission CT parameters and initial ICP	Low	Admission CT findings that contributed to predicting initial degree of intracranial hypertension included (in order of predictive power) cisternal compression, subdural size, ventricular size (III and IV), intracerebral haematoma size, and subarachnoid haemorrhage	ICP monitored by subarachnoid catheter. No data on later development of intracranial hypertension
Eisenberg et al. [8]	753	Multi-centre, retrospective analysis of prospective observational data on prediction of abnormal ICP	Mod	For first 72 h, strongest ($p < 0.001$) independent predictors of percent of monitored time that ICP > 20 mmHg were abnormal mesencephalic cisterns, midline shift, and subarachnoid blood. For ICP occurrences > 20 mmHg, the strongest ($p < 0.001$) was cisternal compression, with age, midline shift, and intraventricular blood reaching $p < 0.05$	Used only end-hour ICP values
Kishore et al. [9]	137 (47 with normal admission CT)	Single-centre, retrospective observational analysis of correlation of final Marshall CT classification with ICP course	Low	Elevated ICP was present in ≥ 55 % of patients with intra- or extra-axial haematomas. 17 % of patients with normal admission CT imaging had ICP > 20 mmHg	Used only intermittent ICP measurements. Did not separate out patients with persistently normal CT imaging
Narayan et al., 1982 [5]	226	Single-centre retrospective observational study of predictors of intracranial hypertension	Low	Association with intracranial hypertension for abnormal admission CT = 53–63 %; for normal admission CT = 13 %. 2+ of predictive variables* with normal CT had 60 % incidence (*age > 40 years, systolic blood pressure ≤ 90 mmHg, or motor posturing)	No magnitude for ICP elevation. No prospective verification of normal CT model. Examined only admission CT imaging. Used only end-hour ICP values
Miller et al., 2004 [10]	82	Single-centre retrospective observational study modeling CT characteristics as predictors of intracranial hypertension	Low	Initial CT ventricle size, basilar cisterns, sulcal size, transfalcal herniation, and gray/white differentiation were associated with, but not predictive of intracranial hypertension	Non-standardised CT variable grading system. Small sample size for modeling. No magnitude for ICP elevation
Lobato et al., 1983 [11]	277	Single-centre, retrospective observational study of outcome of monitored patients	Low	Normal CT imaging post evacuation of extracerebral haematomas did not have ICP problems; normal, non-operative scans had 15 % incidence of intracranial hypertension, none severe (> 35 mmHg). Other combinations of contusions or brain swelling had much higher incidences	No multivariate statistics for ICP. Examined only admission CT imaging
Poca et al. [12]	94	Single-centre, retrospective analysis of prospective observational data on correlation of final Marshall CT classification with ICP course	Low	Development of intracranial hypertension by final Marshall Classification: DI I = 0 %; DI II = 28.6 % (10 % uncontrollable); DI III = 63.2 % (1/3 uncontrollable); DI IV = 100 % (all uncontrollable); EML = 65.2 % (1/2 uncontrollable); NEML = 84.6 % (1/2 uncontrollable)	Did not separately report admission CT class as predictive of ICP course. Used only intermittent ICP measurements
Miller et al. [59]	225	Single-centre, retrospective observational study of ICP and outcome of consecutive sTBI patients	Low	Less than 25 % incidence of persistent ICP > 20 mmHg in patients with normal admission CT imaging	Little detail on patients with normal admission CT

Reference	# of patients	Design	Grade crit.	Results	Caveats
Holliday et al. [106]	17	Single-centre, retrospective observational study of ICP course of patients with normal admission CT imaging	Low	86 % of their patients with normal admission CT and ICP > 25 mmHg had associated pulmonary complications. Patients with “normal” admission CT did not develop intracranial hypertension	Examined only admission CT imaging. Implications of “secondary” ICP elevation unclear. Normal CT could include cisternal compression, slit ventricles
Lobato et al. [107]	46 patients (39 monitored)	Single-centre, retrospective observational study of ICP course of patients with repeatedly normal CT imaging	Low	No patient with persistently normal admission CT had sustained intracranial hypertension. Within the first 24 h, 10 % had transient ICP elevation below 25 mmHg	Examined only admission CT imaging.
O’Sullivan et al. [108]	22 patients (8 with high-resolution monitoring)	Single-centre, retrospective observational analysis of ICP course in patients without signs of ICP elevation on admission CT	Low	88 % had intracranial hypertension (ICP > 20 mmHg), severe (protracted period ≥ 30 mmHg) in 62 %	Primary ICP monitoring by subdural systems
Lee et al. [13]	36	Single-centre, retrospective observational analysis of ICP course in patients with CT diagnosis of DAI	Low	28 % had no ICP > 20 mmHg, 47 % had ICP values 21–30 mmHg and 25 % had ICP values > 30 mmHg. Only 1 patient (3 %) underwent treatment	Used only intermittent ICP measurements. Incomplete description of management methods

ICP elevation and outcome

Reference	# of Patients	Design	Grade crit.	Results	Caveats
Treggiari, 2007 [56]	Four studies (409 pts) for ICP values; five studies (677 pts) for ICP patterns	Systematic review	Moderate	OR of death: ICP 20–40 = 3.5 [95 % CI 1.7–7.3] ICP > 40 = 6.9 [95 % CI 3.9–12.4] Refractory ICP = 114.3 [95 % CI 40.5–322.3]	ICP treated at thresholds; few studies with data available for quantitative analysis

Does ICP-monitor-based management influence outcome in TBI?

Reference	# of Patients	Design	Grade crit.	Results	Caveats
Saul and Ducker, 1982 [37]	233 (106 pre, 127 post)	Single-centre, retrospective, sequential case series’ comparing two protocols	Low	Lower mortality (46 vs. 28 %) associated with a stricter ICP Tx protocol (with lower threshold)	Concomitant change in ICP treatment threshold; many uncontrolled changes associated with protocol
Vukic et al. 1999 [61]	28 (11 pre, 18 post)	Single-centre, prospective, sequential case series comparing no protocol/no monitoring to BTF protocol with ICP monitoring	Low	14 % lower mortality and 50 % more favourable GOS outcome in group managed via monitoring/protocol	Role of ICP monitoring in protocol effects unclear. No statistical analysis

Reference	# of Patients	Design	Grade crit.	Results	Caveats
Clayton et al., 2004 [63]	843 (391 pre, 452 post)	Single centre, retrospective, sequential case series examining effect of an ICP management protocol	Low	Reduction in ICU mortality (19.95–13.5 %; OR 0.47; 95 % CI 0.29–0.75), and hospital mortality (24.55–20.8 %; OR 0.48; 95 % CI 0.31–0.74)	Primary change was in CPP management; role of ICP monitoring unclear
Fakhry et al. 2004 [64]	820 (219 pre-protocol, 188 low compliance, 423 high compliance)	Single-centre retrospective case series from prospective registry of implementing BTF-based management protocol	Low	No significant change in mortality (17.8, 18.6, 13.7). Compliance-related improvement in discharge GOS 4–5 (43.3, 50.3, 61.5 %) and appropriate response on RLA (43.9, 44.0 %, 56.6 %). Shorter ICU and hospital LOS	No ICP data or analysis of ICP-monitoring-specific effects
Spain et al. 1998 [65]	133 (49 pre, 84 post)	Single-centre prospective case series with clinical pathway versus retrospective control pre-pathway	Low	Significant improvement in process variables unrelated to ICP monitoring; increase in hospital mortality associated with pathway (12.2–21.4 %) attributable to withdrawal of care. No difference in functional outcome	Strong confounding by general effects of clinical pathway (became point of paper)
Arabi et al. 2010 [66]	434 (74 pre, 362 post)	Single-centre retrospective case series' from prospective database comparing protocol to pre-protocol period	Low	Protocol use independently associated with reduced hospital mortality (OR 0.45; 95 % CI 0.24–0.86; $p = .02$) and ICU mortality (OR 0.47; 95 % CI 0.23–0.96; $p = .04$)	Small, retrospective control group
Haddad et al. 2011 [67]	477	Single-centre retrospective case series from prospective database examining role of ICP in protocol-related improvements	Low	ICP monitoring not associated with significant independent difference in hospital (OR 1.71, 95 % CI 0.79–3.70, $p = 0.17$) or ICU mortality OR 1.01, 95 % CI 0.41–2.45, $p = 0.99$)	Associated decrease in ICP monitoring frequency not explained. No control for choice to monitor
Bulger et al. 2002 [68]	182	Multi-centre retrospective cohort study from prospective database examining outcome based on “aggressiveness” of TBI care	Low–Mod	Adjusted hazard ratio for death of 0.43 (95 % CI 0.27–0.66) for management at an “aggressive” center compared to a “nonaggressive” center. No significant difference in discharge functional status of survivors	General trauma database lacked important demographic information. ICP as marker, causality not assessed
Cremer et al. 2005 [69]	333	Two-centre retrospective cohort study comparing a centre monitoring ICP versus on not monitoring ICP	Low–Mod	No difference in hospital mortality for ICP group (33 %) versus no-ICP group (34 %; $p = 0.87$). No difference in functional outcome at ≥ 12 months (OR 0.95; 95 % CI 0.62–1.44)	No description of management approaches. Only 67 % monitored at monitoring centre. Excluded deaths ≤ 24 h
Lane et al. 2000 [76]	5,507	Multi-centre retrospective cohort study from prospective database examining correlation of ICP monitoring and outcome	Low–Mod	ICP monitoring independently associated with improved survival ($p < 0.015$)	General trauma database lacked important demographic information. No control for centre differences or choice to monitor
Shafi et al. 2008 [77]	1,646	Multi-centre retrospective cohort study from prospective database examining correlation of ICP monitoring and outcome	Low–Mod	Higher adjusted hospital mortality for monitored patients (OR 0.55; 95 % CI 0.39–0.76; $p < 0.001$)	General trauma database lacked important demographic information. No control for centre differences or choice to monitor. Excluded deaths ≤ 48 h

Reference	# of Patients	Design	Grade crit.	Results	Caveats
Mauritz et al. 2008 [73]	1,856	Multi-centre retrospective cohort study from prospective database examining correlation of ICP monitoring and outcome	Low	No significant association of ICP monitoring with hospital outcome as a single factor nor in interaction with SAPS II	Significant, unexplained centre differences in ICP monitoring and outcome
Farahvar et al. 2012 [17]	1,446	Multi-centre retrospective cohort study from prospective database examining correlation of ICP monitoring and outcome	Low–Mod	Trend toward reduced 2-week mortality for monitored patients by multivariate logistic regression modeling (OR 0.64; 95 % CI 0.41–1.00; $p = 0.05$)	No control for decision to monitor or to treat unmonitored patients for intracranial hypertension
Stein et al. 2010 [78]	127 studies containing >125,000 patients	Meta-analysis of mortality data from 127 studies containing ≥ 90 patients, examining influence of treatment intensity (based on prevalence of ICP monitoring) on 6 month mortality	Low–Mod	“High-intensity” treatment associated with a approximately 12 % lower adjusted mortality rate ($p < 0.001$) and a 6 % higher pooled mean rate of favorable outcomes ($p < 0.001$)	Did not access original data. Ad hoc definition of and threshold for treatment intensity
Chesnut et al. 2012 [79]	324	RCT comparing BTF-based protocol based on ICP monitoring to protocol based on imaging and clinical exam without monitoring	Mod–high	Primary outcome = no significant difference in 6-month composite outcome measure (OR 1.09; 95 % CI 0.74–1.58; $p = 0.49$). Secondary outcome = no significant difference in 14 day mortality (OR 1.36; 95 % CI 0.87–2.11; $p = 0.18$), cumulative 6-month mortality OR 1.10; 95 % CI 0.77–1.57; $p = 0.60$), or 6-month GOS-E (OR 1.23; 95 % CI 0.77–1.96)	Generalizability limited by issues surrounding prehospital care, choice of primary outcome measure, and management protocols
Smith et al. 1986 [80]	77	Prospective randomized trial of patients treated based on ICP versus scheduled treatment	Low	No significant difference in 1 year GOS by univariate analysis. Mean ICP 5.5 mmHg higher in monitor-based-treatment group	Small sample size. Investigation not designed to study ICP monitor utility

Does successfully managing intracranial pressure improve outcome?

Reference	# of patients	Design	Grade crit.	Results	Caveats
Treggiari et al., 2007 [56]	677 (five studies)	Systematic review of association of ICP values and patterns with outcome	Mod	Odds of death in responders were 2.2 times higher (OR 2.2; 95 % CI 1.42–3.30) and the odds of poor recovery (GOS 2 and 3) were four times higher (OR 4.0 95 % CI 2.27–7.04) compared to patients with normal ICP courses (threshold = 20 mmHg)	Did not access original data. Unable to control for numerous confounding variables
Farahvar et al. 2011 [29]	388	Multi-centre retrospective cohort study from prospective database examining ICP response to treatment and outcome	Low	Lower risk of 14 day mortality in patients responding to treatment (OR 0.46; 95 % CI 0.23–0.92; $p = 0.03$). 20 % greater likelihood of treatment response for each 1-h decrease in hours of ICP > 25 mmHg in first 24 h (OR 0.80; 95 % CI 0.71–0.90, $p = 0.0003$)	Results very sensitive to ad hoc definitions of intracranial hypertension and treatment response

Reference	# of patients	Design	Grade crit.	Results	Caveats
Eisenberg et al. 1988 [82]	73	Multi-centre RCT of high-dose pentobarbital versus conventional therapy in managing refractory intracranial hypertension	Mod	30 day survival was 92 % for patients who's ICP responded to treatment versus 17 % in nonresponders. 80 % of all deaths were due to uncontrolled ICP	Survival/recovery not primary outcome. Underpowered
Shiozaki et al. 1993 [83]	33	Single-centre RCT of hypothermia versus conventional therapy in managing refractory intracranial hypertension	Mod	For the 17 hypothermia patients, the 5 patients with non-responsive ICP died; 6-month mortality among responders was 27 %. Among the 17 controls, 3 patients survived (18 % mortality)	ICP courses not described in any detail. Refractory ICP not well defined. Underpowered. Outcome only analysed by study group
Cooper et al. 2011 [84]	155	Multi-centre RCT of decompressive craniectomy versus maximal medical management of early refractory intracranial hypertension	Low	6-month mortality was similar (19 vs. 18 %). Adjusted GOS-E scores were marginally worse for the craniectomy group (adjusted OR 1.66; 95 % CI 0.94–2.94; $p = 0.08$)	ICP response versus outcome not analysed independently. No data specific to non-responders

Is there an optimal ICP treatment threshold the maintenance of which is critical to optimize recovery?

Reference	# of patients	Design	Grade crit.	Results	Caveats
Miller et al., 1977 [58]	160	Single-centre retrospective case series	Low	No ICP threshold for outcome in patients with mass lesion. When ICP was 0–10 mmHg in patients without mass lesions, 85 % made a good recovery (GOS 4–5) and 8 % died. When ICP was 11–20 mmHg, good recovery rate was 64 and 25 % died ($\chi^2 = 5.30$; $p < 0.02$)	All patients treated for elevated ICP. Minimal risk adjustment or multifactorial analysis
Nordby and Gunnerod, 1985 [47]	130	Single-centre retrospective case series	Low	Significantly worse outcome in patients whose ICP exceeded 20 mmHg ($p < 0.001$). ICP ≥ 40 mmHg had high risk of progressing to brain death	All patients treated for elevated ICP. Minimal risk adjustment or multifactorial analysis. Epidural monitoring
Marshall et al. 1979 [72]	100	Single-centre retrospective case series	Low	For patients without mass lesions with ICP < 15 mmHg, 77 % achieved favorable outcome (GOS = 4–5) versus those with ICP ≥ 15 mmHg for ≥ 15 min, wherein 42 % achieved favourable outcome ($p < 0.01$ by univariate analysis). Favorable outcomes were achieved in 43 % with ICP ≥ 15 for 15 min and in 42 % with ICP > 40 mmHg for 15 min	All patients treated for ICP > 15 mmHg. Minimal risk adjustment or multifactorial analysis

Reference	# of patients	Design	Grade crit.	Results	Caveats
Saul and Ducker, 1982 [37]	233	Single-centre, retrospective, sequential case series' comparing two protocols	Low	Mortality rate was 46 % for those treated with a 20–25 mmHg threshold protocol versus 28 % for those treated with a 15 mmHg protocol ($p < 0.0005$ by univariate analysis). For those with ICP's ≥ 25 mmHg, respective mortality was 84 versus 69 % ($p < 0.05$). For those with ICP's ≤ 25 mmHg, respective mortalities were 26 % and 15 % ($p < 0.025$)	Threshold analysis confounded by concomitant general protocol effects. Minimal risk adjustment or multifactorial analysis
Marmarou et al. 2005 [85]	428	Multi-centre retrospective analysis of prospectively collected database	Low	The proportion of measurements with ICP > 20 mmHg was the most powerful predictor of 6 month outcome after age, admission GCS motor score, and abnormal admission pupils. The full model correctly explained 53 % of observed outcomes. ICP proportion modeling power peaked at 20 mmHg	Confounding by choice of threshold, variable responses to supra-threshold values of different magnitudes, the beneficial and toxic effects of treatments, and the interaction of ICP with other variables in individual patients. Their model assumes equal effect of each descriptor over its entire range
Chambers et al. 2001 [87]	207 adults	Single-centre retrospective observational study	Low	ROC analysis of maximum ICP from hourly averages of automated ICP data found optimal prediction of 6 month dichotomized GOS outcome to be 35 mmHg	Studied only maximal ICP values
Ratanalert et al. 2004 [86]	27	Prospective randomized trial of protocolised treatment at two different ICP thresholds (20 vs. 25 mmHg)	Low	No significant difference in 6-month GOS by univariate or multivariate analysis	Very small sample size. Little detail provided on study design and management
Smith et al. 1986 [80]	77	Prospective randomized trial of patients treated based on ICP versus scheduled treatment	Low	No significant difference in 1 year GOS by univariate analysis. Mean ICP 5.5 mmHg higher in monitor-based-treatment group	Small sample size. Investigation not designed to study ICP threshold
Resnick et al. 1997 [88]	37	Single-centre retrospective observational study on patients with ICP > 20 mmHg that persisted for > 96 h	Low	38 % reached GOS 4–5 at ≥ 6 months; 43 % GOS 1–2. Patients < 30 years had better outcome, 57 % reaching GOS 4–5 versus 12.5 % ($p < 0.02$). Patients with good outcomes were significantly younger ($p = 0.0098$). The association of age and GCS with outcome was significant ($p < 0.005$)	No detail on the degree of ICP resistance or magnitude of related insults (low CPP, herniation)
Young et al. 2003 [89]	9	Single-centre retrospective observational study of patients with ICP > 25 for ≥ 2 h	Low	Mortality = 56 %. 44 % survived, with GOS = 4 at rehabilitation discharge	Small series. No quantification of ICP or CPP insults. No comparison to those who died
Vik et al. 2008 [53]	93	Single-centre retrospective observational trial analyzing ICP as AUC	Low	The dose of ICP was an independent predictor of death (OR 1.04; 95 % CI 1.003–1.08; $p = 0.035$) and poor outcome (OR 1.05; 95 % CI 1.003–1.09; $p = 0.034$) at 6 months, by multiple regression	No control for monitoring duration or terminal events. Arbitrary stratification of AUC categories

Reference	# of patients	Design	Grade crit.	Results	Caveats
Kahraman et al. 2010 [90]	30	Single-centre retrospective observational trial using prospective data analyzing manual versus automated ICP as AUC versus mean	Low	For automated data, total ICU AUC had high predictive power for GOS-E 1–4 (area under the ROC curve = 0.92 ± 0.05) and moderate predictive power for in-hospital mortality (0.76 ± 0.15). The percentage of monitoring time that ICP > 20 mmHg had significantly lower predictive power for 3 month GOS-E compared with AUC using 20 mmHg as the cutoff ($p = 0.016$)	

Systemic and Brain Oxygenation

Evidentiary table: PbtO₂ monitoring

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Hoffmann, 1997	32	Retrospective	Cerebrovascular surgery	PbtO ₂	Definition of normal PbtO ₂ thresholds	Normal PbtO ₂ of controls: 31 ± 8 mmHg; normal PbtO ₂ of cerebrovascular surgery subjects was 70 % lower (~ 23 mmHg)	Low
Dings, 1998	101	Observational	TBI	PbtO ₂	Definition of normal PbtO ₂ thresholds	Normal PbtO ₂ values varied depending on probe distance below the dura: 7–17 mm = 33.0 ± 13.3 mmHg; 17–22 mm = 25.7 ± 8.3 mmHg; 22–27 mm = 23.8 ± 8.1 mmHg	Low
Pennings, 2008	25	Observational	Brain surgery	PbtO ₂	Definition of normal PbtO ₂ thresholds	Normal PbtO ₂ = 22.6 ± 7.2 mmHg in the frontal white matter. In 11 patients, measurements were continued for 24 h: PbtO ₂ was 23.1 ± 6.6 mmHg	Low
Doppenberg, 1998 Acta Neurochir Suppl	24	Observational	TBI	PbtO ₂ and PET	Definition of ischemic PbtO ₂ thresholds	Ischemic threshold (CBF = 18 mL/100 g/min) was PbtO ₂ = 22 mmHg. The critical value for PbtO ₂ was 19–23 mmHg	Low
Sarrafzadeh, 2000	35	Retrospective	TBI	PbtO ₂ and CMD	Definition of ischemic PbtO ₂ thresholds	PbtO ₂ < 10 mmHg is critical to induce metabolic changes seen during hypoxia/ ischemia (increased cerebral microdialysis glutamate and lactate/pyruvate ratio)	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Kett-White, 2002a	46	Observational	Aneurysm surgery	PbtO ₂	Definition of ischemic PbtO ₂ thresholds	Temporary clipping caused PbtO ₂ decrease: in patients in whom no subsequent infarction developed in the monitored region, PbtO ₂ was ~11 mmHg; PbtO ₂ < 8 mmHg for 30 min was associated with infarction	Low
Doppenberg, 1998 Surg Neurol	25	Observational	TBI	PbtO ₂ with regional CBF (Xenon CT)	Correlation between PbtO ₂ and CBF	PbtO ₂ strongly correlated with CBF ($R = 0.74$, $p < 0.001$); CBF < 18 mL/100 g/min was always accompanied by PbtO ₂ ≤ 26 mmHg	Low
Valadka, 2002	18	Observational	TBI	PbtO ₂ with regional CBF (Xenon CT)	Correlation between PbtO ₂ and CBF	PbtO ₂ varied linearly with both regional and global CBF	Low
Jaeger, 2005b	8	Observational	Mixed (TBI, SAH)	PbtO ₂ with regional CBF (TDP)	Correlation between PbtO ₂ and CBF	Significant correlation between PbtO ₂ and CBF ($R = 0.36$); in 72 % of 400 intervals of 30 min duration with PbtO ₂ changes larger than 5 mmHg, a strong correlation between PbtO ₂ and CBF was found ($R > 0.6$)	Low
Rosenthal, 2008	14	Observational	TBI	PbtO ₂ with regional CBF (TDP) and SjvO ₂	Correlation between PbtO ₂ and CBF	PbtO ₂ = product of CBF and cerebral arterio-venous O ₂ tension difference	Low
Longhi, 2007	32	Prospective observational	TBI	PbtO ₂	Probe location: normal versus peri-contusional	PbtO ₂ lower in peri-contusional (19.7 ± 2.1 mmHg) than in normal-appearing tissue (25.5 ± 1.5 mmHg); median duration of PbtO ₂ < 20 mmHg was longer in peri-contusional versus normal-appearing tissue (51 vs. 34 % of monitoring time)	Low
Hlatky, 2008	83	Observational	TBI	PbtO ₂	Probe location: normal versus peri-contusional	PbtO ₂ response to hyperoxia in normal ($n = 20$), peri-contusional ($n = 35$) and abnormal ($n = 28$) brain areas: poor response to hyperoxia when Licox was in abnormal brain	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Ponce, 2012	405	Prospective observational	TBI	PbtO ₂	Probe location: normal versus peri-contusional	Average PbtO ₂ lower in peri-contusional (25.6 ± 14.8 mmHg) versus normal (30.8 ± 18.2 mmHg) brain (<i>p</i> < .001). PbtO ₂ was significantly associated to outcome in univariate analyses, but independent linear relationship between low PbtO ₂ and 6-month GOS score was found only when the PbtO ₂ probe was placed in peri-contusional brain	Low
Ulrich, 2013	100	Retrospective	SAH	PbtO ₂	Likelihood of PbtO ₂ monitoring to be placed in vasospasm or infarction territory	The probability that a single PbtO ₂ probe was situated in the territory of severe vasospasm/infarction was accurate for MCA/ICA aneurysms (80–90 %), but not for ACA (50 %) or VBA aneurysms (25 %)	Low
Johnston, 2004	11	Prospective, interventional	TBI	PbtO ₂ and PET	Effect of CPP augmentation (70 → 90 mmHg) on PbtO ₂	Induced hypertension resulted in a significant increase in PbtO ₂ (17 ± 8 vs. 22 ± 8 mmHg, <i>p</i> < 0.001) and CBF (27.5 ± 5.1 vs. 29.7 ± 6.0 mL/100 g/min, <i>p</i> < 0.05) and a significant decrease in oxygen extraction fraction (33.4 ± 5.9 vs. 30.3 ± 4.6 %, <i>p</i> < 0.05)	
Jaeger, 2010	38	Prospective observational	TBI	PbtO ₂	Identification of “optimal” CPP	Optimal CPP could be identified in 32/38 patients. Median optimal CPP was 70–75 mmHg (range 60–100 mmHg). Below the level of optimal CPP, PbtO ₂ decreased in parallel to CPP, whereas PbtO ₂ reached a plateau above optimal CPP. Average PbtO ₂ at optimal CPP was 24.5 ± 6.0 mmHg	
Schneider, 1998	15	Prospective	TBI	PbtO ₂	Effect of moderate hyperventilation	Hyperventilation (PaCO ₂ : 27–32 mmHg) significantly reduced PbtO ₂ from 24.6 ± 1.4 to 21.9 ± 1.7 mmHg	Low
Imberti, 2002	36	Prospective	TBI	PbtO ₂ and SjvO ₂	Effect of moderate hyperventilation	20-min periods of moderate hyperventilation (27–32 mmHg) in most tests (79.8 %) led to both PbtO ₂ and SjvO ₂ decrease.	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Raabe, 2005	45	Retrospective	SAH	PbtO ₂	Effect of induced hypertension and hypervolemia	During the 55 periods of moderate hypertension, an increase in PbtO ₂ was found in 50 cases (90 %), with complications occurring in three patients (8 %); During the 25 periods of hypervolemia, an increase in PbtO ₂ was found during three intervals (12 %), with complications occurring in nine patients (53 %)	Low
Muench, 2007	10	Prospective	SAH	PbtO ₂ and TDP	Effect of induced hypertension and hypervolemia	Induced hypertension (MAP ≈ 140 mmHg) resulted in a significant ($p < .05$) increase of PbtO ₂ and regional CBF. In contrast, hypervolemia/hémodilution induced only a slight increase of regional CBF while PbtO ₂ did not improve	Low
Al-Rawi, 2010	44	Prospective	SAH	PbtO ₂	Osmotherapy with HTS to treat ICP > 20 mmHg	(2 mL/kg) of 23.5 % HTS resulted in a significant increase in PbtO ₂ ($P < 0.05$). A sustained increase in PbtO ₂ (>210 min) was associated with favorable outcome	Low
Francony, 2008	20	RCT	Mixed (17 TBI, 3 SAH)	PbtO ₂	Osmotherapy with MAN versus HTS to treat ICP > 20 mmHg	A single equimolar infusion (255 mOsm dose) of 20 % MAN ($N = 10$ patients) or 7.45 % HTS ($N = 10$ patients) equally and durably reduced ICP. No major changes in PbtO ₂ were found after each treatment	High
Smith, 2005	35	Prospective	Mixed (TBI, SAH)	PbtO ₂	Effect of RBCT	RBCT was associated with an increase in PbtO ₂ in most (74 %) patients	Low
Leal-Noval, 2006	60	Prospective	TBI	PbtO ₂	Effect of RBCT	RBCT was associated with an increase in PbtO ₂ during a 6-h period in 78.3 % of the patients. All patients with basal PbtO ₂ < 15 mmHg showed an increment in PbtO ₂ versus 74.5 % of patients with basal PbtO ₂ ≥ 15 mmHg	Low
Zygun, 2009	30	Prospective	TBI	PbtO ₂	Effect of RBC transfusion	RBCT was associated with an increase in PbtO ₂ in 57 % of patients	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Menzel, 1999b	24	Retrospective	TBI	PbtO ₂ and CMD	Effect of normobaric hyperoxia	$N = 12$ patients in whom PaO ₂ was increased to 441 ± 88 mmHg over a period of 6 h by raising the FiO ₂ from 35 to 100 % versus control cohort of 12 patients who received standard respiratory therapy (mean PaO ₂ 136 mmHg): the mean PbtO ₂ increased in the O ₂ -treated patients up to 360 % of the baseline level during the 6-hour FiO ₂ enhancement period, whereas the mean CMD lactate levels decreased by 40 % ($p < 0.05$)	Low
Nortje, 2008	11	Prospective	TBI	PbtO ₂ and CMD	Effect of normobaric hyperoxia	Hyperoxia (FiO ₂ increase of 0.35–0.50) increased mean PbO ₂ from 28 ± 21 to 57 ± 47 mmHg ($p = 0.015$) and was associated with a slight but statistically significant reduction of CMD lactate/pyruvate ratio (34 ± 9.5 vs. 32.5 ± 9.0 , $p = 0.018$)	Low
Meixensberger, 2003b	91	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	$N = 52$ versus $N = 39$ pts; PbtO ₂ threshold 10 mmHg → no difference in 6-month-GOS (65 vs. 54 %, $p < 0.01$)	Low
Stiefel, 2005	53	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	$N = 28$ versus $N = 25$ pts; PbtO ₂ threshold 25 mmHg → reduced mortality at discharge (25 vs. 44 %, $p < 0.05$)	Low
Martini, 2009	629	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	$N = 123$ versus $N = 506$ pts; PbtO ₂ threshold 20 mmHg → lower functional independence score (FIM) at discharge (7.6 vs. 8.6, $p < 0.01$)	Low
Adamides, 2009	30	Prospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	$N = 20$ versus $N = 10$ pts; PbtO ₂ threshold 15 mmHg → no difference in 6-month GOS	Low
McCarthy, 2009	111	Prospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	$N = 63$ versus $N = 48$ pts; PbtO ₂ threshold 20 mmHg → trend towards better 3-month GOS (79 vs. 61 %, $p = 0.09$)	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Narotam, 2009	168	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	<i>N</i> = 127 versus <i>N</i> = 41 pts; PbtO ₂ threshold 20 mmHg → better 6-month GOS (3.5 vs. 2.7, <i>p</i> = 0.01)	Low
Spiotta, 2010	123	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	<i>N</i> = 70 versus <i>N</i> = 53 pts; PbtO ₂ threshold 20 mmHg → better 3-month GOS (64 vs. 40 %, <i>p</i> = 0.01)	Low
Green, 2013	74	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	<i>N</i> = 37 versus <i>N</i> = 37 pts; PbtO ₂ threshold 20 mmHg → no difference in mortality (65 vs. 54 %, <i>p</i> = 0.34)	Low
Fletcher, 2010	41	Retrospective	TBI	PbtO ₂ therapy versus standard ICP/ CPP management	Effect on outcome	<i>N</i> = 21 versus <i>N</i> = 20 pts; PbtO ₂ threshold 20 mmHg → higher cumulative fluid balance, higher rate of vasopressor use and pulmonary edema	Low

Evidentiary table: SjvO₂ monitoring

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Kiening, 1996	15	Prospective	TBI	SjvO ₂ and PbtO ₂	Quality of data: SjvO ₂ versus PbtO ₂	The “time of good data quality” was 95 % for PbtO ₂ versus 43 % for SjvO ₂ ; PbtO ₂ monitoring could be performed twice as long as SjvO ₂ monitoring	Low
Meixensberger, 1998	55	Prospective	TBI	SjvO ₂ and PbtO ₂	Quality of data: SjvO ₂ versus PbtO ₂	Analyzing reliability and good data quality, PbtO ₂ (~95 %) was superior to SjvO ₂ (~50 %)	Low
Robertson, 1989	51	Observational	Mixed (TBI, SAH, stroke)	SjvO ₂ and PET-scan	Correlation between SjvO ₂ and CBF	AVDO ₂ had only a modest correlation with CBF (<i>R</i> = −0.24). When patients with ischemia, indicated by an increased CMRLactate, were excluded from the analysis, CBF and AVDO ₂ had a much improved correlation (<i>R</i> = −0.74). Most patients with a very low CBF would have been misclassified as having a normal/increased CBF based on AVDO ₂	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Gopinath, 1999 Neurosurgery	35	Observational	TBI	SjvO ₂ and TDP	Correlation between SjvO ₂ and CBF	When the change in regional CBF was at least 10 mL/100 g/min during ICP elevation, the change of regional CBF reflected the change in SjvO ₂ on 85 % of the occasions	Low
Coles, 2004	15	Prospective	TBI	SjvO ₂ and PET-scan	Correlation between SjvO ₂ and CBF	SjvO ₂ correlated well with the amount of ischemic blood volume (IBV) measured by PET scan ($R = 0.8$, $p < 0.01$), however, ischemic SjvO ₂ values < 50 % were only achieved at an IBV of 170 ± 63 mL, which corresponded to an average of 13 % of the brain. Therefore, the sensitivity of SjvO ₂ monitoring in detecting ischemia was low	Low
Keller, 2002	10	Prospective	Large hemispheric stroke	SjvO ₂ and PET-scan	Correlation between SjvO ₂ and CBF	Out of 101 ICP/SjvO ₂ , and 92 CBF measurements, only two SjvO ₂ values were below the ischemic thresholds (SjvO ₂ < 50 %). SjvO ₂ did not reflect changes in CBF	Low
Fandino, 1999	9	Prospective	TBI	SjvO ₂ and PbtO ₂	Value of SjvO ₂ versus PbtO ₂ to predict ischemia	Low correlation between SjvO ₂ and PbtO ₂ during CO ₂ -reactivity test: in comparison to SjvO ₂ , PbtO ₂ is more accurate to detect focal ischemic events	Low
Gopinath, 1999 Crit Care Med	58	Prospective	TBI	SjvO ₂ and PbtO ₂	Value of SjvO ₂ versus PbtO ₂ to predict ischemia	Sensitivities of the two monitors for detecting ischemia were similar	Low
Gupta, 1999	13	Prospective	TBI	SjvO ₂ and PbtO ₂	Value of SjvO ₂ versus PbtO ₂ to predict ischemia	In areas without focal pathology, good correlation between changes in SjvO ₂ and PbtO ₂ ($R^2 = 0.69$, $p < 0.0001$). In areas with focal pathology, no correlation between SjvO ₂ and PbtO ₂ ($R^2 = 0.07$, $p = 0.23$). PbtO ₂ reflects regional brain oxygenation better than SjvO ₂	Low
Robertson, 1998	44	Prospective	TBI	SjvO ₂ and PbtO ₂	Value of SjvO ₂ versus PbtO ₂ to predict ischemia	Good correlation in global ischemic episodes; during regional ischemic episodes, only PbtO ₂ decreased, while SjvO ₂ did not change	Low
De Deyne, 1996	150	Retrospective	TBI	SjvO ₂	Detection of ischemia in the early phase (< 12 h)	Initial SjvO ₂ < 50 % in 57 patients (38 %). jugular bulb desaturation was related to CPP < 60 mmHg and PaCO ₂ < 30 mmHg	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Vigue, 1999	27	Prospective	TBI	SjvO ₂	CPP augmentation with vasopressors and volume resuscitation in the early phase of TBI	Before treatment, 37 % of patients had an SjvO ₂ < 55 %, and SjvO ₂ was significantly correlated with CPP ($R = 0.73$, $p < 0.0001$). After treatment, we observed a significant increase in CPP (from 53 ± 15 to 78 ± 10 mmHg), MAP (79 ± 9 vs. 103 ± 10 mmHg) and SvjO ₂ (56 ± 12 vs. 72 ± 7 %), without a significant change in ICP	Low
Fortune, 1995	22	Observational	TBI	SjvO ₂	ICP therapy	Effective ICP therapy was associated with an improvement in SjvO ₂ ($+2.5 \pm 0.7$ %)	Low
Robertson, 1999	189	RCT	TBI	SjvO ₂	Therapy targeted to CBF/ CPP (CPP > 70 mmHg, PaCO ₂ 35 mmHg) versus to ICP (CPP > 50 mmHg, PaCO ₂ 25–30 mmHg)	CBF-targeted protocol reduced the frequency of jugular desaturation from 50.6 to 30 % ($p = 0.006$); adjusted risk of jugula desaturation 2.4-fold greater with the ICP-targeted protocol. No difference in GOSE score at 6 months. The beneficial effects of the CBF-targeted protocol may have been offset by a fivefold increase in the frequency of adult respiratory distress syndrome	High

Evidentiary table (selected key studies only): non-invasive cerebral oxygenation monitoring (NIRS)

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Buchner, 2000	31	Prosp Obs	SAH, TBI	NIRS With PbtO ₂	Data quality, factors influencing signal, parameter correlation	50–80 % good quality data, signal influenced by optode wetting, galea hematoma, subdural air; partial correlation of NIRS with PbtO ₂	Low
Kirkpatrick, 1998	130	Prosp Obs	Carotid endarterectomy	NIRS with EEG, TCD CBFV	Ischemia thresholds	80 % good quality data	Low
Davie, 2012	12	Prosp Obs	Healthy volunteers	NIRS	Extracerebral signal influence	Head cuff inflation reveals 7–17 % extracranial signal contribution in three commercial NIRS monitors	Low
Yoshitani, 2007	103	Prosp Obs	Cardiac/Neuro-ICU	NIRS	Factors influencing the signal	NIRS signal (rSO ₂) influenced by skull thickness, CSF layer, hemoglobin	Moderate

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Brawanski, 2002	12	Prosp Obs	TBI, SAH	NIRS with PbtO ₂	Inter-monitoring correlation	Good correlation	Low
Rothoerl, 2002	13	Prosp Obs	TBI, SAH	NIRS with PbtO ₂	Inter-monitoring correlation	Good correlation	Low
McLeod, 2003	8	Prosp Obs	TBI	NIRS with PbtO ₂ , SjvO ₂	Inter-monitoring correlation	Good correlation	Low
Ter Minassian, 1999	9	Prosp Obs	TBI	NIRS with SjvO ₂	Inter-monitoring correlation	Poor correlation	Low
Buunk, 1998	10	Prosp CS	Cardiac arrest	NIRS with SjvO ₂	Inter-monitoring correlation	Poor correlation	Low
Weerakkody, 2012	40	Prosp Obs	TBI	NIRS with ICP/ CPP	Inter-monitoring correlation	Good correlation	Low
Zweifel, 2010a	40	Prosp Obs	TBI	NIRS with ICP/ CPP PRx	Inter-monitoring correlation	Good correlation	Moderate
Zweifel, 2010b	27	Prosp Obs	SAH	NIRS with TCD CBFV/ MAP Mx	Inter-monitoring correlation	Good correlation	Moderate
Rothoerl, 2003	9	Prosp Obs	TBI	NIRS with Xe133 perfusion	Inter-monitoring correlation	Poor correlation	Low
Terborg, 2004	25	Prosp CaseCont	Hem AIS	NIRS with MRI perfusion	Inter-monitoring correlation	Good correlation	Moderate
Frisch, 2012	5	Case series	Card arrest	NIRS with PetCO ₂	Inter-monitoring correlation	Poor correlation	Very low
Bhatia, 2007	32	Prosp Obs	SAH	NIRS with DSA	Inter-monitoring correlation	Good correlation	Low
Taussky, 2012	6	Retrospect CS	SAH, AIS, ICH	NIRS with CT perfusion	Inter-monitoring correlation	Good correlation	Very low
Aries, 2012	9	Prosp Obs	AIS	NIRS with SaO ₂ and blood pressure	Signal response to drops in SaO ₂ and BP	Good detection of desaturations less good detection of hypotension	Very low
Hargroves, 2008	7	Prosp Obs	AIS	NIRS	Signal response to position of head of bed	Good reflection of position-related oxygenation changes	Very low
Damian, 2007	24	Retro Obs	AIS	NIRS	Outcome, clinical course, imaging	Bilateral NIRS with interhemispheric difference reflecting clinical course, outcome and effect of decompressive surgery	Low
Bonoczka, 2002	43	RCT interv.	AIS	NIRS with TCD	Response of rSO ₂ and CBFV to vinpocetine	Increase of rSO ₂ in response to vinpocetine	Moderate
Naidech, 2008	6	Prosp CS	SAH	NIRS with TCD, DSA	Change of NIRS signal in vasospasm	No reliable detection of vasospasm by NIRS	Very low
Yokose, 2010	11	Prosp CS	SAH	NIRS With TCD, DSA	Change of NIRS signal in vasospasm	Good detection of vasospasm	Very low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Mutoh, 2010	7	Prosp CS	SAH	NIRS	Response of NIRS signal to dobutamine	Detection of vasospasm by NIRS, NIRS signal increasing with incremental dobutamine	Low
Gopinath, 1993	40	Prosp Obs	TBI	NIRS with CT	Detection of secondary hematoma	Detection secondary hematoma by NIRS	Low
Gopinath, 1995	167	Prosp Obs	TBI	NIRS with CT, ICP, clinical	Time to detection of secondary hematomy	Earlier detection of secondary hematoma than by ICP, clinical signs or CT	Moderate
Budohoski, 2012	121	Prosp Obs	TBI	NIRS with TCD, CBFV, PbtO ₂ , MAP, ICP	Time to cerebral parameter changes MAP and ICP increases	Earlier reflection of MAP and ICP changes by NIRS than by TCD and PbtO ₂	Moderate

Evidentiary table (selected key studies only): systemic monitoring of oxygen

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Sulter, 2000	49	Prosp Obs	AIS	Pulse oximetry SpO ₂ , ABG SatO ₂	Detection SatO ₂ < 96 %	Pulse oximetry appears useful to titrate O ₂ therapy	Low
Tisdall, 2008a	8	Prosp Obs	TBI	ABG PaO ₂ and SatO ₂ , with PbtO ₂ , NIRS, MD	Parameter response to raising FiO ₂	Raising FiO ₂ leads to increase of PaO ₂ , SatO ₂ , PbtO ₂ , NIRS rSO ₂ , and reduction of MD lactate/pyruvate ratio, i.e., ABG O ₂ monitoring is plausibly reflected by cerebral oxygenation monitoring	Low
Diringer, 2007	5	Prosp Obs	TBI	ABG PaO ₂ with PbtO ₂ , PET, CBF and CMRO ₂	Parameter response to raising FiO ₂	Raising FiO ₂ leads to increase of PaO ₂ and PbtO ₂ , while PET CBF and CMRO ₂ remain unchanged, i.e., ABG O ₂ monitoring is not reflected by all parameters of cerebral oxygenation	Low
Zhang, 2011	9	Prosp Obs	ICH, TBI, SAH	ABG PaO ₂ /FiO ₂ with ICP, CPP	Parameter response to raising PEEP	Raising PEEP leads to improvement of pulmonary oxygenation, to increase of ICP, and decrease of CPP	Low
Koutsoukou, 2006	21	RCT	ICH, TBI	ABG PaO ₂ /FiO ₂ with lung mechanics parameters	Lung mechanics in PEEP versus NoPEEP	Improvement of pulmonary oxygenation (assessable by ABG O ₂ monitoring) and lung mechanics in PEEP compared to No PEEP group	Moderate
Muench, 2005	10	Prosp Obs	SAH	ABG PaO ₂ /FiO ₂ with CPP, PbtO ₂	Parameter response to raising PEEP	Raising PEEP leaves pulmonary oxygenation unchanged and leads to decrease in CPP and PbtO ₂ , i.e., no strong correlation between systemic and cerebral O ₂ monitoring	Low
Wolf, 2005	13	Prosp Obs	SAH, TBI	ABG SatO ₂ and PaO ₂ , with FiO ₂ , PbtO ₂	Long-term response of systemic and cerebral oxygenation to raising PEEP	Raising PEEP allows reduction of FiO ₂ after 24 h and is associated with increased PbtO ₂ , i.e., ABG O ₂ monitoring reflects improved long-term cerebral oxygenation	Low
Bein, 2002	11	Prosp Obs	TBI, ICH, SAH	ABG PaO ₂ and SatO ₂ with CPP, SjvO ₂	Response of systemic and cerebral oxygenation/perfusion to raising ventilator pressure	Raising peak pressure leads to increased PaO ₂ and SatO ₂ , while CPP and SjvO ₂ are decreased, i.e., ABG O ₂ monitoring might not reflect net cerebral oxygenation	Low
Nemer, 2011	16	RCT	SAH	ABG PaO ₂ /FiO ₂ with ICP, CPP	Oxygenation and cerebral pressure response to two different recruitment maneuvers	PV recruitment leads to improved pulmonary oxygenation (reflected by ABG O ₂ monitoring) and leaves ICP and CPP unaffected as compared to CPAP recruitment	Moderate
Nekludov, 2006	8	Prosp Obs	TBI, SAH, ICH	ABG PaO ₂ with MAP, ICP, CPP	Systemic oxygenation and cerebral pressures response to proning	Prone positioning leads to improved pulmonary oxygenation (as reflected by ABG O ₂ monitoring), to a slight increase in ICP, a stronger increase in MAP and hence a net increase in CPP	Low

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Davis, 2009	3,420	Retrospect	TBI	AGB PaO ₂	Mortality	Higher mortality both in hypoxemia and extreme hyperoxemia, as reflected by AGB PaO ₂ on admission	Low
Davis, 2004a	59	Prosp Obs	TBI	Pulse oximetry SpO ₂	Mortality, “good outcome”	Pulse oximetry useful to detect outcome-relevant desaturation	Low
Pfenninger, 1991	47	Prosp Obs	TBI	ABG PaO ₂	Correlation of pre-hospital PaO ₂ with level of consciousness	PaO ₂ only weakly correlated with GCS ($r = 0.54$)	Low

Evidentiary table (selected key studies only): systemic monitoring of carbon dioxide

Reference	Patient number	Study design	Patient group	Technique assessment	Endpoint	Findings	Quality of evidence
Davis, 2004b	426	Prosp Reg	TBI	PetCO ₂	Occurrence of inadvertent HV	Pre-hospital monitoring by portable PetCO ₂ helps to avoid HV	Low
Dyer, 2013	56	Prosp Obs	TBI	ABG PaCO ₂ with PetCO ₂	Factors influencing the PaCO ₂ /PetCO ₂ gap	Difference between PaCO ₂ and PetCO ₂ influenced by injury severity, rib fractures, high BMI	Low
Carmona Suazo, 2000	90	Prosp Obs	TBI	AGB PaCO ₂ with PbtO ₂	PbtO ₂ /PaCO ₂ reactivity to HV	HV leads to decrease in PbtO ₂ and PbtO ₂ /PaCO ₂ reactivity	Low
Coles, 2007	10 + 30	Prosp CaseContr	Volunteers, TBI	ABG PaCO ₂ with PET CBF and CMRO ₂ and OEF, SSEP, SjvO ₂		Low PaCO ₂ is associated with decreased PET CBF, increased PET CMRO ₂ and PET OEF, SSEP, while SjvO ₂ remains unchanged when compared to high PaCO ₂ , i.e., ABG PaCO ₂ monitoring of HV reflects cerebral oxygenation compromise not detected by SjvO ₂	Moderate
Carrera, 2010	21	Prosp Obs	SAH, TBI, ICH	PetCO ₂ with PbtO ₂	Cerebral ischemia in HV	Low PetCO ₂ in spontaneous HV associated with decreased PbtO ₂ (to “ischemic” values)	Low
Pfenninger, 1991	47	Prosp Obs	TBI	AGB PaCO ₂	Level of consciousness	Strong correlation of high PaCO ₂ (=hypoventilation) with low GCS ($r = 0.9$)	Low
Davis, 2004	59 + 177c	Prosp CaseContr	TBI	PetCO ₂	Mortality	HV leads to low PetCO ₂ which is associated with mortality in “dose-dependent” fashion; i.e., end-tidal CO ₂ monitoring reflecting mortality	Moderate
Dumont, 2010	65	Retrospect	TBI	ABG PaCO ₂	Mortality	Hypocarbic versus normocarbic versus hypocarbic associated with mortality as 77, 15, 61 %	Low
Muizelaar, 1991	113	RCT	TBI	ABG PaCO ₂	Functional outcome after 3 and 6 months	HV leads to worse outcome compared to NV versus HV + THAM; i.e., systemic CO ₂ monitoring reflecting outcome	Moderate
Solaiman, 2013	102	Retrospect	SAH	AGB PaCO ₂	Functional Outcome (GOS) at 3 months	Duration of hypocapnia associated with worse outcome	Low

Prosp Obs prospective observational study, *Retrospect* retrospective study, *CS* case series, *RCT* randomized controlled trial, *Reg* registry, *Syst Rev* systematic review

Electrophysiology

Studies evaluating EEG to detect NCSz after acute brain injury

Authors	Design	Population	N	Findings
TBI 0–33 % NCSz				
Studel et al. [218]	R CS		50	8 % on routineEEGs
Vespa et al. [107]	P CS		94	22 % NCSz
Ronne-Engstrom et al. [111]	R CS		70	33 % NCSz
Olivecrona et al. [112]	P CS		47	0 % NCSz, 8.5 % clinical seizures pre EEG
SAH 3–31 % NCSz				
Dennis et al. [240]	R CS		233	3 % (31 % or 8 of 26 with EEG)
Claassen et al. [214]	R CS		116	15 % NCSz, 11 % NCSE
Little et al. [241]	R CS		389	3 % (but only very small number got EEG)
ICH 18–28 %				
Vespa et al. [88]	Pr CS		109	28 % NCSz (only one convulsive)
Claassen et al. [87]	R CS		102	18 % NCSz (only one convulsive), 7 % NCSE
PRES				
Kozak et al. [119]	R CS		10	PRES presented in all cases with SE
CNS infection 33 % NCSz				
Carrera et al. [116]	R CS	64 % viral	42	33 % NCSz
AIS 2 % NCSz				
Carrera et al. [124]	P CS	AIS stroke unit	100	2 % NCSz
Mixed neuro ICU populations				
Jordan et al. [242]	R CS	Mixed NICU		NCSz 34 %
Claassen et al. [4]	R CS	ICU/ward	570	11 % NCSz, 20 % NCSE
Pandian et al. [3]	R CS	Mixed NICU	105	No denominator
Amantini et al. [113]	P CS	TBI, ICH, SAH	68	3 % NCSz
Drislane et al. [243]	R CS	All NCSE	91	No denominator
Mecarelli et al. [115]	P CS	ICH/SAH/AIS	232	6 % NCSz, 4 %NCSE (spot EEG < 24 h)

R retrospective, P prospective, CS case series, NCSz nonconvulsive seizures, NCSE nonconvulsive status epilepticus, ICH intracerebral hemorrhage, SAH subarachnoid hemorrhage, AIS acute ischemic stroke, TBI traumatic brain injury, CNS central nervous system

EEG findings after cardiac arrest in patients undergoing therapeutic hypothermia

Authors	Design	N	Findings					Main observation
			BSP (%)	SE (%)	Alpha coma (%)	Not reactive (%)	Attenuated (%)	
Rundgren et al. [130]	P CS	34	15	12	8	n.a.	50	Burst-suppression, gen suppr, SE all died Non-reactive none with TH survived
Rossetti et al. [126]	R CS	96 (70 without TH)	n.a.	33	n.a.	n.a.	n.a.	Poor outcome GPEDs, general suppression, continuous EEG activity good prognosis
Legriél et al. [134]	P CS	51	40	10	5	n.a.	15	25 NCSE, all died except 1 VS
Fugate et al. [133]	P CS	103 (89 without TH)	5	18	0	41	n.a.	SE 100 % mortality
Rossetti et al. [129]	P CS	111	n.a.	(41) ^a	n.a.	51	n.a.	Non-reactive during TH 100 % mort, 4 % of early myoclonus survived
Rossetti et al. [128]	P CS	34	32	(21) ^b	n.a.	n.a.	n.a.	All with burst-suppression, NCSz or EDs, unreactive BG died
Rundgren et al. [205]	P CS	111	n.a.	27	n.a.	n.a.	n.a.	AI with BSP, alpha coma, SE, BG depression had poor outcome at 6 mo (CC4)
Kawai et al. [131]	R CS	26	15	12	8	n.a.	50	BSP all died, good outcome continuous EEG BG
Rittenberger et al. [132]	R CS	101	n.a.	12	n.a.	n.a.	n.a.	9 % with SE survived
Rossetti et al. [127]	P CS	61	n.a.	n.a.	n.a.	38	n.a.	All non-reactive died
Mani et al. [135]	R CS	38		23				All nine patients with seizures died
Alvarez et al. [2]	P CS	34		(26) ^b		38	35	Two brief EEGs equivalent detection rate for epileptiform activity and prognostic accuracy as prolonged study

TH therapeutic hypothermia

^a Early myoclonus

^b Sz or EDs

EEG and delayed cerebral ischemia in SAH

Authors	Design	Diagnostic modality, clinical grade	N	Findings
Rivierez et al. [35]	P CS	Angio, HH I–V	151	Raw EEG D1 predicted D5 confirmed ischemia
Labar et al. [33]	P CS	Angio, HH I–V	11	Four cases qEEG changes preceded clin change
Vespa et al. [36]	P CS	Angio, HH I–V	32	Relative alpha variability: PPV 76 %, NPV 100 %; qEEG preceded other measures by 2 d
Claassen et al. [32]	P CS	DCI; HH III–V	34	>10 % decrease in alpha-delta-ratio: sens 100 %, specificity 76 %
Rathakrishnan et al. [34]	P CS	DCI, HH I–V	12	Mean alpha power: 67 % sens, 73 % spec for worsening, improvement 50 % sensitivity, 74 % specificity

PPV positive predictive value, NPV negative predictive value

Cerebral Metabolism

Evidence supporting the use of microdialysis data to determine clinical outcome

Study	Population	N	Methods	Findings
Timofeev et al., 2011	TBI	223	Analyte values averaged for each patient on each post injury day. Outcome with 6 month GOS, GOS 1, 2–3, 4–5, univariate, non parametric analysis and multivariate logistic regression	Glutamate and L/P ratio higher in patients who died or had an unfavorable outcome compared to those with good outcome. Glucose, pyruvate, and L/P ratio were significant predictors of mortality
Chamoun et al., 2010	TBI	165	Microdialysis probe placed in tissue near PO ₂ probe, hourly dialysate samples collected. Multivariate analysis with logistic regression to identify factors associated with Outcome (6 month GOS)	Two patterns of glutamate levels were identified. (1) Levels that decreased over time (2) Glutamate increased or remained abnormally elevated over time Mortality was associated with pattern 2
Stein et al., 2012	TBI	89	Multivariate model to identify factors associated with GOS ₆ at 6 months. Metabolic crisis defined as Glu < 0.8 mmol/L and LPR > 25	The length of time in metabolic crisis was significantly associated with outcome. The OR for poor outcome for 12 h of metabolic crisis was 2.16(CI 1.05–4.45 $p = 0.036$)
Nagel et al., 2009	SAH	192	Multivariate analysis to identify factors associated with 12 month GOS in patients with low ICP after SAH versus high ICP	Elevated Glutamate and L/P ratio were associated with worse 12 month GOS and were more common in the high ICP group. The majority of patients with elevated ICP displayed abnormal microdialysis pattern <i>before</i> the rise in ICP
Oddo et al., 2012	SAH	31	Episodes of elevated brain lactate were divided into two groups. Those with a low brain tissue oxygen (hypoxic) and normal tissue oxygen (hyperglycolytic). Outcome using dichotomized mRS	Episodes of hypoxic elevations in brain lactate were associated with mortality while episodes of hyperglycolytic lactate were strong predictors of good outcome
Nikaina et al., 2012	ICH	27	Linear regression model to evaluate the relationship between CPP + L/P ratio and 6 month outcome measured by GOS	The combination of CPP > 75 and L/P < 36 was associated with a favorable 6 month GOS $p = .054$

Can clinical therapy change brain metabolism?

	Population	N	Methods	Findings
Vespa et al., 2006	TBI	47	Nonrandomized consecutive design comparing brain chemistry in patients managed with “loose” versus “intensive” insulin therapy	Patients in the intensive therapy group had lower brain glucose concentrations associated with an increase in glutamate and L/P ratio
Oddo et al., 2008	SAH, TBI, ICH, Ischemic stroke	20	Multivariate logistic regression used to examine relationship between multiple physiologic and microdialysis variables and in-hospital mortality	Systemic glucose concentration and insulin dose were independent predictors of metabolic crisis and mortality
Helbok et al., 2010	SAH	28	Multivariate logistic regression to examine relationship between serum glucose and microdialysis patterns	Reductions in serum glucose by 25 % were associated with episodes of elevated L/P ratio and decreased glucose
Vespa et al., 2012	TBI	13	Prospective within subject crossover trial of “tight” versus “loose” glycemic control and measured glucose metabolism using FDG PET	“Tight” glycemic control was associated with elevated L/P ratio and decreased brain glucose as well as an increase in brain global glucose uptake
Tolias et al., 2004	TBI	52	Prospective study of 24 h of normobaric hyperoxia. Microdialysis compared with baseline and also with age, GCS, and ICP matched controls	Normobaric hyperoxia treatment was associated with an increase in brain glucose and a decrease in L/P ratio as well as a reduction in ICP
Nortje et al., 2008	TBI	11	Brain tissue oxygen, cerebral microdialysis, and 15O-PET scans were performed at normoxia and hyperoxia	Normobaric oxygen was associated with an increase in brain tissue oxygen; however, the association with microdialysis changes and oxygen metabolism on PET was variable

	Population	N	Methods	Findings
Rockswold et al., 2010	TBI	69	Patients randomized to normobaric O ₂ treatment, hyperbaric O ₂ treatment or control. Brain oxygen, microdialysis and ICP were monitored	Both normobaric and hyperbaric hyperoxia improved microdialysis parameters. Hyperbaric O ₂ had a more robust and long lasting effect
Marion et al., 2002	TBI	20	30 min of hyperventilation performed at two time points (24 h and 3 days) after injury, microdialysis and local cerebral blood flow in vulnerable tissue was studied	Brief hyperventilation was associated with increased glutamate and elevated lactate and L/P ratio. This relationship was more marked at the early time point
Hutchinson et al., 2002	TBI	13	Hyperventilation with simultaneous PET scan to measure oxygen extraction fraction (OEF)	Hyperventilation was associated with a reduction in microdialysis glucose and an elevated OEF
Sakowitz et al., 2007	TBI	6	ICP, brain oxygen, and microdialysis parameters were recorded before and after therapeutic doses of mannitol	Microdialysis concentrations rose up to 40 % over the first hour after mannitol in a nonspecific pattern
Helbok et al., 2011	SAH ICH	12	ICP, brain oxygen and microdialysis parameters were measured before and after therapeutic mannitol doses	Mannitol therapy was associated with a decrease in ICP as well as an 18 % decrease in L/P ratio without a change in brain glucose
Ho et al., 2008	TBI	16	ICP, brain oxygen, autoregulation, and microdialysis parameters were measured before and after decompressive craniectomy for refractory intracranial hypertension. Outcome was measured with 6 month GOS	There was a decrease in microdialysis lactate, L/P ratio and glycerol in patient treated with decompressive craniectomy in those who had a favorable outcome
Nagel et al., 2009	SAH	7	Data from a database was retrospectively studied to determine the effect of decompressive craniectomy on cerebral metabolism. 12 month GOS assessed for outcome	In patients treated with decompressive craniectomy glucose and glycerol were lower after the procedure. However, L/P ratio and glutamate did not change
Soukup et al., 2002	TBI	58	ICP, brain oxygen, and microdialysis parameters were measured before and after mild therapeutic hypothermia was used to treat refractory ICP	Therapeutic hypothermia was associated with lower microdialysis glucose and lactate consistent with decreased metabolic demand
Berger et al., 2002	CVA	12	ICP and microdialysis parameters measured before and during therapeutic hypothermia used as rescue therapy for large MCA infarcts	Glutamate, lactate and pyruvate were all affected by therapeutic hypothermia. However, the degree of change varied depending on the probe position

Cellular Damage and Degeneration

Biomarkers for outcome following cardiac arrest *without* therapeutic hypothermia treatment

Authors/year	Population	N	Bio-marker	Sample source	Findings
Molecules of CNS Origin					
Zandbergen, 2006	Post cardiac arrest, unconscious after CPR	>24 h	407 NSE, s100β	Serum	100 % of patients with NSE > 33 μg/L at any time had a poor outcome (40 % PPV; 0 % FPR) s100β > 0.7 μg/L at 24–72 h post cardiac arrest predicts poor outcome (47 % PPV; 2 % FPR) Performance of clinical tests was inferior to SSEP and NSE in predicting outcome
Meynaar, 2003	Post cardiac arrest, comatose post CPR		110 NSE	Serum	NSE at 24 and 48 h after CPR was significantly higher in patients who did not regain consciousness versus those who did No one with NSE > 25 μg/L at any time regained consciousness (100 % specificity)

Authors/year	Population	N	Bio-marker	Sample source	Findings
Pfeifer, 2005	Post cardiac arrest within 12 h of ROSC, survived >48 h	97	NSE, s100 β	Serum	NSE > 65 μ g/L predicted increased risk of death and persistent vegetative state at 28 days post CPR (97 % PPV) s100 β > 1.5 μ g/L predicts poor outcome (96 % PPV)
Rosen, 2001	Out of hospital cardiac arrest	66	s100 β , NSE	Serum	s100 β > 0.217 μ g/L and NSE > 23.2 μ g/L at 2 days post cardiac arrest predicted poor 1-year outcome (100 % PPV)
Bottiger, 2001	Non-traumatic out of hospital cardiac arrest	66	s100 β	Serum	Significant differences in s100 β level between survivors and non-survivors after cardiac arrest were observed from 30 min to 7 days post cardiac arrest s100 β > 1.10 μ g/L at 48 h post cardiac arrest predicted brain damage (100 % specificity)
Martens, 1998	Post cardiac arrest, unconscious and ventilated for >24 h	64	NSE, s100 β	Serum	s100 β and NSE were significantly higher in patients who did not regain consciousness compared of those who did s100 β > 0.7 μ g/L is a predictor of not regaining consciousness after cardiac arrest (95 % PPV; 96 % specificity) NSE > 20 μ g/L predicted poor outcome (51 % sensitivity; 89 % specificity)
Hachimi-Idrissi, 2002	Post cardiac arrest	58	s100 β	Serum	s100 β > 0.7 μ g/L at admission predicted not regaining consciousness (85 % specificity; 66.6 % sensitivity; 84 % PPV; 78 % NPV; 77.6 % accuracy)
Schoerhuber, 1999	Non-traumatic out of hospital cardiac arrest	56	NSE	Serum	NSE was significantly higher in patients who had poor 6 month outcome at 12, 24, 48, and 72 h after ROSC NSE cutoffs for poor outcome were: NSE > 38.5 μ g/L at 12 h, NSE > 40 μ g/L at 24 h, NSE > 25.1 μ g/L at 48 h, and NSE > 16.4 μ g/L at 72 h (100 % specificity) NSE > 27.3 μ g/L at any time predicted poor outcome (100 % specificity)
Molecules of non-CNS origin					
Nagao, 2004	Age > 17 years, out of hospital cardiac arrest of presumed cardiac origin	401	BNP	Blood	Rate of survival to hospital discharge decreased in dose-dependent fashion with increasing quartiles of BNP on admission BNP > 100 pg/mL predicted lack of survival until hospital discharge (83 % sensitivity; 96 % NPV)
Kasai, 2011	Post cardiac arrest	357	Ammonia	Blood	Elevated ammonia on ER arrival is associated with decreased odds for good outcome at hospital discharge (OR 0.98 [0.96–0.99]) Ammonia > 192.5 μ g/dL had 100 % NPV for good outcome at discharge 61 patients were treated with TH

Authors/year	Population	N	Bio-marker	Sample source	Findings
Sodeck, 2007	Post cardiac arrest, comatose	155	BNP	Blood	Highest quartile BNP on admission is associated with poor outcome as compared to lowest quartile BNP > 230 pg/mL predicts unfavorable neurological outcome (OR 2.25 [1.05–4.81]) and death at 6 months (OR 4.7 [1.27–17.35])
Shinozaki, 2011	Non-traumatic out of hospital cardiac arrest with ROSC	98	Ammonia, lactate	Blood	Elevated ammonia and lactate on admission were associated with poor outcome Ammonia > 170 µg/dL predicted poor outcome (90 % sensitivity; 58 % specificity) Lactate > 12 mmol/L predicted poor outcome (90 % sensitivity; 52 % specificity)
CSF biomarkers					
Roine, 1989	Out of hospital VF arrest who survived >24 h	67	NSE, CKBB	CSF	NSE and CKBB at 20–26 h post CPR were elevated in patients who did not regain consciousness compared with those who did All patients with NSE > 24 µg/L remained unconscious or died at 3 months (74 % sensitivity; 100 % specificity) CKBB > 17 µg/L predicted poor outcome (52 % sensitivity; 98 % specificity)
Sherman, 2000	Comatose cardiac arrest patients with SSEP studies	52	CKBB	CSF	CKBB > 205U/L predicted non-awakening (49 % sensitivity; 100 % specificity) CSF sampling time not standardized
Martens, 1998	Post cardiac arrest, unconscious, and ventilated for >48 h	34	NSE, s100β	CSF	s100β and NSE were both significantly higher in patients who did not regain consciousness compared of those who did NSE > 50 µg/L (89 % sensitivity; 83 % specificity) and s100β > 6 µg/L (93 % sensitivity; 60 % specificity) predicted death or vegetative state CSF sampling time is not standardized
Rosen, 2004	Post cardiac arrest, survive > 12 days post ROSC	22	NFL	CSF	CSF sampled at 12–30 days after cardiac arrest NFL > 18,668 µg/L predicted dependency in ADL at 1 year (100 % specificity; 46 % sensitivity)
Karkela, 1993	VF or asystolic arrest	20	CKBB, NSE	CSF	Case controlled CSF collected at 4, 28, and 76 h after resuscitation Elevated CKBB at 4 and 28 h, and elevated NSE at 28 and 76 h after cardiac arrest were associated with not regaining consciousness
Oda, 2012	Out of hospital cardiac arrest of presumed cardiac	14	HMGB1, s100β	CSF	CSF sampled at 48 h after ROSC HMGB1 and s100β were significantly higher in poor outcome group compared to good outcome group and to normal controls
Tirschwell, 1997	Post cardiac arrest with CSF CKBB measured	351	CKBB	CSF	Retrospective study CSF sampling time not standardized CKBB > 205U/L predicted non-awakening at hospital discharge (100 % specificity; 48 % sensitivity) Only nine patients with CKBB > 50U/L awakened and none regained independent ADLs

All studies are prospective observational unless otherwise noted

NPV negative predictive value, PPV positive predictive value, FPR false positive rate, OR odds ratio, ROSC return of spontaneous circulation, SSEP somatosensory evoked potential, TH therapeutic hypothermia, VF ventricular fibrillation

Biomarkers for outcome following cardiac arrest *with* therapeutic hypothermia treatment

Authors/ year	Study design	Population	N	Bio-marker	Sample source	Findings
Tiainen, 2003	RCT	Witnessed VF or VT arrest, ≤ 60 min between collapse to ROSC	70	NSE, s100 β	Serum	NSE levels were lower in TH compared to normothermia NSE did not reach 100 % specificity in TH, whereas it does in normothermia TH: NSE > 31.2 $\mu\text{g/L}$ at 24 h, > 26 $\mu\text{g/L}$ at 36 h, and > 25 $\mu\text{g/L}$ at 48 h predicted poor outcome (96 % specificity) Normothermia: NSE > 13.3 $\mu\text{g/L}$ at 24 h, > 12.6 $\mu\text{g/L}$ at 36 h, and > 8.8 $\mu\text{g/L}$ at 48 h had 100 % specificity for poor outcome TH: s100 β > 0.21 $\mu\text{g/L}$ at 24 h (100 % specificity), s100 β > 0.21 $\mu\text{g/L}$ at 36 h and s100 β > 0.23 $\mu\text{g/L}$ at 48 h (96 % specificity) predicted poor outcome
Cronberg, 2011	Pro	Post cardiac arrest with GCS < 8 after ROSC	111	NSE	Serum	Elevated NSE was associated with worse outcome, DWI changes on MRI, and worse neuropathology All patients with NSE > 33 $\mu\text{g/L}$ at 48 h died without regaining consciousness NSE > 27 $\mu\text{g/L}$ predicted poor outcome at 6 months (100 % specificity)
Rundgren, 2009	Pro	In or out-of-hospital cardiac arrest, GCS ≤ 7	107	NSE, s100 β	Serum	NSE > 28 $\mu\text{g/L}$ at 48 h predicted poor 6-month outcome (100 % specificity; 67 % sensitivity) s100 β > 0.51 $\mu\text{g/L}$ at 24 h predicted poor 6-month outcome (96 % specificity; 62 % sensitivity)
Daubin, 2011	Pro	In or out-of-hospital cardiac arrest, comatose > 48 h	97	NSE	Serum	Elevated NSE correlated with worse outcome at 3 months NSE > 47 $\mu\text{g/L}$ predicted poor 3-month outcome (84 % specificity; 72 % sensitivity) NSE > 97 $\mu\text{g/L}$ predicted poor outcome (100 % PPV)
Shinozaki, 2009	Pro	In- or out-of-hospital non- traumatic cardiac arrest with ROSC > 20 min, with GCS ≤ 8	80	NSE, s100 β	Serum	s100 β and NSE are both elevated in poor outcome group. s100 β had better predictive performance than NSE s100 β cutoff for poor outcome are: s100 β > 1.41 $\mu\text{g/L}$ at admission, s100 β > 0.21 $\mu\text{g/L}$ at 6 h, and s100 β > 0.05 $\mu\text{g/L}$ at 24 h post cardiac arrest (100 % specificity)
Stammet, 2013	Pro	Post cardiac arrest	75	NSE, s100 β	Serum	Elevated s100 β and NSE levels are associated with poor outcome at 6 months Adding s100 β to Bispectral index improved predictive value for poor outcome
Rosetti, 2012	Pro	Post cardiac arrest, comatose	61	NSE	Serum	Five cardiac arrest survivors, including three with good outcome, had NSE > 33 $\mu\text{g/L}$
Mortberg, 2011	Pro	Post cardiac arrest, SBP > 80 mmHg $x > 5$ min, GCS ≤ 7 , < 6 h following ROSC	31	NSE, s100 β , BDNF, GFAP	Serum	No association between BDNF and GFAP levels and outcome NSE > 4.97 $\mu\text{g/L}$ at 48 h and NSE > 3.22 $\mu\text{g/L}$ at 96 h post cardiac arrest predicted poor outcome at 6 months (93 % specificity) s100 β > 1.0 $\mu\text{g/L}$ at 2 h (93 % specificity), and s100 β > 0.18 $\mu\text{g/L}$ at 24 h (100 % specificity) post cardiac arrest predicted poor outcome

PPV positive predictive value, *Pro* prospective observational, *RCT* randomized controlled trial, *ROSC* return of spontaneous circulation, *TH* therapeutic hypothermia, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Biomarkers for subarachnoid hemorrhage

Author/year	Study design	Population	N	Bio-marker	Sample source	Findings
Markers of CNS origin						
Weisman, 1997	Pro	Aneurysmal SAH within 3 days of ictus	70	s100 β	Serum	s100 β is higher at 24 h, 3 and 7 days post SAH compared to controls Higher s100 β levels correlate with worse HH grade Higher s100 β in the first week after SAH correlate with worse 6 month outcome
Stranjalis, 2007	Pro	Spontaneous SAH within 48 h of ictus	52	s100 β	Serum	Admission s100 β > 0.3 μ g/L predicted unfavorable outcome and is independent predictor of short-term survival (HR 2.2) (77.8 % sensitivity; 76 % specificity) s100 β correlates positively with HH and Fisher scores s100 β decreased after EVD insertion
Oertel, 2006	Pro	Aneurysmal SAH	51	s100 β , NSE	Serum	s100 β during first 3 days of SAH is higher in those who died compared to survivors All patients with s100 β > 1.0 μ g/L had unfavorable outcome NSE had no association with outcome s100 β is lower in patients with vasospasm (by transcranial doppler)
Coplin, 1999	Pro	Aneurysmal SAH	27	CKBB	CSF	CKBB > 40 μ L is associated with poor outcome at hospital discharge (100 % specificity)
Inflammatory markers						
Pan, 2013	Pro	Aneurysmal SAH	262 SAH, 150 CTRL	pGSN	Blood	pGSN were lower in SAH compared with controls pGSN was an independent predictor of poor functional outcome (OR 0.957) and death (OR 0.953) at 6 months Adding pGSN improved predictive performance of WFNS and Fisher scores for functional outcome but not for mortality
Frijins, 2006	Pro	SAH within 72 h of ictus, exclude perimesencephalic SAH	106	vWF	Serum	vWf > 94.5 nmol/L was independently associated with increased odds for poor outcome at 3 months (OR 1.1–9.8) sICAM-1, sP-selectin, sE-selectin, vWf propeptide, and ED 1-fibronectin were not independently associated with outcome
Mack, 2002	Pro	SAH, excluding those with pro-inflammatory disease process	80	sICAM-1	Serum	sICAM-1 was elevated in SAH (293.3 \pm 15 μ g/L) compared with controls sICAM-1 on post-SAH days 8, 10, and 12 were significantly elevated in those with unfavorable mRS at discharge
Beefink, 2011	Pro	Aneurysmal SAH	67	TNF α , Leukocytes, CRP	Serum	Neither TNF α nor TNF α genotype were associated with DCI or with SAH outcome at 3 months High leukocyte count and high CRP are not associated with DCI or SAH outcome
Chou, 2011	Pro	Spontaneous SAH, within 96 h of ictus	55	MMP9	CSF	Elevation of MMP9 on post SAH day 2–3 is associated with poor outcome (mRS 3–6) at 3 months

Author/year	Study design	Population	N	Bio-marker	Sample source	Findings
Chou, 2011	Pro	Spontaneous SAH, within 96 h of ictus	55	Neutrophil, WBC	Blood	Elevated neutrophil count on post SAH day 3 is associated with poor 3-month outcome Elevated WBC count throughout post SAH days 0–14 is associated with angiographic vasospasm
Chou, 2012	Pro	Spontaneous SAH, within 96 h of ictus	52	TNF α , IL-6	Serum	Elevated TNF α over post-SAH days 0–14 is independently associated with poor long term outcome IL-6 is not associated with SAH outcome Neither TNF α nor IL-6 was associated with angiographic vasospasm
Chou, 2011	Pro	Spontaneous SAH, within 96 h of ictus	42	pGSN	CSF, Serum	Serum pGSN is decreased in SAH compared to controls, and decreases over time in SAH CSF pGSN is decreased in SAH compared to controls Novel pGSN fragments found in SAH CSF but not in controls
Fassbender, 2001	Pro	Aneurysmal SAH within 48 h of ictus	35	IL-1 β , IL-6, TNF α	CSF, Serum	IL-1 β and IL-6 are significantly higher in CSF than in serum in SAH CSF IL-6 on post-SAH day 5 is significantly elevated in poor outcome group CSF TNF α did not show significant association with outcome
Mathiesen, 1997	Pro	SAH patients with EVD	22	IL-1R α , TNF α	CSF	IL-1R α were higher in poor grade SAH (HH 3–4; 318 vs. 82 pg/mL) Elevated IL-1Ra and TNF α on post SAH days 4–10 were associated with poor outcome
Weir, 1989	Retro	Aneurysmal SAH with vital signs and CBC data (76 % missing data)	173	WBC	Blood	Admission WBC > 15 \times 10 ⁹ /L shows 55 % mortality versus 25 % mortality in the lower WBC group
Kiikawa, 1997	Retro	Fisher grade 3 SAH treated with aneurysm clipping within 24 h of ictus	103	WBC	Blood	WBC counts during days 3–5, 6–8, 9–11, and 12–14 after onset of SAH were significantly higher in patients with than in patients without symptomatic vasospasm
Other biomarkers						
Niskakangas, 2001	Case control	Aneurysmal SAH	108	ApoE4	Blood	Presence of ApoE4 was associated with unfavorable outcome (OR 2.8 [1.18–6.77])
Juvela, 2009	Case control	SAH within 48 h of ictus	105	ϵ 2, ϵ 4-containing genotypes	Blood	Apolipoprotein E ϵ 2 or ϵ 4-containing genotypes were not associated with outcome or occurrence of cerebral infarction
Laterna, 2005	Case control	SAH HH grade 1–3	101	ApoE4 genotype	Blood	Presence of Apo E4 genotype is associated with negative overall outcome Apo E4 genotype is associated with development of DIND
Leung, 2002	Case control	Spontaneous SAH	72	ApoE4 genotype	Blood	ApoE4 genotype is associated with poor 6 month outcome (OR 11.3 [2.2–57.0])
Kay, 2003	Case Control	Spontaneous SAH requiring EVD	19	s100 β , ApoE	CSF	s100 β is significantly higher in SAH compared to controls ApoE is significantly lower in SAH compared to controls Lower ApoE was associated with better clinical outcome

Author/year	Study design	Population	N	Bio-marker	Sample source	Findings
Laterna, 2007	Meta-analysis	Consecutive SAH, with 3 month follow up data	696	ApoE4 genotype	Blood	Apo E4 genotype is associated with negative outcome (OR 2.558 [1.610–4.065]) and delayed ischemia (OR 2.044 [1.269–3.291])
Moussoutas, 2012	Pro	SAH with EVD, HH grade 3–5, endovascular aneurysm treatment	102	Epinephrine	CSF	Elevated CSF epinephrine within 48 h of admission is independently associated with mortality at 15 days (OR 1.06 [1.01–1.10]) and with death and disability at 30 days (OR 1.05 [1.02–1.09])
Yarlagadda, 2006	Pro	Spontaneous SAH, >21 years	300	BNP, cTI	Serum	Initial BNP > 600 pg/mL is associated with death (OR 37.7 [5.0–286.2]) cTI > 0.3 mg/L (on post-SAH day 9 ± 4) is associated with death (OR 4.9 [2.1–26.8]) No standardized time of biosample collection
Naidech, 2005	Pro	Spontaneous non-traumatic SAH	253	cTI	Serum	Peak cTI was independently predictive of death or severe disability at hospital discharge (OR 1.4 [1.1–1.9]) cTI not independently predictive of 3 month outcome by mRS
Ramappa, 2008	Retro	SAH diagnosed by CT scan or CSF, SAH ICD-9 code, with cTI measured	83	cTI	Blood	Peak cTI and GCS on presentation independently predicted in-hospital mortality

Pro prospective observational, *Retro* retrospective, *CTRL* control subjects, *CBC* complete blood count, *HH* grade Hunt and Hess grade, *WFNS* World Federation of Neurosurgeons classification, *DIND* delayed ischemic neurological deficit, *DCI* delayed cerebral ischemia, *mRS* modified Rankins score, *OR* odds ratio

Biomarkers for acute ischemic stroke

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Markers of CNS origin						
Kazmierski, 2012	Pro	AIS	458	s100β, OCLN, CLDN5, ZO1	Serum	Patients with clinical deterioration due to hemorrhagic transformation had higher s100β, OCLN, and CLDN/ZO1 ratio
Foerch, 2004	Pro	AIS within 6 h of onset with proximal MCA occlusion	51	s100β	Serum	Mean s100β were higher in patients with malignant cerebral edema defined s100β > 1.03 μg/L at 24 h post AIS predicted malignant infarction (94 % sensitivity; 83 % specificity)
Missler, 1997	Pro	AIS diagnosed by CT	44	s100β, NSE	Serum	s100β correlated with infarct volume and with 6 month outcome NSE correlated with infarct volume but not with clinical outcome Did not adjust for stroke subtype or tPA treatment

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Foerch, 2005	Pro	AIS within 6 h of onset	39	s100 β	Serum	s100 β at 48–72 h post AIS correlated with 6 month outcome and with infarct volume s100 β \leq 0.37 μ g/L at 48 h post stroke predicted functional independence at 6 months (87 % sensitivity; 78 % specificity)
Hermann, 2000	Pro	Anterior circulation AIS	32	s100 β , GFAP	Serum	s100 β and GFAP correlated with total infarct volume and neurologic status at hospital discharge Did not adjust for stroke subtype or tPA treatment
Foerch, 2003	Pro	AIS \leq 5 h of onset with M1 occlusion	23	s100 β	Serum	s100 β < 0.4 μ g/L at 48–96 h post-AIS predicted MCA recanalization within 6 h (86 % sensitivity; 100 % specificity)
Biomarkers of inflammation and blood brain barrier						
Den Hergot, 2009	RCT	AIS \leq 12 h onset, no liver disease, prior mRS < 2	561	CRP	Serum	From RCT for paracetamol for ischemic stroke CRP measured within 12 h of stroke onset CRP > 7 mg/L is associated with poor outcome (OR 1.6 [1.1–2.4]) and death (OR 1.7 [1.0–2.9])
Idicula, 2009	Nested Pro	AIS \leq 24 h onset	498	CRP	Serum	CRP > 10 mg/L is independently associated with high NIHSS and high long term mortality at 2.5 years
Montaner, 2006	Pro	AIS in MCA territory treated with IV tPA within 3 h; exclude inflammatory disease or infection	143	CRP	Serum	CRP measured before tPA administration CRP was higher in those who died after thrombolysis compared with survivors (0.85 vs. 0.53 mg/dL) CRP is independently associated with mortality at 3 months (OR 8.51 [2.16–33.5])
Winbeck, 2002	Pro	AIS \leq 12 h onset, NOT treated with IV tPA	127	CRP	Serum	CRP > 0.86 mg/dL 24 h and at 48 h post-stroke are associated with death and lower likelihood of event-free survival at 1 year
Topakian, 2008	Pro	AIS in MCA territory treated with IV tPA \leq 6 h of onset, exclude CRP > 6 mg/dL	111	CRP	Serum	CRP measured before tPA administration CRP level was not associated with NIHSS within 24 h or outcome at 3 months
Shantikumar, 2009	Pro	AIS surviving >30 days	394	CRP	Serum	CRP higher in subject who died compared to survivors CRP is independently predictive of mortality after adjusting for conventional risk factors
Elkind, 2006	Retro	Age > 40, reside in northern Manhattan > 3 months	467	hs-CRP	Serum	Highest quartile of hs-CRP is associated with increased risk of stroke recurrence (HR = 2.08 [1.04–4.18]) and with combined outcome of stroke, MI, or vascular death (HR = 1.86 [1.01–3.42])
Huang, 2012	Retro	Age > 40, reside in northern Manhattan > 3 months	741	hs-CRP	Serum	hs-CRP > 3 mg/L was associated with higher mortality at 3 months and all-cause mortality (HR = 6.48 [1.41–29.8])
Castellanos, 2003	Pro	Hemispheric AIS within 7.8 \pm 4.5 h of onset	250	MMP9	Plasma	MMP9 \geq 140 μ g/L predicted hemorrhagic transformation (61 % PPV; 97 % NPV)

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Castellanos, 2007	Pro	AIS \leq 3 h treated with IV tPA	134	c-Fn, MMP9	Serum	MMP9 \geq 140 μ g/L predicted hemorrhagic transformation (92 % sensitivity; 74 % specificity; 26 % PPV; 99 % NPV) c-Fn \geq 3.6 μ g/mL predicted hemorrhagic transformation (100 % sensitivity; 60 % specificity; 20 % PPV; 100 % NPV)
Moldes, 2008	Pro	AIS treated with IV tPA	134	ET-1, MMP9, c-Fn	Serum	ET-1, MMP9, and c-Fn measured upon admission before tPA bolus. ET-1 and c-Fn significantly higher in those with severe cerebral edema ET-1 $>$ 5.5 fmol/mL before tPA was independently associated with severe brain edema in multivariate analysis
Serena, 2005	Case control	Malignant MCA infarction, $<$ 70 years	40 AIS, 35 CTRL	c-Fn, MMP9	Plasma	c-Fn and MMP-9 were significantly higher in patients with malignant MCA infarcts c-Fn $>$ 16.6 μ g/mL predicted malignant infarction (90 % sensitivity; 100 % specificity; 89 % NPV; 100 % PPV)
Montaner, 2003	Pro	AIS in MCA territory treated with IV tPA within 3 h	41	MMP9	Plasma	Higher baseline (pre-tPA) MMP9 was associated with hemorrhagic transformation in dose-dependent fashion MMP9 was predictive of hemorrhagic transformation in multivariate model (OR 9.62)
Montaner, 2001	Pro	Cardioembolic AIS in MCA territory	39	MMP9	Plasma	Elevated baseline MMP9 was associated with late hemorrhagic transformation in multivariate regression (OR 9)
Castellanos, 2004	Pro	AIS treated with IV tPA by ECASS II criteria	87	c-Fn	Plasma	c-Fn was independently associated with hemorrhagic transformation in multivariate analysis (OR 2.1). 71 of the patients were treated within 3 h of AIS onset. Similar results were found in these patients
Guo, 2011	Pro	First onset AIS	172 AIS, 50 CTRL	pGSN	Plasma	Samples from first 24 h of stroke onset obtained. pGSN decreased in AIS compared to controls pGSN was independent predictor for 1-year mortality pGSN $>$ 52 mg/L predicted 1-year mortality (73 % sensitivity; 65.2 % specificity)
Yin, 2013	Pro	AIS	186 AIS, 100 CTRL	Visfatin	Plasma	Visfatin was higher in AIS than in controls Visfatin was independent predictor of 6-month clinical outcome Adding visfatin did not improve predictive performance of NIHSS
Other biomarkers						
Haapaniem, 2000	Case control	AIS	101 AIS, 101 CTRL	ET-1	Plasma	No difference in ET-1 levels between stroke and controls

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Lampl, 1997	Pro	AIS within 18 h from onset	26	ET-1	CSF, Plasma	CSF ET-1 correlated with volume of the lesion and higher in cortical infarcts compared to subcortical infarcts. Plasma ET-1 was not elevated
Chiquete, 2012	Pro	AIS	463	UA	Serum	UA \leq 4.5 mg/dL at hospital admission was associated with very good 30 day outcome (OR 1.76 [1.05–2.95]; 81.1 % NPV)
Matsumoto, 2012	Retro	AIS from non-valvular AF within 48 h of onset	124	d-dimer	Plasma	d-dimer level at hospital admission is independently associated with infarct volume Highest d-dimer tertile group had worse outcome compared to middle and lowest tertiles

AF atrial fibrillation, NPV negative predictive value, PPV positive predictive value, Pro prospective observational, RCT randomized controlled trial, Retro retrospective, CTRL control subjects, NIHSS NIH stroke scale, OR odds ratio

Biomarkers for intracerebral hemorrhage

Authors/Year	Study design	Population	N	Bio-marker	Sample source	Findings
Markers of CNS origin						
Hu, 2012	Pro	Basal ganglia ICH within 6 h of onset	176	Tau	Serum	tau > 91.4 pg/mL predicted poor 3-month outcome (83.6 % sensitivity; 75.8 % specificity) Addition of tau improved prognostic value of NIHSS for outcome but not for mortality
Hu, 2010	Pro	Basal ganglia ICH	86 ICH, 30 CTRL	s100 β	Plasma	s100 β was significantly associated with IVH, GCS scores, and ICH volumes s100 β is independently associated with mortality at 1 week (OR 1.046) s100 β > 192.5 pg/mL predicted 1-week mortality (93.8 % sensitivity; 70.4 % specificity)
Delgado, 2006	Pro	ICH	78	s100 β	Blood	s100 β was higher in patients who deteriorated early and in patients with a poor neurological outcome
Brea, 2009	Pro	ICH and AIS	44 ICH, 224 AIS	NSE	Blood	NSE elevation at 24 h post ICH was independently associated with poor outcome (OR 2.6 [1.9–15.6])
James, 2009	Pro	ICH	28	s100 β , BNP	Blood	s100 β and BNP levels correlated with outcome at hospital discharge Inclusion of biomarkers added little to the predictive power of ICH score
Cai, 2013	Case control	Basal ganglia ICH	112 ICH, 112 CTRL	pNF-H	Plasma	pNF-H is higher in ICH compared to controls pNF-H is an independent predictor of 6 month mortality (OR 1.287), 6-month unfavorable outcome (OR 1.265), and early neurological deterioration (OR 1.246) Addition of pNF-H did not improve predictive value of NIHSS

Authors/Year	Study design	Population	N	Bio-marker	Sample source	Findings
Biomarkers of inflammation						
Leira, 2004	Pro	ICH within 12 h of onset	266	Neutrophils, fibrinogen	Blood	Higher neutrophil count (OR 2.1) and fibrinogen > 523 mg/dL (OR 5.6) on admission were independently associated with early neurological deterioration
Di Napoli, 2011	Pro	ICH	210	WBC, CRP, glucose	Blood	Higher WBC, CRP, and glucose were significantly related to mortality Only CRP remained significantly related to mortality when adjusted for ICH score and the combination of ICH score and CRP had the best predictive ability
Agnihotri, 2011	Retro	Spontaneous ICH	423	WBC	Blood	Change in WBC (difference between max WBC in first 72 h and WBC on admission) correlated with worse discharge disposition and decline in modified Barthel index at 3 months
Zhao, 2013	Pro	Basal ganglia ICH within 6 h of onset	132 ICH, 68 CTRL	pGSN	Plasma	pGSN was lower in ICH compared to controls pGSN is an independent predictor of 6-month mortality and unfavorable outcome in multivariate analysis pGSN improved prognostic value of NIHSS for poor outcome but not for mortality
Castillo, 2002	Pro	ICH within 24 h of onset	124	Glutamate, TNF α	Blood	Glutamate level was an independent predictor of poor outcome TNF α correlated with volume of peri-hematoma edema
Wang, 2011	Pro-posthoc analysis	ICH within 24 h of onset	60	sICAM-1, sE-selectin	Plasma	Higher levels of sICAM-1 and sE-selectin were found in patients who had a poor outcome at hospital discharge
Li, 2013	Pro	ICH within 24 h of onset	59	MMP3, MMP9	Plasma	Elevated MMP3 was independently associated with peri-hematoma edema volume MMP3 > 12.4 μ g/L and MMP9 > 192.4 μ g/L were associated with poor outcome in multivariate analysis
Hernandez-Guillamon, 2012	Pro	ICH within 48 h of onset	66 ICH, 58 CTRL	VAP-1/SSAO	Plasma	VAP-1/SSAO activity < 2.7 pmol/min mg was independent predictor of neurological improvement after 48 h (OR 6.8)
Fang, 2005	Pro	ICH	43	IL-11	Plasma	Samples collected in first 4 days of ICH Plasma IL-11 higher in non-survivors compared to survivors
Diedler, 2009	Retro	Supratentorial ICH	113	CRP	Blood	CRP is independent predictor of poor long-term functional outcome
Gu, 2013	Pro	Basal ganglia ICH within 6 h of onset	85 ICH, 85 CTRL	Visfatin	Plasma	Visfatin was higher in ICH compared to controls Visfatin level was independent predictor of hematoma growth. (OR 1.154 [1.046–3.018]) and of early neurological deterioration (OR 1.195 [1.073–3.516])
Huang, 2013	Case control	Basal ganglia ICH	128 ICH, 128 CTRL	Visfatin	Plasma	ICH patients had higher visfatin compared to controls Visfatin correlated with NIHSS and is independent predictor for 6-month mortality and unfavorable outcome
Zhang, 2013	Pro	Basal ganglia ICH	92 ICH, 50 CTRL	Leptin	Plasma	Leptin higher in ICH compared to controls Leptin on admission is independent predictor of 6-month mortality and unfavorable outcome

Authors/Year	Study design	Population	N	Bio-marker	Sample source	Findings
Other biomarkers						
Chiu, 2012	Pro	ICH within 24 h of onset, > 16 years old	170	d-dimer	Serum	d-dimer is independently associated with 30-day mortality (OR 2.72)
Delgado, 2006	Pro	ICH	98	d-dimer	Plasma	d-dimer levels were associated with presence of IVH or SAH extension d-dimer > 1,900 µg/L is independently associated with early neurological deterioration (OR 4.5) and with mortality (OR 8.75)
Rodriguez-Luna, 2011	Pro	Supratentorial ICH within 6 h of onset	108	LDL-C	Serum	Lower LDL-C levels were associated with hematoma growth, early neurological deterioration and 3-month mortality but not with NIHSS or ICH volume
Ramirez-Moreno, 2009	Pro	ICH within 12 h of onset	88	LDL-C	Serum	Lipid profile measured in first hour after admission Low LDL-C levels were independently associated with death after ICH in multivariate analysis (HR = 3.07) LDL-C correlated with NIHSS, GCS, and ICH volume
Hays, 2006	Retro	ICH	235	cTnI	Blood	Elevated cTnI was independent predictor of in-hospital mortality
Chen, 2011	Pro	ICH	64 ICH, 114 CTRL	Oxidative markers	Blood	Blood collected within 3 days of ICH Measured 8-OHdG, G6PD, GPx, MDA, vitamin E, vitamin A 8-OHdG elevation was independently associated with 30-day lower Barthel index but not with outcome by mRS
Wang, 2012	Pro	ICH within 24 h of onset	60 ICH, 60 CTRL	Nuclear DNA	Plasma	Nuclear but not mitochondrial DNA correlated with GCS and ICH volume on presentation Nuclear DNA > 18.7 µg/L on presentation was associated with poor outcome at discharge (63.6 % sensitivity; 71.4 % specificity)
Huang, 2009	Pro	Basal ganglia ICH	36 ICH, 10 CTRL	MP	Plasma, CSF	Plasma and CSF MP levels were associated with GCS score, ICH volume, IVH, and survival Controls have suspected SAH
Zheng, 2012	Case control	ICH	79	miRNAs	Blood	Patients with hematoma expansion had different expression pattern of miRNAs (19 with increased expression, 7 with decreased expression)
Zhang, 2012	Pro	Basal ganglia ICH	89 ICH, 50 CTRL	Copeptin	Plasma	Copeptin level is an independent predictor for 1-year mortality, poor outcome, and early neurological deterioration Copeptin did not improve prognostic value of NIHSS

Pro prospective observational, RCT randomized controlled trial, Retro retrospective, CTRL control subjects, OR odds ratio

Biomarkers for traumatic brain injury

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Markers of CNS origin						
Okonkwo, 2013	Pro	Mild, moderate, and severe TBI	215	GFAP-BDP	Blood	Levels of GFAP-BDP were related to number of CT scan lesions and to neurological recovery A level of 0.68 µg/L was associated with a 21.61 OR for a positive CT and a 2.07 OR for failure to return to pre-injury baseline
Metting, 2012	Pro	Mild TBI	94	s100β, GFAP	Blood	Levels of GFAP but not s100β were related to outcome, but the PPV was not high (<50 %)
Vos, 2010	Pro	Moderate and severe TBI	79	s100β, GFAP	Blood	Levels of s100β and GFAP on admission were associated with poor outcome at 6 months and with mortality at 6 months even after adjusting for injury severity
Vos, 2004	Pro	Severe TBI	85	s100β, NSE, GFAP	Blood	s100β, NSE, and GFAP were all higher in non-survivors and in those with poor 6-month outcome s100β > 1.13 µg/L predicted death with 100 % discrimination
Wiesmann, 2009	Pro	Mild, moderate, and severe TBI	60	s100β, GFAP	Blood	Levels of s100β and GFAP were correlated with 6 month GOS Levels of s100β at 24 h post-injury had the highest correlation
Pelinka, 2004	Pro	TBI within 12 h	92	s100β, GFAP	Blood	GFAP and s100β were higher in non-survivors and predicted mortality
Nylen, 2008	Pro	Severe TBI	59	s100β, s100a1b, s100βb	Blood	Levels of s100β, s100a1b, and s100βb were all related to 1 year GOS
Nylen, 2006	Pro	Severe TBI	59	GFAP	Blood	Levels of GFAP were independently associated with 1-year outcome
Olivecrona, 2009	Pro	Severe TBI	48	s100β, NSE	Blood	Levels of NSE and s100β were not significantly related to outcome at 3 or 12 months
Topolovec-Vranic, 2011	Pro	Mild TBI within 4 h	141	s100β, NSE	Blood	s100β predicted poor cognitive outcome at 1 week NSE is independently associated with poor cognitive outcome at 6 weeks post-injury
Rainey, 2009	Pro	Severe TBI within 24 h	100	s100β	Blood	s100β at 24 h post injury were higher in patients with unfavorable outcome s100β > 0.53 µg/L predicted poor outcome (>80 % sensitivity; 60 % specificity)
Thelin, 2013	Retro	Severe TBI	265	s100β	Blood	Levels of s100β between 12 and 36 h of injury were correlated with 6–12 months GOS and remained significantly related to outcome after adjustment for injury severity factors
Rodriguez-Rodriguez, 2012	Pro	Severe TBI	55	s100β	Blood urine	Blood and urine s100β at 24 h post-TBI were significantly higher in non-survivors Serum s100β > 0.461 µg/L (88.4 % specificity) and urine s100β > 0.025 µg/L (62.8 % specificity) predicted mortality
Kay, 2003	Case control	TBI with GCS < 8	27 TBI, 28 CTRL	ApoE, s100β	CSF	s100β is elevated and ApoE is decreased in TBI compared with controls
Mondello, 2012	Case control	Severe TBI	95	UCH-L1	Blood, CSF	Blood and CSF levels of UCH-L1 were higher in patients with lower GCS, in patients who died, and in patients with unfavorable outcome. Levels at 6 h had the highest correlation Cumulative serum UCH-L1 > 5.22 µg/L predicted death with OR 4.8

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Brophy, 2011	Pro	Severe TBI GCS \leq 8	86 (blood), 59 (CSF)	UCH-L1	Blood, CSF	Non-survivors had higher median serum and CSF UCH-L1 levels in the first 24 h
Papa, 2010	Pro	TBI GCS \leq 8 with EVD	41 TBI, 25 CTRL	UCH-L1	CSF	UCH-L1 was higher in TBI compared with controls at all time points up to 168 h Levels of UCH-L1 were higher in patients with a lower GCS at 24 h, post-injury complications, in those died within 6 weeks, and in those with poor outcome at 6 months
Papa, 2012	Pro	Mild and moderate TBI GCS 9–15	96 TBI, 199 CTRL	UCH-L1	Blood	UCH-L1 within 4 h of injury distinguished TBI from uninjured controls (AUC = 0.87 [0.82–0.92]) UCH-L1 was associated with severity of injury in TBI
Liliang, 2010	Pro	Severe TBI	34	Tau	Blood	Tau levels were significantly higher in patients with a poor outcome Remained significant when adjusted for injury severity factors
Pineda, 2007	Pro	Severe TBI	41	SBDP145, SBDP150	CSF	SBDP145 and 150 levels were significantly related to outcome at 6 months
Brophy, 2009	Case control	Severe TBI	38	SBDP145, SBDP150	CSF	SBDP145 and 150 levels were higher in patients with worse GCS and longer ICP elevation
Mondello, 2010	Pro	Severe TBI	40 TBI, 24 CTRL	SBDP145, SBDP120	CSF	SBDP145 > 6 μ g/L (OR 5.9) and SBDP120 > 17.55 μ g/L (OR 18.34) predicted death SBDP145 within 24 h of injury correlated with GCS score
Inflammatory markers						
Schneider Soares, 2012	Pro	Mild, moderate, and severe TBI	127	IL-10, TNF α	Blood	Levels of IL-10 but not TNF α were related to mortality, even when adjusted for injury severity characteristics
Stein, 2012	Pro	Severe TBI	68	IL-8, TNF α	Serum	High levels of both IL-8 and TNF α predicted subsequent development of intracranial hypertension (specificity was high but sensitivity was low)
Tasci, 2003	Pro	Mild, moderate, and severe TBI	48	IL-1	Blood	IL-1 levels within 6 h correlated with the initial injury severity (GCS) and with GOS, but timing of the GOS is not described
Antunes, 2010	Pro	TBI with hemorrhagic contusions	30	IL-6	Blood	IL-6 levels at 6 h were higher in patients who would subsequently clinically deteriorate due to evolving contusions
Combinations of markers						
Diaz-Arrastia, 2013	Pro	Mild, moderate, and severe TBI	206	UCH-L1, GFAP	Blood	Levels of UCH-L1 were higher with moderate-severe than with mild TBI UCH-L1 levels were poorly predictive of complete recovery but better at predicting poor outcome For predicting complete recovery, UCH-L1 in combination with GFAP was not better than GFAP alone. For predicting favorable versus unfavorable outcome, UCH-L1 is marginally better than GFAP and both together are better than either alone

Authors/year	Study design	Population	N	Bio-marker	Sample source	Findings
Czeiter, 2012	Pro	Severe TBI	45	GFAP, UCH-L1, SBDP145	Serum, CSF	GFAP, UCH-L1, and SBDP145 all had at least one measure that was significantly related to unfavorable outcome When included in a model with IMPACT predictors of outcome, serum GFAP during first 24 h and the first CSF UCH-L1 value obtained were significantly related to mortality and only serum GFAP during first 24 h was significantly related to unfavorable outcome In combination, the IMPACT core model with the first CSF GFAP value, the first serum GFAP value, and the first CSF SBDP145 value performed the best

Pro prospective, *PPV* positive predictive value, *Retro* retrospective, *CTRL* control subjects, *GOS* Glasgow outcome scale, *OR* odds ratio, *PPV* positive predictive value

ICU Processes of Care and Quality Assurance

Evidence summary for specialized neurocritical care

Study	Design	N	Population	Findings
Warne, 1991 [15]	Retrospective	121	TBI	Care in neuro-ICU resulted in decreased mortality and higher GOS scores
Diringer, 2001 [22]	Analysis of prospective registry data	1,038	ICH	ICH patients in neurological or neurosurgical ICU had lower hospital mortality rate than ICH patients in general ICU; presence of full time intensivist associated with lower mortality rate
Mirski, 2001 [14]	Retrospective	128	ICH	ICH patients in neuroscience ICU had lower mortality, and improved discharge disposition than ICH patients in general ICU. Neuroscience ICU patients had shorter hospital length of stay and lower costs than national benchmarks
Elf, 2002 [19]	Retrospective	226	TBI	Care in neuro-ICU resulted in decreased mortality and improved functional outcome, measured by GOS scores
Patel, 2002 [20]	Retrospective	285	TBI	Specialized neurointensive care resulted in decreased mortality and higher incidence of favorable outcome
Suarez, 2004 [16]	Analysis of prospective registry data	2,381	Critically ill neuroscience patients	Decreased hospital mortality, shorter hospital and ICU length of stay after neurocritical care team was introduced
Varelas, 2004 [13]	Observational cohort with historical controls	2,366	All NICU admissions	Decrease in mortality and length of stay, and improved discharge disposition after implementation of neurointensivist-led team
Varelas, 2006 [25]	Retrospective	592	TBI	Decreased mortality and hospital length of stay, increased odds of discharge to home or rehabilitation after neurointensivist appointed
Lerch, 2006 [18]	Retrospective	59	Aneurysmal SAH	Specialized neurocritical care associated with higher incidence of favorable outcome, measured by GOS
Bershad, 2008 [26]	Retrospective	400	Acute ischemic stroke	Neurointensive care team associated with decreased ICU and hospital length of stay, and increased proportion of discharges home
Lott, 2009 [23]	Prospective, multi-site	16,415	Intracranial hemorrhage, ischemic stroke	Lower mortality and higher incidence of favorable outcome among units with neuro-specialized care
Josephson, 2010 [12]	Retrospective	512	SAH	Neuro-intensivist co-management associated with decreased mortality
Palminteri, 2010 [21]	Retrospective	287	ICH	No difference in mortality with neurointensivist; higher proportion of favorable outcome with neurointensivist-managed care

Study	Design	N	Population	Findings
Samuels, 2011 [17]	Retrospective	703	Aneurysmal subarachnoid hemorrhage	Patients treated by neurocritical care team more likely to receive definitive aneurysm treatment and be discharged home
Knopf, 2012 [29]	Retrospective	2,096	AIS, ICH, aneurysmal SAH	Compared data prior to, during, and after departure of a neurointensivist (NI). For AIS, departure of the NI resulted in decreased functional outcome; for ICH, there was no effect of a NI, but shorter length of stay for patients in specialized neurocritical care unit, compared to a general ICU. For SAH, NI resulted in longer ICU LOS, but improved discharge disposition and mortality
Burns, 2013 [30]	Retrospective	74	ICH	Introduction of a neurocritical care consult service resulted in more timely and sustained SBP control, and more dysphagia screens prior to initiation of oral feeding.

Evidence summary for protocol-directed care

Study	Design	N	Population	Findings
Elf, 2002 [19]	Retrospective	154	TBI	Organized secondary insult management protocol and neurointensive care improved mortality rates and percentage of favorable outcome using GOS scores after 6 months
Patel, 2002 [20]	Retrospective	285	TBI	Patients with severe head injury treated by ICP/ CPP targeted protocol and neurocritical care specialists had higher percentage of favorable outcome measured by GOS scores 6 months post-injury
Arabi, 2010 [40]	Retrospective/ prospective	434	TBI	Implementation of protocol management based on BTF guidelines was associated with reduction in hospital and ICU mortality
Eker, 1998 [41]	Prospective	91	TBI	Protocol targeting brain volume regulation and microcirculation reduced mortality and improved percentage of favorable outcome measured by GOS 6 months post-injury
McKinley, 1999 [42]	Retrospective/ prospective	24	TBI	ICP management protocol resulted in more consistent and improved ICP control, and less variation in CPP
Vukic, 1999 [43]	Retrospective	39	TBI	Protocol based on BTF guidelines for ICP management resulted in decreased mortality and improved percentage of favorable GOS scale scores
McIlvoy, 2001 [44]	Retrospective/ prospective	125	TBI	BTF guidelines used to develop 4-phase protocol for ICP/ CPP management, resulting in decreased hospital and ICU length of stay, decreased number of ventilator days and incidence of pneumonia, and earlier tracheostomy
Palmer, 2001 [45]	Retrospective/ prospective	93	TBI	BTF guideline implementation improved odds of good outcome, measured by GOS at 6 months
Vitaz, 2001 [46]	Retrospective/ prospective	162	TBI	Standardized clinical pathway for ICP/ CPP management resulted in decreased hospital and unit length of stay and decreased ventilator days
Clayton, 2004 [47]	Retrospective	669	TBI	CPP management protocol decreased ICU and hospital mortality, but had no effect on length of stay
Fakhry, 2004 [48]	Retrospective/ prospective	830	TBI	Protocol developed from BTF guidelines decreased hospital length of stay and costs, and demonstrated a decreased trend in mortality and improved functional recovery
Cremer, 2005 [49]	Retrospective/ prospective	333	TBI	ICP/ CPP targeted algorithm resulted in increased number of ventilator days and therapy intensity, with no difference in mortality when compared to supportive care control group
Talving, 2013 [50]	Prospective	216	TBI	Observational study comparing patients managed with ICP monitoring versus no monitoring and compliance with BTF guidelines. In hospital mortality higher in patients with no ICP monitoring. ICP monitoring group had longer ICU and hospital length of stay. BTF guideline compliance was 46.8 %
Biersteker, 2012 [51]	Observational multi-site	265	TBI	Investigated compliance and outcomes of BTF guidelines for ICP monitoring. Guideline compliance was 46 %. Guideline compliance was not associated with mortality or unfavorable outcome when controlling for baseline and clinical characteristics
Meretoja, 2010 [52]	Observational, multi-registry	61,685	AIS	Compared data from 333 hospitals classified as comprehensive stroke centers, primary stroke centers, and general hospitals. Mortality rates lower in stroke centers for up to 9 years
Smith, 2010 [53]	Longitudinal cohort registry	6,223	AIS	Organized stroke care resulted in decreased 30 day mortality for each ischemic stroke subtype
Schwamm, 2009 [54]	Prospective quality initiative	322, 847	AIS, TIA	Centers that participated in Get with the Guidelines-Stroke reported higher compliance with all stroke performance measures
Gropen, 2006 [55]	Retrospective quality initiative	1,442	AIS	Designated stroke centers utilizing Brain Attack Coalition guidelines experienced shorter door to MD contact, CT scan time, and t-PA administration time.

Monitoring in Emerging Economies

Data for demographics of TBI studies

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Resource utilization in the management of TBI—an audit from a rural setup in a developing country	Agrawal, 2011 [5]	Wardha, India	Retrospective	162	Adults and children	79.0 %	36 (1–83)	RTA 67 %	Rural part of India. N = 381 patients all grades of TBI
Prognosis of traumatic head injury in South Tunisia: a multivariate analysis of 437 cases	Bahloul, 2004 [6]	Tunisia	Retrospective	253	Adults	90.0 %	28 (15–98)	RTA 86 %	Mixed grades of TBI severity in the ICU. N = 437 all grades of TBI
Severe head injury among children: prognostic factors and outcome	Bahloul, 2009 [7]	Tunisia	Retrospective	222	Children	73.0 %	7.5 (0.3–15)	RTA 76 %	
Trauma admissions to the intensive care unit at a reference hospital in Northwestern Tanzania	Chalya, 2011 [8]	Tanzania	Retrospective	192	Adults and children	85.0 %	4–71	RTA 71 %	Trauma admissions to the ICU. Severe TBI accounted for 37 % of admissions and 95 % of emergency admissions. 312 overall trauma cases; TBI 95 % of these
Head injury mortality in two centers with different emergency medical services and intensive care	Colohan, 1989 [9]	India (New Delhi); US (Charlottesville, Virginia)	Prospective observational study at two centers	1,373, mixed New Delhi; 822 Charlottesville	Adults	81 % (New Delhi); 69 % (Charlottesville)	25 (New Delhi); 32 (Charlottesville)	RTA 60 % both series	All grades of TBI severity. Compared demographics and outcomes at Charlottesville, Virginia and New Delhi. India Groups not completely comparable, so controlled for GCS motor score
Examination of the management of traumatic brain injury in the developing and developed world: focus on resource utilization, protocols, and practices that alter outcome	Harris, 2008 [10]	Jamaica, US	Prospective observational study at three centers	269	Adults	81 % (Jamaica); 74 % (Atlanta)	34 (Jamaica); 38 (Atlanta)	RTA 66 % (Jamaica); 44 % (Atlanta)	Studied two centers in Jamaica, one in Atlanta, Georgia. Mixed grades of TBI severity; N = 1,607. Atlanta: higher percentage of severe TBI; better outcome; older patients; more ICP monitoring (13 %); median time to death a bit later. Jamaica: more assaults (approx 40 %), younger patients, higher rates of penetrating injuries. No difference in mild/moderate injury mortality, but significantly different for severe TBI
Cost effectiveness analysis of using multiple neuromodalities in treating severe traumatic brain injury in a developing country like Malaysia	Ibrahim, 2007 [13]	Malaysia	Prospective, observational	62	Adults	92.0 %	33.8	RTA 85.5 %	Study comparing baseline neuromonitoring and MMM. 32 patients were managed with MMM, 30 with baseline neuromonitoring (ICP and conventional care)
Prognostic study of using different monitoring modalities in treating severe traumatic brain injury	Idris, 2007 [14]	Malaysia	Prospective randomized study	52	Adults	90.0 %	35 (15–75)	RTA 86 %	Randomized to two different surgeons for care. MMM versus ICP only
Outcome of severe traumatic brain injury: comparison of three monitoring approaches	Isa, 2003 [15]	Malaysia	Prospective, observational	82 total (17 MMM; 31 ICP; 34 none)	Adults and children	82–85 %	27	NR	Historical comparison of three groups: No monitoring; ICP monitoring only; MMM

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Early prediction of outcome in very severe closed head injury	Jain, 2008 [16]	India	Prospective, observational	102	Adults and children	91.0 %	31.7 (6–75)	RTA 44 %; railway traffic accidents in 36 %	Included only patients with a GCS of 5 or less. Overall mortality 76 %
Delayed traumatic intracranial hemorrhage and progressive traumatic brain injury in a major referral centre based in a developing country	Jeng, 2008 [12]	Malaysia	Retrospective	16	Adults	86.0 %	33	RTA 81.5 %	Imaging study. Mixed grades of TBI severity; <i>N</i> = 81
Outcome of children with traumatic brain injury in rural Malaysia	Kumaraswamy, 2002 [17]	Malaysia	Prospective	33	Children	75.0 %	6–13	RTA 100 %	Mixed grades of TBI severity
Traumatic brain injury in a rural and urban Tanzanian hospital—a comparative, retrospective analysis based on computed tomography	Maier, 2013 [41]	Tanzania	Retrospective	680	Adults and children	Ratio 5.7:1 (rural); 2.1:1 (urban)	33.7 (rural); 40.5 (urban)	RTA 46.3 % (urban); rural 25.4 %. Included injuries due to wild and domestic animals	Review of imaging. More pathology encountered in the rural area, long distances to travel; unusual mechanisms of injury
Prognosis of head injury: an experience in Thailand	Ratanalert, 2002 [19]	Thailand	Retrospective	300	Adults and children	87.0 %	30 (5–76)	84 % RTA (66 % motorcycle accidents)	Excluded brain death presentations
Care of severe head injury patients in the Sarawak General Hospital: intensive care unit versus general ward	Sim, 2011 [11]	Malaysia	Prospective	35	Adults	91.0 %	37 (13–75)	RTA 80 %	65.7 % of patients were ventilated in the general ward; 34.3 % managed in the ICU. Decision made by anesthetic team based largely on availability of ICU bed. Inclusion/exclusion criteria for management not specified. Ward mortality higher; however, mean age of ward managed patients was higher than ICU patients and GCS was lower. Groups not easily comparable
Intensive care and survival analyses of traumatic brain injury	Sut, 2010 [20]	Turkey	Retrospective	126	Adults	80.2 %	34.5	RTA 60 %	
Post-traumatic seizures—a prospective study from a tertiary level centre in a developing country	Thapa, 2010 [66]	India	Prospective observational	130	Adults and children	81.0 %	28 (0.08–89)	RTA 48 %	Excluded late admissions and GCS 4 or less. All grades of TBI severity. 520 total; 25 % sTBI; overall mortality 11.5 %; severe TBI mortality not separately reported

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Epidemiology of TBI in Eastern China 2004: a prospective large case study	Wu, 2008 [21]	China	Prospective	2,983	Adults and children	77.0 %	39 (0–98)	RTA 61 %	Standardized questionnaire in the region over a 1-year period. All patients admitted with a diagnosis of head injury to one of 77 hospitals in the region. All grades of TBI severity. Severe and moderate TBI each about 20 %
Continuous measurement of the cumulative amplitude and duration of hyperglycemia best predicts outcome after traumatic brain injury	Yuan, 2012 [22]	China (Shanghai)	Prospective observational	56	Adults	76.8 %	46	RTA 61 %	78 % underwent craniotomy or craniectomy; not likely a consecutive series; also higher mean age. Moderate and severe TBI
Outcome of head injuries in general surgical units with an offsite neurosurgical service	Zulu, 2007 [23]	South Africa, KZN	Prospective observational	42	Adults	83.0 %	31 (12–80)	NR	Outcome of patients in general surgical ICU with offsite neurosurgery transfer. 316 total patients mixed grades of injury; 12 % had severe TBI
The relationship between intracranial pressure and brain oxygenation in children with severe traumatic brain injury	Rohlwink, 2012 [43]	South Africa	Retrospective	75	Children	65.0 %	6.4 (0.3–14)	RTA 80 %	
The relationship between basal cisterns on CT and time-linked intracranial pressure in paediatric head injury.	Kouvarellis, 2011 [67]	South Africa	Retrospective	104	Children	63.0 %	6 (0.42–14)	RTA 82 %	
The effect of increased inspired fraction of oxygen on brain tissue oxygen tension in children with severe traumatic brain injury	Figaji, 2010 [26]	South Africa	Prospective, observational	28	Children	NR	5.8 (0.75–11)	NR	
Pressure autoregulation, intracranial pressure, and brain tissue oxygenation in children with severe traumatic brain injury	Figaji, 2009 [44]	South Africa	Prospective, observational	24	Children	83.0 %	6.3 (1–11)	RTA 75 %	
The effect of blood transfusion on brain oxygenation in children with severe traumatic brain injury	Figaji, 2010 [27]	South Africa	Retrospective	17	Children	NR	5.4 (0.75–12)	NR	
Transcranial Doppler pulsatility index is not a reliable indicator of intracranial pressure in children with severe traumatic brain injury	Figaji, 2009 [45]	South Africa	Prospective, observational	34	Children	NR	6.5 (0.75–14)	NR	
Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part I: Relationship with outcome	Figaji, 2009 [46]	South Africa	Prospective observational	52	Children	75.0 %	6.5 (0.75–14)	RTA 77 %	

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Acute clinical grading in pediatric severe traumatic brain injury and its association with subsequent intracranial pressure, cerebral perfusion pressure, and brain oxygenation	Figaji, 2009 [62]	South Africa	Retrospective	52	Children	NR	6.5 (0.25–14)	RTA 77 %	
Does adherence to treatment targets in children with severe traumatic brain injury avoid brain hypoxia? A brain tissue oxygenation study	Figaji, 2008 [63]	South Africa	Prospective, observational	26	Children	85.0 %	6.8 (0.75 to 14)	RTA 81 %	
Intracranial pressure and cerebral oxygenation changes after decompressive craniectomy in children with severe traumatic brain injury	Figaji, 2008 [68]	South Africa	Retrospective	18	Children	NR	7.8 (0.25–14)	NR	
Head trauma in China	Jiang, 2012 [69]	China	Retrospective	1,626	Adults and children		1–92	NR	Mixed TBI grade severity, Databank analysis of 47 hospitals over 9 months
Pediatric neurotrauma in Kathmandu, Nepal: implications for injury management and control	Mukhida, 2006 [70]	Nepal	Retrospective	46	Children	65.0 %	0–18	RTA 35 %	Patients in the city region took about 8 h to get to the hospital while patients in the rural area took more than a day to get to hospital. Ventriculostomy used in 3 % of total 352 patients (46 sTBI). Delayed transfer to hospital may have selected patients. Patients who came from the rural area paradoxically had lower mortality, possibly for this reason
Decreased risk of acute kidney injury with intracranial pressure monitoring in patients with moderate or severe brain injury	Zeng, 2013 [57]	Shanghai	Prospective, observational	47	Adults	64.3 %	43 (18–68)	NR	Prospective comparison of ICP-monitored and non-monitored moderate and severe TBI patients. Examined GOS at 6 month and acute kidney injury. Non-randomized. 168 all grades of TBI
Use of indomethacin in brain-injured patients with cerebral perfusion pressure impairment: preliminary report	Biestro, 1995 [60]	Uruguay	Prospective, interventional	11	Adults	73.0 %	24	NR	Non-consecutive series. Ten TBI, one SAH
Osmotherapy for increased intracranial pressure: comparison between mannitol and glycerol	Biestro, 1997 [59]	Uruguay	Prospective, interventional	16	Adults	88.0 %	37 (15–69)	NR	Both effective, mannitol better for bolus and glycerol for baseline treatment
Optimizing cerebral perfusion pressure during fiberoptic bronchoscopy in severe head injury: effect of hyperventilation	Previgliano, 2002 [71]	Argentina	Prospective, interventional	34	Adults	88.0 %	39	NR	

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Incidence of intracranial hypertension related to jugular bulb oxygen saturation disturbances in severe traumatic brain injury patients	Schoon, 2002 [48]	Argentina	Retrospective	116	Adults	64.7 %	30.9 (16–67)	NR	
Jugular venous oxygen saturation or arteriovenous difference of lactate content and outcome in children with severe traumatic brain injury	Perez, 2003 [49]	Argentina	Prospective, observational	27	Children	52.0 %	10 (1–16)	NR	
Influence of the respiratory physiotherapy on intracranial pressure in severe head trauma patients	Thiesen, 2005 [72]	Brazil	Retrospective	35	Adults	77.0 %	25 (17–49)	NR	
Serum Hsp70 as an early predictor of fatal outcome after severe traumatic brain injury in males	da Rocha, 2005 [56]	Brazil	Prospective, observational	20	Adults	N/A	34.5 (18–64)	RTA 70 %	Males only included in the series
Effects of dexmedetomidine on intracranial hemodynamics in severe head injured patient	Grille, 2005 [73]	Uruguay	Prospective, interventional	12	Adults	90.0 %	33	NR	
Cerebral hemodynamic changes gauged by transcranial Doppler ultrasonography in patients with posttraumatic brain swelling treated by surgical decompression	Bor-Seng-Shu, 2006 [52]	Brazil	Prospective, observational	19	Adults	68.4 %	33.3	RTA 89.5 %	
Role of serum S100B as a predictive marker of fatal outcome following isolated severe head injury or multitrauma in males	da Rocha, 2006 [55]	Brazil	Prospective, observational	30	Adults	NR	34 (19–64)	RTA 78 %	S100B within 48 h post-injury has significant predictive value for mortality
Optimized hyperventilation preserves 2,3-diphosphoglycerate in severe traumatic brain injury	Torres, 2007 [54]	Brazil	Prospective, observational	11	Adults	90.9 %	25.5 (15–49)	RTA 63.6 %	
Indomethacin and cerebral autoregulation in severe head injured patients: a transcranial Doppler study	Puppo, 2007 [31]	Uruguay	Prospective, interventional	16	Adults	88.0 %	39	NR	

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Value of repeat cranial computed tomography in pediatric patients sustaining moderate to severe traumatic brain injury	Da Silva, 2008 [33]	Brazil	Retrospective	22	Children	NR	6 (1–14)	RTA 46 %	Excluded patients who died in the first 24 h; moderate and severe TBI. <i>N</i> = 63 total
Cerebral CO ₂ reactivity in severe head injury. A transcranial Doppler study	Puppo, 2008 [29]	Uruguay	Prospective, interventional	16	Adults	85.0 %	40 (17–60)	NR	
Early prognosis of severe traumatic brain injury in an urban Argentinian trauma center	Petroni, 2010 [34]	Argentina	Prospective, observational	148	Adults	81.0 %	24 (14–77)	RTA 87 %	Excluded patients who were sedated or intubated, had a penetrating head injury, were brain dead on arrival or if consent was refused. Almost 90 % mortality in those over age 50
Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury.	Fridman, 2010 [74]	Argentina	Prospective, interventional	8	Adults	50.0 %	22–41	NR	Non-consecutive series
Factors associated with intracranial hypertension in children and teenagers who suffered severe head injuries	Guerra, 2010 [35]	Brazil	Retrospective	191	Children	NR	9.7	RTA 79.5 %	Most ICP monitors with subdural or subarachnoid Richmond screw
Non-invasive intracranial pressure estimation using support vector machine	Chacon, 2010 [75]	Chile-Uruguay	Prospective, observational	8	Adults	NR	25.8 (16–48)	NR	
Neuron-specific enolase, S100B, and glial fibrillary acidic protein levels as outcome predictors in patients with severe traumatic brain injury	Bohmer, 2011 [76]	Brazil	Prospective, observational	20	Adults	90.0 %	29	NR	Consecutive series
A trial of intracranial-pressure monitoring in traumatic brain injury	Chesnut, 2012 [37]	Bolivia-Ecuador	Prospective RCT	324	Adults	87.0 %	29	76 % RTA (majority motorcycles)	Multicenter study in Bolivia and Ecuador. Only 45 % came in with an ambulance. Median time to hospital 3.1 h
Delayed intracranial hypertension and cerebral edema in severe pediatric head injury: risk factor analysis	Bennett Colomer, 2012 [38]	Chile	Retrospective	31	Children	58.0 %	8.9	NR	
Bedside study of cerebral critical closing pressure in patients with severe traumatic brain injury: a transcranial Doppler study	Puppo, 2012 [28]	Uruguay	Prospective, observational	12	Adults	83.0 %	32	NR	
Mortality and morbidity from moderate to severe traumatic brain injury in Argentina	Rondina, 2005 [40]	Argentina	Prospective, observational	169 in Argentina; 103 in Oregon	Adults	85 % (Argentina); 75 % (Oregon)	33 (Argentina); 40 (Oregon)	NR	Included moderate and severe TBI

Article title	First author	City/country	Study design	Patient numbers	Case mix	Males	Age	Mechanism of injury	Comment
Highlighting intracranial pressure monitoring in patients with severe acute brain trauma	Falcao, 1995 [77]	Brazil	Retrospective	100	Adults	81.0 %	11–70	RTA 71 %	
Comparison between two static autoregulation methods	Puppo, 2002 [78]	Uruguay	Prospective, observational	14	Adults	71.0 %	37 (16–63)	NR	
Outcomes following prehospital airway management in severe traumatic brain injury	Sobuwa, 2013 [79]	South Africa	Retrospective	124	Adults	89 %	32	RTA 67 %	
Prognostic factors in children with severe diffuse brain injuries: a study of 74 patients	Pillai, 2001 [80]	India	Retrospective	74	Children	67.3 %	0–15	RTA 70 %	Children with severe diffuse TBI
Assessment of endocrine abnormalities in severe traumatic brain injury: a prospective study	Tandon, 2009 [81]	India	Prospective observational	99	Adults and children	87 %	32.5	NR	

sTBI severe traumatic brain injury, *N* sample size (for severe TBI unless specified), *NR* not reported, *mechanism of injury* percentage of study patients involved in road traffic accidents (RTA), *Age* mean age (range) or only range where mean age was not reported

Data for clinical outcome after severe TBI and utilization of monitoring

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
Resource utilization in the management of TBI—rural setup	Agrawal, 2011 [5]	Wardha, India	Retrospective	38.0 %	NR	No	No	162	Adults and children	Rural part of India. No ICP monitoring available. 70 % of severe TBI deaths in the first 24 h, the rest within 2-week period
Prognosis of traumatic head injury in South Tunisia: a multivariate analysis of 437 cases	Bahloul, 2004 [6]	Tunisia	Retrospective	38.0 %	NR	NR	NR	253	Adults	Mixed grades of TBI severity in the ICU. Only 1 % died after day 5; 78 % died within the first 48 h
Severe head injury among children: prognostic factors and outcome	Bahloul, 2009 [7]	Tunisia	Retrospective	24.3 %	GOS; mean 8 months, minimum 6 months; 52 % good recovery	No	No	222	Children	16 % died after day 7
Delayed intracranial hypertension and cerebral edema in severe pediatric head injury: risk factor analysis	Bennett Colomer, 2012 [38]	Chile	Retrospective	35.4 %	NR	80 %	NR	31	Children	Children
Osmotherapy for increased intracranial pressure: comparison between mannitol and glycerol	Biestro, 1997 [59]	Uruguay	Prospective, interventional	56.0 %	NR	100 % (selected)	No	16	Adults	Prospective study to compare mannitol and glycerol in sTBI
Neuron-specific enolase, S100B, and glial fibrillary acidic protein levels as outcome predictors in patients with severe traumatic brain injury	Bohmer, 2011(76)	Brazil	Prospective, observational	25.0 %	NR	NR—EVD	NR	20	Adults	

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
A trial of intracranial-pressure monitoring in traumatic brain injury	Chesnut, 2012 [82]	Bolivia-Ecuador	Prospective, RCT	40 % (39 % ICP group vs. 41 %)	6 month GOS-E; GOAT; DRG; neuropsychological tests	50 %	NR	324	Adults	Multicenter RCT in Bolivia and Ecuador. Excluded patients who had a GCS of 3/15 with fixed, dilated pupils or who were deemed to have an unsurvivable injury. Only 45 % came in with an ambulance. Median time to hospital 3.1 h. Good recovery in 31 % of ICP group and 26 % of standard group. Mortality at 2 weeks 21 % and 30 %; at 6 months 39 and 41 %
Head injury mortality in two centers with different emergency medical services and intensive care	Colohan, 1989 [9]	India (New Delhi); US (Charlottesville, Virginia)	Prospective observational study at two centers	GCS motor score 5: 12. % (ND); 4.8 % (CV). Motor score 2–4: 56.2 % (ND); 40.9 % (CV)	NR	Of total: 15 % CV (87 % for GCS 5 or less); 0 % ND	No	Mixed patients: 1,373 (551 ND; 822 CV).	Adults	All grades of TBI severity. Compared demographics and outcomes at Charlottesville, Virginia (CV) and New Delhi (ND). India. Groups were not completely comparable, so they controlled for GCS motor score
Serum Hsp70 as an early predictor of fatal outcome after severe traumatic brain injury in males	da Rocha, 2005 [56]	Brazil	Prospective, observational	50.0 %	GOS at discharge only	NR	NR	20	Adults	
Role of serum S100B as a predictive marker of fatal outcome following isolated severe head injury or multitrauma in males	da Rocha, 2006 [83]	Brazil	Prospective, observational	48.0 %	NR	NR	NR	30	Adults	
Highlighting intracranial pressure monitoring in patients with severe acute brain trauma	Falcao, 1995 [77]	Brazil	Retrospective	38.0 %	NR	100 % (selected)	NR	100	Adults	

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part I: relationship with outcome	Figaji, 2009 [46]	South Africa	Prospective, observational	9.6 %	GOS, Pediatric Cerebral Performance Category Score. Good outcome 77 %	100 %	Brain oxygen, TCD, ICMPlus	52	children	Non-consecutive series—only patients who received ICP and brain oxygen monitoring
Effects of dexmedetomidine on intracranial hemodynamics in severe head injured patient	Grille, 2005 [73]	Uruguay	Prospective, interventional	10.0 %	NR	100 % (selected)	SjVO ₂	12	Adults 9/1	Non-consecutive; selected for intracranial monitoring
Factors associated with intracranial hypertension in children and teenagers who suffered severe head injuries	Guerra, 2010 [84]	Brazil	Retrospective	51.5 %	NR	69 %	NR	191	Children	
Examination of the management of traumatic brain injury in the developing world: focus on resource utilization, protocols, and practices that alter outcome	Harris, 2008 [85]	Jamaica, US	Prospective, observational	56.8 % (Ja.); 53.8 % Ja.); 32.3 % (AG)	GOS, FIM	13.5 % (AG); 0.1 (Ja.); 4.5 % (Ja.)—of all grades of severity	No	269	Adults	Study at two centers in Jamaica (Ja.), one in Atlanta, Georgia (AG). All grades of severity included; N = 1,607. Significant patient characteristic differences. No difference in mortality for mild/moderate TBI, but significantly different for severe TBI. CT scans were obtained in 95 % (AG); 20.3 % (Ja.); 68 % (Ja.)
Cost effectiveness analysis of using multiple neuromodalities in treating severe traumatic brain injury in a developing country like Malaysia	Ibrahim, 2007 [13]	Malaysia	Prospective, observational	NR	Barthel index at 6 months: 46.83 (conventional); 63.75 (MMM)	100 %	Licox, TCD, SjVO ₂ , EEG	62	Adults	Study comparing baseline neuromonitoring and MMM. 32 patients were managed with MMM, 30 with baseline neuromonitoring (ICP and conventional care). Followed up to 1 year post admission. Statistically significant better functional outcome with MMM. Higher costs of MMM—suggest that this is compensated by better patient outcomes

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
Prognostic study of using different modalities in treating severe traumatic brain injury	Idris, 2007 [14]	Malaysia	Prospective randomized study	28.8 %—ICU mortality	Barthel index; 6 months; 38 % independent	100 %	MMM: TCD, Licox, regional CBF (Saber 2000), SJVO ₂ , EEG	52	Adults	Randomized to two different surgeons for care—MMM versus ICP only. Several exclusions due to severity; attempted to focus on patients who were salvageable. No statistically significant difference between groups, but functional independence higher in MMM group (21.2 % vs. 17.3 %). Some differences between groups at randomization; not completely equal
Outcome of severe traumatic brain injury: comparison of three monitoring approaches	Isa, 2003 [15]	Malaysia	Prospective, observational	0 % (MMM); 25.8 % (ICP only); 26.4 (no monitoring)	DRS at 3, 6, and 12	Yes—different across the three groups	ICP, Saber 2,100 CBF Sensor, Licox and TCD, NIRS, Laser Doppler, Microdialysis, SJVO ₂	82 total (17 MMM; 31 ICP; 34 none)	Adults and children	Historical comparison of three groups: No monitoring; ICP monitoring only; MMM. Excluded patients with bilaterally fixed pupils. Groups not easily comparable. GCS score 3–5; 53 % (MMM); 55 % (ICP only); 79 % (no monitoring). Abnormal pupils 70.6 % (MMM); 54.8 % (ICP only); 41 % (no monitoring)
Head trauma in China	Jiang, 2012 [69]	China	Retrospective	21.8 %	GOS post-discharge; 50.1 % favorable outcome	24.50 %	NR	1,626	Adults and children	Mixed TBI grade severity, Databank analysis. N = 7,145
Head injuries in Papua New Guinea	Liko, 1996 [86]	Papua New Guinea	Retrospective and Prospective	55.6 %	NR	No	No	45	Adults and children	Study data included three prospective and retrospective results from 1984 to 1993
Pediatric neurotrauma in Kathmandu, Nepal: implications for injury management and control	Mukhida, 2006 [70]	Nepal	Retrospective	28 % (ICU mortality only)	GOS, time not specified (66 % of total)	22 %	No	46	Children	Patients in the city region took about 8 h to get to the hospital while patients in the rural area took more than a day to get to hospital. Ventriculostomy used in 3 % of total 352 patients (46 sTBI). Delayed transfer to hospital may have selected patients. Patients who came from the rural area paradoxically had lower mortality, possibly for this reason

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
Jugular venous oxygen saturation or arteriovenous lactate content and outcome in children with severe traumatic brain injury	Perez, 2003 [87]	Argentina	Prospective, observational	15.0 %	3 months Pediatric Cerebral Performance Category; 81 % favorable	100 % (selected)	SjVO ₂ and AVDL	27	Children 52 %/ 48 %	Uncertain if this was a consecutive series
Early prognosis of severe traumatic brain injury in an urban Argentinian trauma center	Petroni, 2010 [88]	Argentina	Prospective, observational	58.8 % (33.8 % within the first 24 h, 5.4 % postacute care)	GOS—E 6 month	NR	NR	148	Adults	Excluded patients who were sedated or intubated, had a penetrating head injury, were brain dead on arrival or if consent was refused. Almost 90 % mortality in those over age 50
Prognostic factors in children	Pillai, 2001 [89]	India	Retrospective	56.8 %	GOS at discharge only; 20 % had a 'good outcome'	NR	NR		Children	
Head injury in a sub Saharan Africa urban population	Qureshi, 2013 [18]	Malawi	Prospective, observational	66.7 %	NR	No	No	15		Study over 3 months. Mixed grades of TBI severity. Mortality calculated from percentages tabled. Overall mortality for all grades of injury of inpatient TBI was 12.4 %. There was no prehospital care
Prognosis of head injury: an experience in Thailand	Ratanalert, 2002 [19]	Thailand	Retrospective	46.0 %	GOS 6 months; good outcome 42 %	13 %	No	300	Adults and children	Excluded brain death presentations
Secondary injury in traumatic brain injury—a prospective study	Reed, 2002 [90]	South Africa	Prospective, observational	47.5 %	GOS at discharge or at follow-up clinic: 46 % favorable outcome	NR	No	61	Adults	No patient with an acute SDH had surgery within 4 h of injury. The mean time between injury and assessment by a neurosurgeon was 6 h. Outcome data only available for 77 % of patients

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
Mortality and morbidity from moderate to severe traumatic brain injury in Argentina	Rondina, 2005 [40]	Argentina	Prospective, observational	24.8 % (Argentina); 6.8 % (Oregon)—of consented patients (selected)	Yes, but mortality only	NR	NR	169 in Argentina, 103 in Oregon	Adults	Prospective, observational study of outcomes from TBI in Argentinian hospitals that had adopted the acute care guidelines comparison with Oregon. Mortality is reported for screened and consented patients (272 of 661). The mortality rate for screened but not consented patients with severe TBI is not clear because the numbers of all patients screened and not consented is not reported separately for Argentina/Oregon, only the number of deaths. Mortality for all screened patients consented and not consented was 32 % (combined). Excluded patients who died within the first 24 h—60 and 80 % of deaths occurred in the first 24 h in Argentina and Oregon respectively and were not included in the analysis. A greater proportion of Oregon deaths (60 % of the studied sample) occurred late (at home or 'other')
Care of severe head injury patients in the Sarawak General Hospital: intensive care unit versus general ward	Sim, 2011 [11]	Malaysia	Prospective	25.7 % (16.7 % in ICU; 30.4 % in the ward)	GOS on discharge only—Good recovery 40 %	NR	NR	35	Adults	65.7 % of patients were ventilated in the general ward; 34.3 % managed in the ICU. Decisions made by anesthetic team were based largely on availability of ICU bed. Inclusion/exclusion criteria for management not specified. Ward mortality higher; however, mean age of ward managed patients was higher than ICU patients and GCS was lower. Groups not easily comparable

Article Title	Author	City, country	Study design	Overall sTBI mortality	Post discharge and outcome reporting	ICP	Other monitoring	N	Case mix	Comment
Outcomes in critical care delivery at Jimma University Specialised Hospital, Ethiopia	Smith, 2013 [91]	Ethiopia	Retrospective	52 % (of all head injured ICU admissions)	NR	NR	NR	370 (total)		Review of outcomes in general critical care over 12 months. Overall mortality rate for all admissions to ICU was 50 %; surgical admissions 43 %. Identified delayed presentation as a key factor; inadequate staffing, diagnostic and interventional limitations
Outcomes following prehospital airway management in severe traumatic brain injury	Sobuwa, 2013 [79]	South Africa	Retrospective	38.7 %	GOS at discharge only; 59.7 % 'good outcome'	NR	NR	124	Adults	
Intensive care and survival analyses of traumatic brain injury	Sut, 2010 [20]	Turkey	Retrospective	50 % (27 % in the first 48 h). ICU mortality only	NR	NR	NR	126	Adults	ICU mortality for severe TBI only + cost analysis. Mean stay costs were 4,846 USD and daily cost 575 USD. Costs per life saved 9,533 USD; costs per life-year saved 313.6 USD
Assessment of endocrine abnormalities in severe traumatic brain injury: a prospective study	Tandon, 2009 [81]	India	Prospective, observational	50.5 %	GOS 6 months	NR	NR	99	Adults and children	Ten percent of patients died after hospital discharge
Epidemiology of TBI in Eastern China 2004: a prospective large case study	Wu, 2008 [92]	China	Prospective	33.0 %	NR	NR	NR	2,983	Children and adults	Standardized questionnaire in the region over a 1-year period. All patients admitted with a diagnosis of head injury to one of 77 hospitals in the region. All grades of TBI severity. Severe and moderate TBI each about 20 %; mortality overall 11 %
Outcome of head injuries in general surgical units with an offsite neurosurgical service	Zulu, 2007 [23]	South Africa, KZN	Prospective, observational	67.0 %	NR	No	No	42	Adults	Outcome of patients in general surgical ICU with offsite neurosurgery transfer. 316 total patients mixed grades of injury; 12 % had severe TBI

sTBI severe traumatic brain injury, ICP utilization of ICP monitors, other monitoring utilization of other MMM, N sample size (for severe TBI unless specified), NR not reported

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