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Intracranial pressure monitoring in the intensive care unit: An international prospective observational StudY on iNtrAcranial PreSsurE in intensive care (SYNAPSE-ICU).

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Corresponding Author:	GIUSEPPE CITERIO University Milano Bicocca Monza, ITALY
First Author:	Chiara Robba
Order of Authors:	Chiara Robba
	Francesca Graziano
	Paola Rebora
	Francesca Elli
	Carlo Giussani
	Mauro Oddo
	Geert Meyfroidt
	Raimund Helbok
	Fabio S Taccone
	Lara Prisco
	Jean-Louis Vincent
	Jose Suarez
	Nino Stocchetti
	GIUSEPPE CITERIO
Manuscript Region of Origin:	ITALY
Abstract:	Background Indications for intracranial pressure (ICP) monitoring in patients with acute brain injury and its effects on patient outcomes are uncertain. Methods In this multicentre, international, prospective, observational study all adult patients admitted to the intensive care unit (ICU) for haemorrhagic stroke or traumatic brain injury, with altered levels of consciousness at ICU admission or within the first 48 hours were considered for inclusion. The aims of the study were to describe current ICP monitoring practice in patients with acute brain injury and to assess variations in indications for monitoring and management, and their association with long-term patient outcomes. Findings 2395 patients were included in the study (54% traumatic brain injury; 25% intracerebral haemorrhage; 22% subarachnoid haemorrhage). The median age was 55 years and 65% were male. Patients with ICP monitoring (1332, 56%) were younger and had a lower prevalence of comorbidities than those without. There was considerable variability in use of ICP monitoring across centres (median odds ratio [MOR]=4.50). Six-month mortality was lower in patients with ICP monitoring than in those without (441 (34%) vs 517 (49%), p<0.0001). In patients with at least one unreactive pupil, ICP monitoring was associated with significantly lower 6-month mortality (hazard ratio [HR]=0.35, 95% CI: 0.25-0.47), and better neurological outcome (OR=0.38, 95% CI: 0.26-0.56). The median therapy intensity level (TIL) was higher in patients with ICP

	monitoring and an increment of one point in TIL was associated with a reduction in the hazard of death. Interpretation Use of ICP monitoring and ICP management varies greatly among centres and countries. Use of ICP monitoring may be associated with a more aggressive therapeutic approach and with lower 6-month mortality in more severe cases.

Intracranial pressure monitoring in the intensive care unit: An international, prospective, observational StudY on iNtrAcranial PreSsurE in intensive care (SYNAPSE-ICU).

Chiara Robba, MD, PhD[1,2*], Francesca Graziano, PhD[3,4*], Paola Rebora, PhD[3,4*], Francesca Elli, PhD[3], Carlo Giussani, MD, PhD, Prof.[3,5], Mauro Oddo, MD, Prof.[6], Geert Meyfroidt, MD, PhD, Prof[7], Raimund Helbok, MD, Prof[8], Fabio S. Taccone, MD, PhD, Prof[9], Lara Prisco, MD[10], Jean-Louis Vincent, MD, PhD, Full Prof[9], Jose I. Suarez, MD, Prof[11], Nino Stocchetti, MD, Full Prof[12,13], Giuseppe Citerio, MD, Prof[3,14] and the Synapse-ICU Investigators[§]

[1]Anesthesia and Intensive Care, Policlinico San Martino, IRCCS for Oncology and Neuroscience, Genoa, Italy

[2]Department of Surgical Science and Integrated Diagnostic, University of Genoa, Italy

[3]School of Medicine and Surgery, University of Milano - Bicocca, Monza, Italy

[4]Bicocca Bioinformatics Biostatistics and Bioimaging Center B4, School of Medicine and Surgery, University of Milano - Bicocca, Milan, Italy

[5]Neurosurgery, Ospedale San Gerardo, Azienda Socio-Sanitaria Territoriale di Monza, Monza, Italy

[6]Department of Intensive Care Medicine, CHUV-Lausanne University Hospital, Lausanne, Switzerland

[7]Department of Intensive Care Medicine, University Hospitals, Leuven, Belgium

[8]Department of Neurology, Neurocritical Care Unit, Medical University of Innsbruck, Innsbruck, Austria

[9]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

[10]Nuffield Department of Clinical Neurosciences, OUH Trust, Oxford, UK

[11]Division of Neurosciences Critical Care, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

[12]Department of Physiopathology and Transplant, Università degli Studi di Milano, Milan, Italy

[13]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[14]Neurointensive Care Unit, Ospedale San Gerardo, Azienda Socio-Sanitaria Territoriale di Monza, Monza, Italy

* equally contributed to the manuscript

[§]The SYNAPSE-ICU Investigators, non-authors contributors, are listed in the Online Supplements (File 1)

Corresponding author

Giuseppe Citerio

School of Medicine and Surgery, University of Milano - Bicocca, Milan, Italy

Email giuseppe.citerio@unimib.it

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Research in context

Evidence before this study

The most recent Brain Trauma Foundation guidelines, applying more stringent criteria than previous editions, downgraded the available evidence on monitoring of intracranial pressure (ICP) in patients with traumatic brain injury, leaving clinicians without clear guidance. The only randomised controlled trial that has explored the role of monitoring and treatment of increased intracranial volumes in these patients showed no clear outcome benefits associated with ICP monitoring. However, the sample size of this study was small, and it has been widely criticised because of several methodological issues. In other acute neurological emergencies, such as haemorrhagic stroke, evidence in favour of ICP monitoring is even weaker. To identify new research in the area, we conducted a search of the PubMed database, excluding experimental studies, case reports and reviews, using the following terms: (until March 20th, 2021: "traumatic brain injury"[All Fields] OR "head trauma"[All Fields] OR "head injury"[All Fields]) AND ("intracranial pressure"[Mesh] OR "monitoring"[MeSH] OR "subarachnoid haemorrhage"[MeSH] OR "intracranial haemorrhage"[Mesh] OR "stroke"[MeSH] OR "brain injury"[Supplementary Concept] OR "intensive care"[MeSH] OR ("outcome"[MeSH Terms] OR "Glasgow coma scale"[All Fields] OR "Glasgow outcome scale extended"[All Fields]) OR “mortality” AND ("humans"[MeSH Terms] AND English[lang]) NOT (child* OR infant* OR pediatrics)). No additional relevant studies were retrieved. Large collaborative studies are therefore needed to provide a framework for precision medicine and comparative effectiveness research in this setting.

Added value of this study

The SYNAPSE-ICU study was a large, international, multicentre, observational study conducted to provide insight into the contemporary landscape of ICP monitoring in different acute cerebral pathologies. The results highlight considerable variability among centres (median odds ratio=4.50) and countries in use of ICP monitoring. Use of ICP monitoring is associated with a more aggressive therapeutic approach and with improved outcomes in the most severe cases.

Implications of all the available evidence

Results from the SYNAPSE-ICU study help clarify the current clinical use of ICP monitoring and treatment across different countries with different resources, and in different types of brain injury. Although causal inferences cannot be drawn from these observational data, the results suggest that, in severe cases, ICP monitoring may be associated with a more aggressive therapeutic approach and better long-term clinical results.

ABSTRACT

Background

Indications for intracranial pressure (ICP) monitoring in patients with acute brain injury and its effects on patient outcomes are uncertain.

Methods

In this multicentre, international, prospective, observational study all adult patients admitted to the intensive care unit (ICU) for haemorrhagic stroke or traumatic brain injury, with altered levels of consciousness at ICU admission or within the first 48 hours were considered for inclusion. The aims of the study were to describe current ICP monitoring practice in patients with acute brain injury and to assess variations in indications for monitoring and management, and their association with long-term patient outcomes.

Findings

2395 patients were included in the study (54% traumatic brain injury; 25% intracerebral haemorrhage; 22% subarachnoid haemorrhage). The median age was 55 years and 65% were male. Patients with ICP monitoring (1332, 56%) were younger and had a lower prevalence of comorbidities than those without. There was considerable variability in use of ICP monitoring across centres (median odds ratio [MOR]=4.50). Six-month mortality was lower in patients with ICP monitoring than in those without (441 (34%) vs 517 (49%), p<0.0001). In patients with at least one unreactive pupil, ICP monitoring was associated with significantly lower 6-month mortality (hazard ratio [HR]=0.35, 95% CI: 0.25-0.47), and better neurological outcome (OR=0.38, 95% CI: 0.26-0.56). The median therapy intensity level (TIL) was higher in patients with ICP monitoring and an increment of one point in TIL was associated with a reduction in the hazard of death.

Interpretation

Use of ICP monitoring and ICP management varies greatly among centres and countries. Use of ICP monitoring may be associated with a more aggressive therapeutic approach and with lower 6-month mortality in more severe cases.

Funding

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Trial registration number: NCT03257904

List of abbreviations

ABI; acute brain injury

CI; confidence interval

CT; computed tomography

GCS; Glasgow Coma Scale

GOSE; Glasgow Outcome Scale Extended

HICs; high-income countries

HR; hazard ratio

ICH; intracranial haemorrhage

ICP; intracranial pressure

ICPmon; intracranial pressure monitoring

ICU; intensive care unit

IQR; interquartile range

LMICs; low- and middle-income countries

MOR; median odds ratio

OR; odds ratio

SAH; subarachnoid haemorrhage

SD; standard deviation

TBI; traumatic brain injury

TIL; therapy intensity level

Introduction

Elevated intracranial pressure (ICP) is one of the major complications of acute brain injury (ABI)[1] and large cohort studies have shown that it is independently associated with a higher risk of death and poor outcome.[2-5] Although ICP monitoring is widely used and considered a fundamental component of the management of patients with ABI admitted to the intensive care unit (ICU),[6,7] several uncertainties remain.

Firstly, the indications for ICP monitoring have not been completely clarified. The most recent Brain Trauma Foundation guidelines[8] suggest the use of ICP monitoring in the management of severe traumatic brain injury (TBI), but the indications, type of monitoring device to be used and optimal duration of the monitoring are not clearly defined. Secondly, no strong evidence exists to support the superiority of ICP monitoring-driven therapy versus other therapeutic approaches. The only randomised controlled trial comparing TBI management based on ICP monitoring or on clinical examination and imaging showed no outcome benefit for ICP monitoring.[9,10] Finally, most studies on ICP monitoring have focused on TBI patients, and there are few data available on its use in those with haemorrhagic stroke, such as aneurysmal subarachnoid haemorrhage (SAH) or intracranial haemorrhage (ICH). Although elevated ICP is frequent in non-traumatic ABI and correlates with poor outcome,[11-13] no robust data are available to provide clinicians with guidance on ICP management in this setting, and recommendations are therefore usually based on TBI guidelines.[8,14-16]

As a result of these uncertainties, there is considerable variability at a global level in the use of ICP monitoring to guide treatment strategies.[17,18] We therefore designed the SYNAPSE-ICU study to describe current practice of ICP monitoring in ABI worldwide. We assessed the variability in use of ICP monitoring across centres and countries, treatment intensity in patients with and without ICP monitoring, and the association of ICP monitoring with patient outcomes.

Methods

Study Population

SYNAPSE-ICU (Registered at ClinicalTrial.gov NCT03257904) was an international, prospective, observational, cohort study. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines (Appendix, Electronic Supplementary Material, ESM, pp 5).

The protocol has already been published elsewhere and details of the study are available via open access (https://bmjopen.bmj.com/content/9/4/e026552.long).[19] The inclusion criteria were age ≥18 years; a diagnosis of ABI following TBI, ICH or SAH; altered level of consciousness, defined as a Glasgow Coma Scale (GCS) eye response score of 1 (no eye-opening) and a GCS motor response score ≤5 (not

obeying commands) on ICU admission or neuroworsening defined as a spontaneous decrease of 2 points or more in the GCS motor score compared with the previous examination and/or new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2mm or deterioration in neurological or computed tomography (CT) status sufficient to warrant immediate medical or surgical intervention within 48 hours after ICU admission. Patients not admitted to the ICU and/or with other forms of ABI were excluded from the study.

Primary endpoints were 6-month mortality and 6-month Glasgow Outcome Scale Extended (GOSE) score.[20] An unfavourable neurological outcome was defined as a GOSE score <5. Secondary endpoints were mortality and GOSE score at ICU and hospital discharge. Details regarding data collection management and definitions are given in the Appendix (p 2).

Statistical methods

Detailed information is available in the Appendix, pp 2,3. To estimate the association between use of ICP monitoring and 6-month outcome independently of measured baseline covariates, we used a propensity score method with inverse probability of treatment weighting. Pupil reactivity modified the association between receipt of ICP monitoring and outcome, so we divided the cohort into two groups: patients in whom both pupils were reactive and patients with at least one unreactive pupil. For each group, we created a pseudo-population to mitigate the selection bias in the decision to use ICP monitoring. These pseudo-populations were created using inverse probability of ICP monitoring weights computed from a multivariable Cox model (accounting for the insertion time) on the propensity to undergo ICP monitoring. The variables included in the model were age, sex, GCS, primary diagnosis, highly pathological CT scan (defined as Marshall classification ≥ 3 in TBI, Fisher grade ≥ 3 in SAH, and ICH size ≥ 30 ml in ICH), history of cardiovascular or neurological disease, country and national economic level (defined according to the World bank criteria), and the interaction term between GCS and country economic level. Weighted regression models with robust standard error were applied to the pseudo-populations to assess the association of ICP monitoring with 6-month mortality and GOSE. For the association with 6-month mortality, we applied a weighted, time-dependent, Cox model in which subjects entered the ICP monitoring group on the actual day of insertion of the ICP monitor to account for a potential survival time bias. For the association with 6-month neurological outcome, we applied a weighted logistic regression model. Centre was included as a random effect in both models to account for variability among centres. We performed a sensitivity analysis excluding severely ill patients (with both pupils unreactive and GSC=3) and patients who died within 48 hours.

Sub-analyses stratifying for the underlying disease (TBI, SAH, ICH) were also performed using the same methodology as that used in the overall sample. All the analyses were performed using R software (version 4.0.3). First type error was set at 0.05.

Role of the funding source

This research was partly funded by the European Society of Intensive Care Medicine (ESICM). The funder had no role in data collection, analysis, interpretation, writing of the manuscript or the decision to submit.

Results

Between 15 March 2018 and 31 March 2019, 4776 consecutive patients were screened and 2395 were included from 146 sites in 42 countries worldwide. Demographic and clinical characteristics of the included patients are shown in Table 1. The median age of the study population was 55 years, and 1567 (65%) were male; 1954 (82%) were from high-income countries (HICs). On ICU admission, 1973 (82%) patients had an altered level of consciousness (GCS score 3-8), 767 (34%) had at least one unreactive pupil, and 1535 (64%) had a highly pathological CT scan. Neuroworsening occurred in 842 (37%) patients. The primary diagnosis was TBI in 1287 (54%) patients, SAH in 521 (22%) and ICH in 587 (25%), with median ages of 47, 57 and 64 years, respectively. Most TBI and ICH patients were male (80% and 59%, respectively), whereas the majority of SAH patients were female (63%; Table 1).

ICP monitoring vs no ICP monitoring

1332 (56%) patients had ICP monitoring during ICU stay (Table 1). These patients were younger than those who were not monitored (median age 53 vs 58 years, p<0.0001) and had a lower prevalence of pre-injury comorbidities. 1185 (89%) patients with ICP monitoring and 769 (72%) without ICP monitoring were from HICs (p<0.0001). At hospital admission, the percentage of patients in whom both pupils were unreactive was significantly lower in the ICP monitoring group (18% vs 27%, p<0.0001). The percentage of patients with a highly pathological CT scan on admission was similar in patients with and without monitoring (65% and 63.0%; p=0.355).

Characteristics of patients with ICP monitoring

Among the patients with ICP monitoring, TBI was the primary diagnosis in 710 (53%), SAH in 341 (26%) and ICH in 281 (21%; Table 2). The main reason for placing an ICP monitoring device was clinical status (low GCS score), both overall (71%) and in each primary diagnosis group (74% for TBI, 69% for SAH and 64% for ICH). The main reasons for not using ICP monitoring were because the patient's clinical status

was considered by the clinician to be too severe (25%), or because of the neuroimaging findings (25%; i.e., considered too severe or not sufficiently severe to require invasive monitoring); in 18% of patients, it was because of local policy. The ICP monitor was more frequently inserted in the operating theatre than in other locations (65% of cases), and most often by neurosurgeons (97%). A parenchymal probe was inserted in 767 (59%) patients and an intraventricular drainage in 465 (36%). The ICP monitoring catheter varied according to the primary diagnosis. In TBI patients, an intraparenchymal device was most frequently used (73%), whereas SAH and ICH patients more frequently had an intraventricular catheter inserted (53% and 54%, respectively). 1148 (86%) patients had the ICP monitoring device applied within the first day after admission. The mean duration of monitoring was 8 (SD 8.8) days in TBI patients, 14.3 (SD 10.3) in SAH and 10.6 (SD 7.7) in ICH. The median maximum ICP value recorded during the first week was 22 mmHg (IQR 15-30). The median daily at 8 AM ICP value measured from the first day of monitoring was 10.67 mmHg (IQR 7.33-14.33) (Table 2).

Variability in use of ICP monitoring across countries and centres

The variability in use of ICP monitoring across centres is represented as a map chart showing unadjusted ICP monitoring probability for centres (Figure 2A). The unadjusted median odds ratio (MOR) for variability in use of ICP monitoring across centres was 4.81. After adjustment for patient- and practice-level variables with centre as a random effect, the variability remained significant (MOR=4.50; Figure 2B). Model-based adjusted variability of ICP monitoring use between centres is described in Figure 2B as a caterpillar plot of predicted random intercept for each centre corresponding to the adjusted log odds of ICP monitoring use. More details about specific centre characteristics and ICP use are given in the Appendix, ESM, Table S1, pp 12-14. The mean insertion time of ICP monitoring of each center was within day 2 after ICU admission in almost all centers (141 out of 146).

ICP monitoring and therapy intensity level

The median value of the maximum therapy intensity level (TIL) score calculated during the first week of ICU stay was 7 [IQR 5-10]; distribution of TIL by day is shown in the Appendix, Figure S1, pp 15. The median value of the TIL score was higher in patients with ICP monitoring than in those without, 9 [IQR 7-12] vs 5 [IQR 3-8] ($p<0.0001$) overall; 8 [IQR 6-11] vs 5 [IQR 3-8] ($p<0.0001$) on day 1; 6 [IQR 4-8] vs 4 [IQR 2-6] ($p<0.0001$) on day 3; and 5 [IQR 3-7] vs 3 [IQR 2-5] ($p<0.0001$) on day 7. See details of TIL in Appendix, ESM Table S2, pp16.

Association between the use of ICP monitoring and outcome

Mortality data were available at 6 months in 2367 (99%) patients with a median follow-up of 184 days. Mortality was lower in patients with ICP monitoring than in those without (Appendix, ESM Table S3, pp 18). The GOSE was available at 6 months for 2202 (92%) patients: the incidence of unfavourable neurological outcome was significantly lower in patients with ICP monitoring than in those without (60% vs 65%; p=0.039). The 6-month mortality rate for TBI patients from HICs was higher in those without ICP monitoring (159, 43%) than in those with monitoring (174, 29%), but the incidence of unfavourable neurological outcome was similar in the two groups (211, 60% and 313, 57%). In low-middle income countries (LMICs) the mortality rate at 6 months was 28% (55 cases) in patients without ICP monitoring and 29% (31 events) in those with, and the incidences of unfavourable outcome were 39% (69) and 40% (36), respectively. Among patients with intraventricular drainage, 402 (57%) had unfavourable neurological outcome compared to 300 (43%) who had favourable outcome; 284 (65%) patients with parenchymal device had favourable outcome vs 150 (35%). The daily median ICP value was associated with unfavourable outcome (GOSE, OR=1.01, 95% CI:1.00-1.01).

After propensity score weighting, there was a good balance in baseline covariates for patients with and without ICP monitoring with standardised differences always lower than 7% (Appendix, ESM Table S4, pp 19). The use of ICP monitoring was associated with significantly lower 6-month mortality in patients with at least one unreactive pupil (HR=0.35, 95% CI:0.26-0.47) (Table 3). When further adjusting for TIL, the use of ICP monitoring was still associated with significantly lower mortality, and an increment in TIL was also associated with a reduction of mortality (HR=0.94, 95% CI:0.91-0.98).In patients with bilateral pupillary reactivity there were no significant differences in mortality in patients with/without ICP monitoring (HR=1.02, 95% C:0.78-1.34). A sensitivity analysis excluding patients with a poor clinical status (GCS score of 3 and two unreactive pupils on admission) and those who died within 48 hours confirmed these results.

In patients with at least one unreactive pupil, the odds ratio of having a poor neurological outcome at 6 months comparing patients with/without ICP monitoring was 0.38 (95% CI 0.26-0.56); at sensitivity analysis, OR was 0.85 (95% CI:0.48-1.45). In patients with bilateral pupillary reactivity OR was 1.34 (95% C:1.11-1.63).

Results weighted by propensity score with multiple imputations for missing covariates confirmed the results (Appendix, ESM Table S5, page 20). A sensitivity analysis excluding the centres that did not use ICP monitoring because of local policy also confirmed these results (Appendix, ESM Table S6, page 21). These results were consistent across the different ABI pathologies, particularly for TBI and SAH patients. For the ICH group also in patients with bilateral pupillary reactivity ICP monitoring was associated with lower mortality. While in patients with at least one unreactive pupil the OR for unfavourable outcome at 6 months was 0.23 (95% CI:0.04-1.00).

Discussion

SYNAPSE-ICU is the largest, prospective international study to explore ICP monitoring in terms of current use, indications, therapeutic intensity level and possible association with outcome. The large sample of patients, high rates of follow-up for an observational study and the inclusion of different types of brain injury from different countries, mean our results provide a unique and representative picture of the status of ICP monitoring and management. The global approach is the main strength and novelty of this study, enabling the exploration of clinical ICP monitoring practice across different geographical areas. The main finding of this study is that there is considerable variability in the indications for and use of ICP monitoring among centres (MOR=4.50). Clinical status and results from neuroimaging are the main factors used by clinicians in decisions to insert an ICP monitoring device. Our results suggest that ICP monitoring may lead to a more aggressive therapeutic approach aimed at controlling ICP and may be associated with reduced mortality in the most severely ill patients.

Use of ICP monitoring is a cornerstone to guide treatment for severe TBI.[16] Compared with previous editions,[21,22] the most recent Brain Trauma Foundation guidelines[8] downgraded the strength of recommendation for ICP monitoring in TBI. Indications for monitoring therefore remain unclear and, in clinical practice, the decision to insert an ICP monitoring device seems to be based mainly on experience and local policies.[17,23-25] The only published randomised controlled trial to explore the effects on outcomes of TBI managed using an ICP monitoring-driven protocol vs clinical examination was small and conducted in Latin America by a group of intensivists, who routinely manage severe TBI without ICP monitoring.[9] This trial found no significant between-group differences in patient functional or neuropsychological status at 6 months, and no differences in 6-month mortality (39% vs 41%, p=0.60). However, this trial has been widely criticized, and several methodological issues have been highlighted that affect interpretation of its results.[26] These issues include the inadequate sample size and the specific setting, both of which preclude generalisability to other patient populations; it has also been criticised for failing to provide information on the effect on outcome of the clinical management of ICP, as opposed to the monitoring. To date, only a few prospective case-control or cohort studies have been conducted in this area, and they support an association between ICP monitoring-based treatment and improved outcomes.[2-5]

In the present study, factors influencing the decision to insert an ICP monitoring device included patients' pre-injury characteristics (ICP monitoring was more frequently used in younger patients and in those with fewer comorbidities), as well as the severity of the injury based on clinical assessment and neuroimaging. The decision not to monitor was often based on local policies, which may explain, in part, the large variability in practice across countries and centres that we observed. Indeed, in Europe and

Central/North American countries, ICP monitoring is more widely used. The probability of patients having ICP monitoring also differed markedly across centres. This observation is probably related to the lack of universal guidelines, but also to differences in economic resources in different geographic areas. Compared to HICs, LMICs have more non-academic institutions, with smaller hospitals and population catchment areas, and less frequent routine use of ICP monitoring, probably due to a lack of availability of catheters or monitors.

Data on the indications and reasons for performing ICP monitoring were similar across all the types of ABI we studied. This is an important point, given that there is no clearly defined consensus on monitoring (including monitoring duration) or specific ICP thresholds for treatment to guide clinicians caring for patients with non-traumatic ABI.[27- 29] In the absence of evidence in these specific subgroups, the indications for ICP monitoring are based on those applied in TBI patients and include a state of coma (GCS score ≤8), CT findings suggestive of increased ICP and neuroworsening. In our study, severe clinical status and pathological radiological findings were the main reasons for choosing whether to monitor ICP in patients with SAH and ICH. In contrast with what was observed in TBI patients, the type of device most frequently used in patients with SAH or ICH was the intraventricular catheter, as it allows cerebrospinal fluid drainage, an inherently useful therapeutic option.

Patients with ICP monitoring had a significantly higher TIL than those without. This is in contrast to results from the study by Chesnut et al.[9], which reported a higher TIL in patients who were managed according to clinical status and CT findings compared to those with ICP monitoring. This difference could be a consequence of the study designs (randomised controlled trial vs observational), with different results when patients are managed “real-life” compared to the setting of a randomised controlled trial with prespecified treatment strategies. Longer hospital stays and more aggressive therapy in ICP monitored TBI patients were also reported by Cremer et al.[30] and may be linked to a phenotype of patients who more frequently undergo ICP monitoring, as suggested in our study: severely injured, but still potentially able to benefit from aggressive treatment. Finally, our results suggest that in patients with more severe neurological status (unreactive pupils), use of ICP monitoring may be associated with reduced ICU, in-hospital and 6-month mortality rates. After adjusting for confounding factors, ICP monitoring was associated with reduced 6-month mortality in patients with at least one unreactive pupil, which was consistent across the subgroups of TBI and SAH. For ICH, this effect was borderline significant, possibly due to the sample size. Moreover, use of therapy in monitored patients was associated with improved outcome: an increment of one point in the TIL was associated with a reduction in the hazard of an unfavourable outcome. Less clear was the effect of ICP monitoring on GOSE, especially after sensitivity analysis.

Our results highlight the importance not only of ICP monitoring, but of aggressive ICP monitoring-driven treatment, which can effectively improve mortality in more severe patients with clinical signs of intracranial hypertension, but potentially leading to higher rate of unfavourable neurological outcomes.

The main limitation lies in the observational nature of the study, which makes it impossible to draw causal inferences. Nevertheless, ICP monitoring is currently considered a standard of care in the management of ABI patients in many centres.[16] Ethical constraints would therefore make it difficult to conduct large multicentre RCTs involving non-monitored control patients. We tried to overcome this limitation by having a pre-planned statistical plan and using a propensity score analysis with a rigorous analysis of the findings. Other limitations should also be mentioned. Firstly, we decided to select patients with ABI and thus grouped together patients with three different pathologies, all characterised by increased intracranial volume, but with different trajectories and predictors.[31] To overcome this limitation, we provide some analyses in the three subgroups (TBI, SAH and ICH). Secondly, neurological severity was evaluated on admission. We did not insert information on disease trajectories or complications during the ICU stay into our models. In addition, the presence of unmeasured confounders could affect our results, however we performed sensitivity analysis simulating a latent confounder and we found that our results were robust needing a confounder strongly associated with mortality (I.e.HR=6.5) to lose statistical significance in patients with at least one unreactive pupil. Thirdly, because of funding constraints, we were unable to provide on-site monitoring for all the source documents used to gather the data entered into the database. However, we did monitor for outlier or incongruent data and the study coordinator had regular contact with the centres to try and maximise data quality. Fourthly, we did not include withdrawal of life-sustaining measures in our analysis, although it is conceivable that there were differences between the groups that may have altered the results. To address this limitation, we performed a sensitivity analysis, excluding in both groups patients who had severe neurological status on admission and those who died within 48 hours; this analysis supported our original results. Finally, although we collected a large amount of data, additional information could have been useful, including data on temperature instability, the daily volume of cerebrospinal fluid drainage, and the patient's neurocritical trajectory during the ICU stay.

Conclusions

In conclusion, the results from the present study suggest a phenotype of patients in whom ICP monitoring may be associated with improved 6-month outcome. The use of ICP monitoring is more frequent in patients with severe ABI with specific pre-injury (age, comorbidities) and injury-related (CT findings, clinical status on admission) characteristics. Monitoring of ICP is associated with a more

aggressive therapeutic approach and a higher TIL in the ICU and may have a protective effect on 6-month mortality in more severe cases.

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Declarations

Ethical approval

The study was approved at the sponsor site by the Ethics Committee 'Brianza' ASST-Monza on November 21st, 2017 and was performed according to the Helsinki Declaration and the International Conference on Harmonization for Good Clinical Practice. Since comatose patients could not provide informed consent at the time of study recruitment, each centre referred to local/national law on the issue of lack of capacity. If the patients regained capacity at the follow-up visit, they were required either to provide informed consent to the use of the acute and follow-up data or to refuse to participate in the research.

National/local approvals at the international study sites were obtained by the National Coordinators and local PIs according to the local regulations.

Data sharing statements

The data supporting the findings of the study are available upon reasonable request after approval of a proposal from the corresponding author (GC). Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, will be made available to others. Related documents will also be available, such as the study protocol, statistical analysis plan, informed consent form.

Competing interests

GC reports grants, personal fees as Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics, all outside the submitted work. FST received lecture fees from BD and ZOLL and personal fees as Advisory Board Member from Nihon Khoden and Neuroptics, all outside the submitted work. RH received speakers' fees from BARD Medical, ZOLL Medical and Integra, and an Advisory Board fee for the Bard Medical INTREPID trial, all outside the submitted work. NS received personal fees from Integra. MO received grants from the Swiss National Science Foundation, and he is a consultant and member of the Scientific Advisory Board of Neuroptics. JIS is Chair of the DSMB for the Bard Medical INTREPID trial outside the submitted work. The other authors declare no competing interests.

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Authors' contributions

Chiara Robba: drafting the manuscript, participation in data interpretation, critical revision of the manuscript, final approval of the version to be published.

Paola Rebora and Francesca Graziano: data analysis and verification of the data, interpretation, drafting the manuscript, critical revision of the manuscript, final approval of the version to be published.

Francesca Elli: data collection management, data quality check, drafting the manuscript, critical revision of the article, final approval of the version to be published.

Carlo Giussani, Mauro Oddo, Geert Meyfroidt, Raimund Helbok, Fabio Taccone, Lara Prisco, Jean-Louis Vincent, Jose Suarez, Nino Stocchetti: participation in the definition of the protocol, critical revision of the manuscript, final approval of the version to be published

Giuseppe Citerio: conception of the work (PI), funding application, enrolment of the participants centres, supervision of the data collection, participation in data analysis verification of the data and interpretation, drafting the manuscript, critical revision of the manuscript, final approval of the version to be published. GC is the guarantor of the entire manuscript and responsible for the decision to submit the manuscript.

All the authors have seen and approved the final text.

The SYNAPSE-ICU investigators (listed in the electronic supplementary material) participated in the data collection and they are non-author contributors.

Table 1 - Characteristics of the study cohort, divided by use/non-use of intracranial pressure (ICP) monitoring and by type of underlying brain injury

	Total	**no ICP monitoring**	**ICP monitoring**	**P value[+]**	**TBI**	**SAH**	**ICH**
N (%)	2395	1063 (44)	1332 (56)		1287 (54)	521 (22)	587 (25)
Age (median [IQR])	55 [39, 69]	58 [40, 73]	53 [39, 65]	<0.0001	47 [31, 65]	57 [48, 66]	64 [52, 74]
Male	1567 (65)	701 (66)	866 (65)	0.665	1026 (80)	194 (37)	347 (59)
High-income country	1954 (82)	769 (72)	1185 (89)	<0.0001	977 (76)	452(87)	525(89)
History of cardiovascular disease[a]	992 (43)	489 (48)	503 (39)	<0.0001	353 (29)	253 (50)	386 (67)
History of neurological disease[a]	285 (12)	145 (14)	140 (11)	0.014	117 (10)	47 (9)	121 (21)
Pupils[b]				<0.0001			
● Both reactive	1491 (66)	620 (62)	871 (70)		804 (66)	352 (71)	335 (61)
● One unreactive	273 (12)	110 (11)	163 (13)		162 (13)	39 (8)	72 (13)
● Both unreactive	494 (22)	274 (27)	220 (18)		246 (20)	105 (21)	143 (26)
GCS score on admission[a]				0.001			
● 3-5	1197 (52)	527 (51)	670 (52)		633 (51)	267 (53)	297 (53)
● 6-8	776 (34)	378 (37)	398 (31)		450 (36)	139 (28)	187 (33)
● 9-15	339 (15)	126 (12)	213 (17)		163 (13)	95 (19)	81 (14)
Highly pathological CT scan[c]	1535 (64)	670 (63)	865 (65)	0.355	666 (52)	472 (91)	397 (68)

Neuroworsening[d]	842 (37)	354 (34)	488 (39)	0.037	381 (31)	222 (44)	239 (42)

[a] 83 patients with missing data

[b] 137 patients with missing data

[c] defined as Marshall classification ≥ 3 (in TBI) Fisher grade ≥ 3 (in SAH) or ICH size ≥ 30mL (in ICH)

[d] 95 patients with missing data

Abbreviations: GCS = Glasgow Coma Scale; TBI = traumatic brain injury; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; CT = computed tomography

Data are n(%), mean (SD) or median [IQR].

[+]Mann-Whitney U test and chi-squared test for the comparison of ICP monitoring and no ICP monitoring groups

Table 2 – Characteristics of patients with intracranial pressure (ICP) monitoring by type of underlying brain injury

	Total	TBI	SAH	ICH	P value
N (%)	1332	710 (53%)	341 (26%)	281 (21%)	
Insertion location[a]					<0.0001
● ICU	359 (28)	221 (33)	82 (25)	56 (21)	
● Emergency department	78 (6)	43 (6)	27 (8)	8 (3)	
● Operating theatre	820 (65)	400 (60)	218 (67)	202 (76)	
● Other	6 (1)	5 (1)	0 (0.0)	1 (<0.5)	
Inserted by[a]					0.524
● Neurosurgeon	1227 (97)	652 (98)	319 (98)	256 (96)	
● Neurointensivist	26 (2)	11 (2)	7 (2)	8 (3)	
● Other	10 (1)	6 (1)	1 (<0.5)	3 (1)	
Catheter type[b]					<0.0001
● Parenchymal	767 (59)	505 (73)	143 (43)	119 (43)	
● Subdural	61 (5)	40 (6)	13 (4)	8 (3)	
● Epidural	5 (<0.5)	4 (1)	0 (0.0)	1 (<0.5)	
● Intraventricular	465 (36)	141 (20)	176 (53)	148 (54)	
Antimicrobial prophylaxis[c]	763 (64)	440 (69)	166 (55)	157 (63)	<0.0001
Catheter changed	272 (20)	132 (19)	77 (23)	63 (22)	0.209
Reason for change					0.209
● catheter mispositioned	46 (13)	27 (15)	11 (11)	8 (10)	
● catheter misplaced/accidentally removed	31 (9)	13 (7)	9 (9)	9 (11)	
● catheter faulty/broken	41 (11)	21 (11)	13 (13)	7 (9)	
● site infection	8 (2)	1 (1)	6 (6)	1 (1)	
● neurosurgery	54 (15)	27 (15)	16 (16)	11 (14)	
● other	186 (51)	96 (52)	46 (46)	44 (55)	
Insertion time					0.570
● day 0 (pre-ICU admission)	69 (5)	35 (5)	22 (7)	12 (4)	

• day 1 (at ICU admission)	1079 (81)	570 (80)	271 (80)	238 (85)	
• day 2	143 (11)	80 (11)	39 (11)	24 (9)	
• day ≥3	41 (3)	25 (4)	9 (3)	7 (3)	
Mean duration of ICP monitoring[d]	10.18 (9.36)	8.04 (8.82)	14.32 (10.28)	10.60 (7.65)	<0.0001
Median ICP max value during the 1st week	22 [15-30]	22 [16-30]	21 [16-30]	19 [14-26]	0.005
Median daily ICP at 8 AM during the 1st week	10.67 [7.33-14.33]	11.5 [8.00-15.00]	10.00 [6.67-14.08]	9.67 [7.00-13.33]	<0.0001

[a] 69 patients with missing data

[b] 34 patients with missing data

[c] 140 patients with missing data

[d] 85 patients with missing data

Data are n(%), mean (SD) or median [IQR].

Abbreviations: ICU= intensive care unit; TBI = traumatic brain injury; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage

Table 3. Association between ICP monitoring (yes versus no) and 6-month outcomes (mortality and unfavourable outcome) weighted by the propensity score with random effect of centres overall and stratified by diagnosis.

	6-month mortality [a]		**unfavourable outcome at 6 months (GOSE < 5)** [b]	
Strata	**N deaths**	**HR (CI95%)**	**N events**	**OR (CI 95%)**
Pupils both reactive	428	1.02 (0.78-1.34)	683	1.34 (1.11-1.63)
At least one unreactive pupil	408	0.35 (0.26-0.47)	518	0.38 (0.26 0.56)
Sensitivity analyses: excluding severely ill patients, [c] **and patients who died within 48 hours**				
Pupils both reactive	398	0.93 (0.72-1.20)	633	1.51 (1.24-1.85)
At least one unreactive pupil	185	0.35 (0.23 0.52)	233	0.85 (0.48-1.45)
By diagnosis				
TBI				
Pupils both reactive	192	1.27 (0.87-1.85)	311	1.67 (1.27-2.20)
At least one unreactive pupil	184	0.31 (0.20-0.47)	249	0.53 (0.30-0.93)
SAH				
Pupils both reactive	99	0.64 (0.36-1.16)	164	1.19 (0.71-2.03)
At least one unreactive pupil	74	0.25 (0.13-0.47)	94	0.15 (0.05-0.39)
ICH				
Pupils both reactive	137	0.57 (0.38-0.87)	208	0.83 (0.49-1.39)
At least one unreactive pupil	150	0.34 (0.22-0.53)	175	0.23 (0.04-1.00)

[a] outcome missing in 28 subjects

[b] 6-month GOSE missing in 193 subjects

[c] patients with admission GCS score = 3 and unreactive pupils

Abbreviations: TBI = traumatic brain injury; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; N = number of; HR = hazard ratio; GOSE: Glasgow Outcome Scale Extended

Figure legends

Figure 1 - Flow-chart of the study population.

*Other: patient death after ICU admission; patient transfer to other ward/hospital; patient participation in other clinical trials; recruitment of the max n. of patients for each primary diagnosis; not known

[+] No ABI: ABI different from TBI/SAH/ICH (encephalitis, epilepsy, stroke, post-surgery haemorrhage, brain tumour haemorrhage).

Abbreviations: ABI = acute brain injury; mGCS= motor component of Glasgow Coma Scale; IC = informed consent; ICH = intracerebral haemorrhage; TBI = traumatic brain injury; SAH = subarachnoid haemorrhage

Figure 2 - Variability in use of ICP monitoring among countries.

Panel A) world map of unadjusted probability of ICP monitoring use (logistic regression model with the centre as a random effect).

Panel B) caterpillar plot of predicted random intercept for each centre corresponding to the adjusted log odds of ICP monitoring use (logistic regression model with centre as a random effect adjusted for sex, age, pupillary reactivity, diagnosis, country income level, GCS and pathological CT scan, MOR = 4.50). Predicted random intercepts with corresponding prediction intervals (higher values indicate higher propensity to use ICP monitoring) are given on the horizontal axis; centres are given on the vertical axis. 73.3% of the patients were in Europe, 14.0% in America, 9.7% in Asia, 2.3% in Africa and 0.7% in Oceania.

Appendix. Pdf

Electronic Supplementary Material –ESM

-Data collection management and statistical analysis

-STROBE Statement

-Supplementary Tables and analysis

Intracranial pressure monitoring in the intensive care unit: An international, prospective, observational StudY on iNtrAcranial PreSsurE in intensive care (SYNAPSE-ICU).

Chiara Robba, MD, PhD[1,2*], Francesca Graziano, PhD[3,4*], Paola Rebora, PhD[3,4*], Francesca Elli, PhD[3], Carlo Giussani, MD, PhD, Prof.[3,5], Mauro Oddo, MD, Prof.[6], Geert Meyfroidt, MD, PhD, Prof[7], Raimund Helbok, MD, Prof[8], Fabio S. Taccone, MD, PhD, Prof[9], Lara Prisco, MD[10], Jean-Louis Vincent, MD, PhD, Full Prof[9], Jose I. Suarez, MD, Prof[11], Nino Stocchetti, MD, Full Prof[12,13], Giuseppe Citerio, MD, Prof[3,14] and the Synapse-ICU Investigators[§]

[1]Anesthesia and Intensive Care, Policlinico San Martino, IRCCS for Oncology and Neuroscience, Genoa, Italy

[2]Department of Surgical Science and Integrated Diagnostic, University of Genoa, Italy

[3]School of Medicine and Surgery, University of Milano - Bicocca, Monza, Italy

[4]Bicocca Bioinformatics Biostatistics and Bioimaging Center B4, School of Medicine and Surgery, University of Milano - Bicocca, Milan, Italy

[5]Neurosurgery, Ospedale San Gerardo, Azienda Socio-Sanitaria Territoriale di Monza, Monza, Italy

[6]Department of Intensive Care Medicine, CHUV-Lausanne University Hospital, Lausanne, Switzerland

[7]Department of Intensive Care Medicine, University Hospitals, Leuven, Belgium

[8]Department of Neurology, Neurocritical Care Unit, Medical University of Innsbruck, Innsbruck, Austria

[9]Department of Intensive Care, ~~Hopital~~ Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

[10]Nuffield Department of Clinical Neurosciences, OUH Trust, Oxford, UK

[11]Division of Neurosciences Critical Care, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

[12]Department of Physiopathology and Transplant, Università degli Studi di Milano, Milan, Italy

[13]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[14]Neurointensive Care Unit, Ospedale San Gerardo, Azienda Socio-Sanitaria Territoriale di Monza, Monza, Italy

* equally contributed to the manuscript

[§]The SYNAPSE-ICU Investigators, non-authors contributors, are listed in the Online Supplements (File 1)

Corresponding author

Giuseppe Citerio

School of Medicine and Surgery, University of Milano - Bicocca, Milan, Italy

Email giuseppe.citerio@unimib.it

Word count: ~~3276~~3633

Research in context

Evidence before this study

The ~~last~~most recent Brain Trauma Foundation guidelines ~~removed indications on the~~, applying more stringent criteria than previous editions, downgraded the available evidence on monitoring of intracranial pressure (ICP) in patients with traumatic brain injury ~~patients. The available evidence has been downgraded applying more stringent criteria~~ , leaving ~~the~~ clinicians without clear guidance. ~~Besides, the~~The only ~~randomized~~randomised controlled trial ~~performed, including not only~~ that has explored the role of monitoring ~~but also the~~and treatment of increased intracranial volumes~~, didn't demonstrate clear benefits~~ in ~~terms of~~these patients showed no clear outcome~~.~~ benefits associated with ICP monitoring. However, ~~its~~the sample size of this study was small, and it ~~was largely criticized for~~has been widely criticised because of several methodological issues.

In other acute neurological emergencies, such as haemorrhagic ~~strokes~~stroke, evidence in favour of ICP monitoring is even weaker.

~~Therefore, large~~To identify new research in the area, we conducted a search of the PubMed database, excluding experimental studies, case reports and reviews, using the following terms: (until March 20th, 2021: "traumatic brain injury"[All Fields] OR "head trauma"[All Fields] OR "head injury"[All Fields]) AND ("intracranial pressure"[Mesh] OR "monitoring"[MeSH] OR "subarachnoid haemorrhage"[MeSH] OR "intracranial haemorrhage"[Mesh] OR "stroke"[MeSH] OR "brain injury"[Supplementary Concept] OR "intensive care"[MeSH] OR ("outcome"[MeSH Terms] OR "Glasgow coma scale"[All Fields] OR "Glasgow outcome scale extended"[All Fields]) OR "mortality" AND ("humans"[MeSH Terms] AND English[lang]) NOT (child* OR infant* OR pediatrics)). No additional relevant studies were retrieved. Large collaborative studies ~~for providing the~~are therefore needed to provide a framework for precision medicine and comparative effectiveness research ~~are needed~~ in this setting.

Added value of this study

The SYNAPSE-ICU study~~,~~ was a large, international, multicentre, observational~~, multicenter~~ study ~~across different countries, provides detailed insights~~conducted to provide insight into the contemporary landscape of ICP monitoring in different ~~types of~~ acute cerebral pathologies. The results highlight ~~a great~~considerable variability ~~in the monitoring use and the management of ICP between centers (MOR~~among centres (median odds ratio=4.50) and countries~~.~~ in use of ICP monitoring. Use of ICP monitoring is associated with a more aggressive therapeutic approach and ~~it is associated~~ with ~~reduced mortality~~improved outcomes in the most severe cases.

Implications of all the available evidence

~~Although our observational data cannot conclude with causal inferences, these results can~~Results from the SYNAPSE-ICU study help ~~to better specify~~clarify the ~~phenotype~~current clinical use of ~~patients~~

~~requiring~~ ICP monitoring and treatment across different countries with different resources, and in different types of brain injury. Although causal inferences cannot be drawn from these observational data, the results suggest that, in ~~selected~~severe cases, ICP monitoring may be associated with ~~improved 6-month outcomes~~a more aggressive therapeutic approach and better long-term clinical results.

ABSTRACT

Background~~:~~

Indications for intracranial pressure (ICP) monitoring ~~(ICPm)~~ in patients with acute brain ~~injured (ABI) patients~~ injury and its effects on patient outcomes are uncertain.

Methods~~: This study is a multicenter~~

In this multicentre, international, prospective, observational study~~, including~~ all adult patients admitted to the intensive care unit (ICU) for haemorrhagic stroke or traumatic brain injury, with altered levels of consciousness at ICU admission or within the first 48 hours~~. Aims~~ were considered for inclusion. The aims of the study were to describe ~~the~~ current ICP monitoring practice ~~of ICPm~~ in ~~ABI~~ patients with acute brain injury and to assess ~~the~~ variations in ~~ICPm~~ indications for monitoring and management, and ~~its effect on~~their association with long-term ~~patients' outcome~~patient outcomes.

Findings~~:~~

2395 patients were included in the ~~analysis (53.7~~study (54% traumatic brain injury; ~~24.5~~25% intracerebral haemorrhage; ~~21.8~~22% subarachnoid haemorrhage). The median age was 55 years and 65~~.4~~% were male. Patients ~~who received ICPm~~with ICP monitoring (1332, ~~55.6~~56%) were younger and had a lower prevalence of comorbidities~~. Considerable~~ than those without. There was considerable variability in ~~ICPm use was observed between countries and centers (~~use of ICP monitoring across centres (median odds ratio [MOR~~=~~]=4.50). ~~6~~Six-month mortality was lower in ~~the ICPm~~patients with ICP monitoring than in ~~the no ICPm group~~those without (441 (~~33.5~~34%) vs 517 (49~~.3~~%), p<0.~~001~~0001). In patients with at least one unreactive pupil, ~~ICPm~~ICP monitoring was associated with significantly lower 6~~ months~~ month mortality (~~Hazard Ratio,~~ hazard ratio [HR~~=~~]=0.~~37~~35, 95% CI: 0.~~28~~25-0.~~50~~47), and better neurological outcome (~~Odds Ratio~~ OR=0.~~53~~38, 95% CI: 0.~~33~~ 26-0.~~84), but not~~56). The median therapy intensity level (TIL) was higher in patients with ~~normal pupillary reactivity~~ICP monitoring and an increment of one point in TIL was associated with a reduction in the hazard of death.

Interpretation~~: ICPm use~~

Use of ICP monitoring and ICP management ~~vary~~varies greatly ~~between centers~~among centres and countries. ~~The use of ICPm can lead to~~ Use of ICP monitoring may be associated with a more aggressive therapeutic approach and ~~may be associated~~ with lower 6-~~months~~month mortality in more severe cases~~, whereas the effect on GOSE is less clear~~.

Funding~~:~~

Partially funded by the European Society of Intensive Care Medicine (ESICM~~)~~).

Trial registration number: NCT03257904

List of abbreviations

ABI; acute brain injury

CI; confidence interval

CT; computed tomography

GCS; Glasgow Coma Scale

~~mGCS; motor component of the Glasgow Coma Scale~~

GOSE; Glasgow Outcome Scale Extended

HICs; high-income countries

~~IC; informed consent~~

HR; hazard ratio

ICH; intracranial haemorrhage

ICP; intracranial pressure

~~ICPm~~ICPmon; intracranial pressure monitoring

ICU; intensive care unit

IQR; interquartile range

LMICs; low- and middle-income countries

~~MICE; multivariate imputation by chained equations~~

MOR; median odds ratio

~~MRI; magnetic resonance imaging~~

~~LOS; length of stay~~

OR; odds ratio

SAH; subarachnoid haemorrhage

SD; standard deviation

TBI; traumatic brain injury

TIL; therapy intensity level

Introduction

Elevated intracranial pressure (ICP) is one of the major complications of acute brain injury (ABI~~),~~)[1] and large cohort studies have shown that it ~~to be~~is independently associated with a higher risk of death and poor outcome ~~after ABI~~.[2-5] Although ICP monitoring ~~(ICPm)~~ is widely used and considered a fundamental component of the management of ~~ABI~~ patients with ABI admitted to the intensive care ~~units (ICUs~~unit (ICU)),[6,7] several uncertainties remain.

~~First~~Firstly, the indications for ~~ICPm~~ICP monitoring have not been completely clarified. The most recent Brain Trauma Foundation guidelines[8] suggest the use of ~~ICPm~~ ICP monitoring in the management of severe traumatic brain injury (TBI), but the indications, type of ~~ICPm~~monitoring device to be used and ~~proper~~optimal duration of the monitoring are not clearly defined.

~~Second~~ Secondly, no ~~clear~~strong evidence exists ~~supporting~~to support the superiority of ~~ICPm~~ICP monitoring-driven therapy versus other therapeutic approaches. The only ~~randomized~~randomised controlled trial comparing TBI management based on ~~ICPm as opposed to~~ICP monitoring or on clinical examination and imaging ~~failed to demonstrate an~~showed no outcome benefit for ~~ICPm~~ICP monitoring.[9,10]

Finally, most studies on ~~ICPm~~ICP monitoring have focused on TBI patients, ~~whereas~~ and there are few data ~~are~~ available on its use in those with haemorrhagic ~~strokes~~stroke, such as aneurysmal subarachnoid haemorrhage (SAH) or intracranial haemorrhage (ICH). ~~Indeed, although~~Although elevated ICP is frequent in non-traumatic ABI and correlates with poor outcome,[11-13] no robust data are available to provide clinicians with guidance on ICP management in this setting, and recommendations are therefore usually based on TBI guidelines.[8,14-16]

~~Due to~~ As a result of these uncertainties, ~~at a global level,~~ there is considerable variability at a global level in the use of ~~ICPm driven~~ICP monitoring to guide treatment strategies.[17,18]

~~To address these issues, we~~ We therefore designed the SYNAPSE-ICU study~~, which aims~~ to describe current practice ~~regarding the use~~ of ~~ICPm~~ICP monitoring in ABI~~, to assess~~ worldwide. We assessed the variability in ~~ICPm use between centers~~use of ICP monitoring across centres and countries, ~~the~~ treatment intensity in ~~ICPm~~patients with and ~~no ICPm groups~~without ICP monitoring, and ~~to evaluate~~ the ~~impact~~association of ~~ICPm on~~ICP monitoring with patient outcomes.

Methods

Study Population

SYNAPSE-ICU (Registered at ClinicalTrial.gov NCT03257904) ~~is~~was an international, prospective, observational, cohort study. The study is reported according to the Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) Statement guidelines (Appendix, Electronic Supplementary Material, ESM, pp 5).

The protocol has already been published elsewhere and details of the study are available via open access~~.~~ (https://bmjopen.bmj.com/content/9/4/e026552.long).[19] ~~This study was reported as for The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines (Electronic Supplementary Material, ESM).~~

The inclusion criteria were~~:~~ age ≥18 years; a diagnosis of ABI following TBI, ICH or SAH; altered level of consciousness, defined as a Glasgow Coma Scale (GCS) eye response score of 1 (no eye-opening) and a GCS motor response score ≤5 (not obeying commands) ~~either~~ on ICU admission or neuroworsening ~~with no eye opening and~~defined as a spontaneous decrease of 2 points or more in the GCS motor score ~~decreased~~compared with the previous examination and/or new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2mm or deterioration in neurological or computed tomography (CT) status sufficient to ~~≤5~~warrant immediate medical or surgical intervention within 48 hours after ICU admission. Patients not admitted to the ICU and/or ~~presenting~~with other forms of ABI ~~(e.g., infections of the central nervous system, ischemic stroke)~~ were excluded from the study.

Primary endpoints were 6-month mortality and 6-month Glasgow Outcome Scale Extended (GOSE) score.[20] An unfavourable neurological outcome was defined as a GOSE score <5. Secondary endpoints were mortality and GOSE score at ICU and hospital discharge. Details regarding data collection management~~,~~ and definitions ~~and detailed statistical analysis~~ are ~~reported~~given in ~~ESM, File 1.~~the Appendix (p 2).

Statistical methods

Detailed information is available in the Appendix, pp 2,3. To estimate the ~~effect~~ association between use of ~~ICPm on~~ICP monitoring and 6-month outcome independently of measured baseline covariates, ~~the~~we used a propensity score method ~~was used. As we found that pupil~~with inverse probability of treatment weighting. Pupil reactivity modified the association between ~~ICPm~~receipt of ICP monitoring and outcome, so we divided the cohort into two ~~strata~~groups: patients in whom both pupils were reactive and patients with at least one unreactive pupil. For each ~~stratum~~group, we created a pseudo-population ~~(that mimics a randomized trial)~~ to mitigate the selection bias in ~~ICPm assignment. This~~ the decision to use ICP monitoring. These pseudo~~-population was~~ populations were created using inverse probability of ~~ICPm~~ICP monitoring weights computed ~~by~~from a multivariable Cox model (accounting for the insertion time) on the propensity to undergo ~~ICPm in which the~~ ICP monitoring. The variables included in the model were age, sex, GCS, primary diagnosis, highly ~~pathologic~~pathological CT scan~~,~~ (defined as Marshall classification ≥ 3 in TBI, Fisher grade ≥ 3 in SAH, and ICH size ≥ 30 ml in ICH),

history of cardiovascular ~~and~~or neurological ~~history, center and~~disease, country and national economic level (defined according to the World bank criteria), and the interaction term between GCS and country economic level. Weighted regression models with robust standard error were applied to the pseudo-~~population~~populations to assess the ~~impact~~association of ~~ICPm on~~ICP monitoring with 6-~~months outcome. When dealing with~~month mortality ~~up to~~ and GOSE. For the association with 6-~~months~~-month mortality, we applied a weighted, time-dependent, Cox model in which subjects ~~enter in~~entered the ~~ICPm~~ICP monitoring group ~~at~~on the actual day of insertion ~~day, accounting~~of the ICP monitor to account for a potential survival time bias. For the association with 6-month neurological outcome ~~at 6 months~~, we applied a weighted logistic regression model. Centre was included as a random effect in both models to account for variability among centres. We performed a sensitivity analysis excluding ~~extremely severe~~severely ill patients (with both pupils unreactive ~~pupils~~ and GSC=3) and patients who died within 48 hours.

Sub-analyses stratifying for the underlying disease (TBI, SAH, ICH) were also performed using the same methodology as that used in the overall sample. All the analyses were performed using R software (version 4.0.3). First type error was set at 0.05.

Role of the funding source

This research was partly funded by the European Society of Intensive Care Medicine (ESICM). The funder had no role in data collection, analysis, interpretation, writing of the manuscript or the decision to submit.

Results

~~Overall~~Between 15 March 2018 and 31 March 2019, 4776 consecutive ~~subjects~~patients were screened ~~for inclusion (Figure 1); the enrolled cohort consisted of~~ and 2395 ~~patients recruited at~~were included from 146 sites ~~distributed across~~ in 42 countries worldwide ~~(73.3% of the patients were enrolled in Europe, 14.0% in America, 9.7% in Asia, 2.3% in Africa and 0.7% in Oceania). Demographics~~. Demographic and clinical characteristics of the included patients are ~~reported~~shown in Table 1. The median age of the ~~overall~~ study population was 55 years, and 1567 (65~~.4%) patients~~%) were male~~. Overall,~~, 1954 (~~81.6%) of them~~82%) were ~~recruited~~ from high-income countries (HICs). On ICU admission, 1973 (82~~.3~~%) patients had an altered level of consciousness (GCS score 3-8), 767 (34%) ~~patients showed abnormal pupil reactivity (~~had at least one ~~or two~~ unreactive ~~pupils)~~pupil, and 1535 (64~~.1~~%) had a highly ~~pathologic CT scan. Neuro-worsening (defined as a spontaneous GCS-motor score decrease of 2 points or more compared with the previous examination and/or a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2mm and/or deterioration in neurological or~~

~~Computed Tomography (CT) status sufficient to warrant immediate medical or surgical intervention during first the first week of the ICU stay) occurred during the first week of ICU stay in 842 (36.6%) patients.~~

pathological CT scan. Neuroworsening occurred in 842 (37%) patients. The primary diagnosis was TBI in 1287 (~~53.7~~54%) patients, SAH in 521 (~~21.8~~22%) and ICH in 587 (~~24.5%, Table 1). Their~~25%), with median ages ~~were~~of 47~~ (TBI group),~~, 57 ~~(SAH group)~~ and 64 ~~(ICH group)~~ years~~.~~

, respectively. Most TBI and ICH patients were male (~~79.7~~80% and 59~~.1~~%, respectively), whereas the majority of SAH patients were female (~~62.8%). In the non-TBI groups (SAH and ICH), a higher rate of cardiovascular pathologies before ABI was observed (28.7% in TBI vs 50.0% in SAH and 67.0% in ICH), and the percentage of patients affected by neurological diseases was twice as high in the ICH group than in the TBI and SAH groups (21.2% in ICH vs 9.5% in TBI and 9.3% in SAH). Information on pupil reactivity, CT scan and neuro-worsening occurred in the first week of ICU stay are available in~~ 63%; Table 1).

ICP monitoring vs no ICP monitoring

1332 (56%) patients had ICP monitoring during ICU stay (Table 1~~.~~

~~*ICPm vs no-ICPm subgroups*~~

~~Overall, 1332 (55.6%) patients received ICPm during their hospitalization (Table 1).~~). These patients were younger than ~~the non-~~those who were not monitored (~~no-ICPm) group (~~median age 53 vs 58 years, p<0.~~001~~0001) and had a lower prevalence of pre-injury comorbidities~~ (cardiovascular 39.0% vs 47.9%, p<0.001; neurological 10.8% vs 14.3%, p= 0.014).~~ 1185 (~~88.9~~89%) patients with ~~ICPm~~ICP monitoring and 769 (72~~.3%) patients~~%) without ~~ICPm~~ICP monitoring were ~~recruited in~~from HICs (p<0.~~001~~0001). At hospital admission, the percentage of patients in whom both pupils were unreactive was significantly lower in the ~~ICPm group than in the no-ICPm group (17.5% vs 27.3%, p<0.001).~~ICP monitoring group (18% vs 27%, p<0.0001). The percentage of patients with a highly pathological CT scan on admission was similar in patients with and without monitoring (65% and 63.0%; p=0.355). ~~In both groups, most patients showed a highly pathologic CT scan on admission (64.9% and 63.0%, respectively; p=0.355), and about a third of them experienced an episode of neuro-worsening during the first week of ICU stay, with a higher incidence in the ICPm group (38.5% vs 34.2%, p=~~

Characteristics of patients with ICP monitoring

Among the patients with ICP monitoring~~0.037).~~

~~*ICPm group characteristics*~~

~~In the ICPm group~~, TBI was the primary diagnosis in 710 (53~~.3%) patients,~~%), SAH in 341 (~~25.6~~26%) and

ICH in 281 (21~~.1%,~~%; Table 2). The main reason for placing an ~~ICPm~~ ICP monitoring device was clinical status (low GCS score~~)~~), both ~~in the~~ overall ~~population (70.7~~(71%) and in each primary diagnosis group (74~~.4% of~~% for TBI, ~~68.8% of~~69% for SAH and ~~63.6% of~~64% for ICH ~~patients~~). The ~~decision~~ main reasons for not ~~to insert an ICPm device was taken either~~ using ICP monitoring were because the ~~patient, according to clinician's judgment, presented with too severe~~ patient's clinical ~~conditions (25~~status was considered by the clinician to be too severe (25%), or because of the ~~characteristics of the~~ neuroimaging ~~(24.7%). No ICPm was due to local policy in 18.1% of cases. ICPm~~findings (25%; i.e., considered too severe or not sufficiently severe to require invasive monitoring); in 18% of patients, it was because of local policy. The ICP monitor was more frequently inserted in the operating theatre ~~(64.9~~than in other locations (65% of cases), and ~~mainly~~most often by ~~the~~ neurosurgeons (97~~.1~~%). A parenchymal probe was inserted in 767 (59~~.1~~%) patients~~, whereas 465 (35.8%) received~~ and an intraventricular drainage in 465 (36%). The ICP monitoring catheter~~. The ICPm technique used~~ varied according to the primary diagnosis. In TBI patients, ~~the~~an intraparenchymal device was ~~the~~ most frequently used (73~~.2~~%), whereas SAH and ICH patients more ~~commonly~~frequently had an intraventricular catheter inserted (53% and ~~53.6~~54%, respectively).

1148 (86%) patients had the ICP monitoring device applied within the first day after admission. The mean duration of ~~ICPm~~monitoring was 8 (SD 8.8) days in TBI patients, 14.3 (SD 10.3) in SAH and 10.6 (SD 7.7) in ICH~~, and ICPm~~. The median maximum ICP value recorded during the first week was 22 mmHg (~~SD~~IQR 15-30). The median daily at 8 AM ICP value measured from the first day of monitoring was 10.67 mmHg (IQR 7.33-14.33) (Table 2).

Variability in ~~ICPm~~ use ~~between~~of ICP monitoring across countries and ~~centers~~centres

The variability in ~~ICPm~~ use ~~between centers within countries~~ of ICP monitoring across centres is ~~shown on~~ represented as a map chart ~~in~~ showing unadjusted ICP monitoring probability for centres (Figure 2A~~.~~). The unadjusted median odds ratio (MOR) for variability in ~~ICPm use~~use of ICP monitoring across centres was 4.81 ~~for centers. This variability, although lower, was still substantial after~~. After adjustment for ~~the~~ patient- and practice-level variables ~~when randomly picking out two centers~~with centre as a random effect, the variability ~~in ICPm use between them was~~ remained significant (MOR=4.50~~.~~; Figure 2B). Model-based adjusted variability of ~~ICPm~~ICP monitoring use between ~~centers~~centres is described in Figure 2B as a caterpillar plot~~. Variability in ICPm was high by country, too, with an~~ of predicted random intercept for each centre corresponding to the adjusted ~~MOR~~log odds of ~~3.1.~~ICP monitoring use. More details about specific ~~center~~centre characteristics and ICP use are ~~described~~given in the Appendix, ESM, Table S1~~.~~, pp 12-14. The mean insertion time of ICP monitoring of each center was within day 2 after ICU admission in almost all centers (141 out of 146).

ICP monitoring and therapy intensity level ~~(TIL)~~

The median value of the maximum ~~TIL~~therapy intensity level (TIL) score calculated during the first week of ICU stay ~~in the overall population~~ was 7 [IQR 5~~,~~ 10]; distribution of TIL by day is ~~reported~~shown in the Appendix, Figure S1~~.~~

~~In the ICPm group- compared to no-ICPm group the~~, pp 15. The median value of the TIL score was higher~~,~~ in ~~particular, the median (IQR) of maximum TIL was~~patients with ICP monitoring than in those without, 9 [IQR 7-12] vs 5 [IQR 3-8] (p<0~~,001); at day 1 was~~.0001) overall; 8 [IQR 6-11] vs 5 [~~3-~~IQR 3-8] (p<0.0001) on day 1; 6 [IQR 4-8] ~~(p<0,001); at day 3 was 6 [~~vs 4~~-8~~ [IQR 2-6] (p<0.0001) on day 3; and 5 [IQR 3-7] vs ~~4 [2-6] and at day 7 was 5 [3-7] vs 3 [~~3 [IQR 2-5~~], p<0,001.~~] (p<0.0001) on day 7. See details of TIL in Appendix, ESM Table S2, pp16.

Association between the use of ICP monitoring and outcome

~~Cumulative mortality~~ Mortality data were available at 6 months ~~was available~~ in 2367 (99%) patients with a median follow-up of 184 days. ~~The ICPm~~Mortality was lower in patients ~~had lower mortality~~ with ICP monitoring than ~~the no-ICPm group (~~in those without (Appendix, ESM Table ~~S2). In detail, six-month (441 deaths (33.5%) vs 517 (49.3%), p<0.001), in-hospital (357 (27.7%) vs 436 (41.9%), p<0.001) and ICU (289 (22.1%) vs 391 (37.5%), p<0.001) mortality rates were all significantly lower in the monitored patients than in the no-ICPm group. At 6 months,~~ S3, pp 18). The GOSE was available at 6 months for 2202 (92%) patients: ~~ICPm patients also had a significantly lower~~the incidence of unfavourable neurological outcome ~~compared~~was significantly lower in patients with ~~the no-ICPm group~~ICP monitoring than in those without (60~~.1~~% vs ~~64.5~~65%; p=0.039). ~~ICPm~~The 6-month mortality rate for TBI patients from HICs was higher in those without ICP monitoring (159, 43%) than in those with monitoring (174, 29%), but the incidence of unfavourable neurological outcome was similar in the two groups (211, 60% and 313, 57%). In low-middle income countries (LMICs) the mortality rate at 6 months was 28% (55 cases) in patients ~~had longer ICU~~without ICP monitoring and ~~hospital stays compared~~29% (31 events) in those with~~,~~ and the ~~no-ICPm ones (ICU: 16 days vs 6 days, p<0.001; hospital: 26 days vs 11 days, p<0.001~~incidences of unfavourable outcome were 39% (69) and 40% (36), respectively. Among patients with intraventricular drainage, 402 (57%) had unfavourable neurological outcome compared to 300 (43%) who had favourable outcome; 284 (65%) patients with parenchymal device had favourable outcome vs 150 (35%). The daily median ICP value was associated with unfavourable outcome (GOSE, OR=1.01, 95% CI:1.00-1.01).

After propensity score weighting, ~~the no-ICPm and ICPm groups showed~~there was a good balance in baseline covariates ~~(see~~for patients with and without ICP monitoring with standardised differences always lower than 7% (Appendix, ESM Table ~~S3). ICPm~~S4, pp 19). The use of ICP monitoring was associated with significantly lower 6~~-months~~ month mortality in patients with at least one unreactive

pupil (~~Hazard Ratio,~~ HR=0.~~37, 95% CI: 0.28-0.50, Table 3).~~ 35, 95% CI:0.26-0.47) (Table 3). When further adjusting for TIL, the use of ICP monitoring was still associated with significantly lower mortality, and an increment in TIL was also associated with a reduction of mortality (HR=0.94, 95% CI:0.91-0.98).In patients with bilateral pupillary reactivity~~,~~ there were no significant differences in mortality ~~between the two ICPm groups did not differ~~in patients with/without ICP monitoring (HR=1.~~04~~02, 95% ~~CI~~ C:0.~~84~~78-1.~~28). Sensitive~~34). A sensitivity analysis excluding patients~~, in both groups, with a ~~very severe~~poor clinical ~~condition~~status (GCS score of 3 ~~on admission~~ and two unreactive pupils~~) that~~ on admission) and those who died within 48 hours~~,~~ confirmed these results.

~~As far as 6-month, in~~In patients with at least one unreactive pupil, the ~~odd~~odds ratio of having a poor neurological ~~negative~~ outcome at 6 months comparing patients with/without ICP monitoring was ~~reduced (OR=~~0.~~53,~~38 (95% CI~~:~~ 0.~~33~~26-0.~~84), while it~~56); at sensitivity analysis, OR was ~~higher in~~0.85 (95% CI:0.48-1.45). In patients with bilateral pupillary reactivity ~~(OR=1.39, 95%CI 1.01-1.91). At sensitivity analysis, the association in patients with one or both unreactive pupils was not significant (~~OR~~=0.92, 95% CI 0.50-1.72), and in patients with both reactive pupils OR was 1.52 (95% CI 1.10-2.10).~~ was 1.34 (95% C:1.11-1.63).

Results weighted by propensity score with multiple imputations for missing covariates confirmed the results ~~and are presented in Table S4.~~(Appendix, ESM Table S5, page 20). A sensitivity analysis excluding the centres that did not use ICP monitoring because of local policy also confirmed these results (Appendix, ESM Table S6, page 21).

These results were consistent across the different ABI pathologies, particularly for TBI and SAH patients. For the ICH group also in patients with bilateral pupillary reactivity ICP monitoring was associated with lower mortality. While in patients with at least one unreactive pupil the OR for unfavourable outcome at 6 months was 0.23 (95% CI:0.04-1.00).

Discussion

SYNAPSE-ICU is the largest, prospective international~~, prospective~~ study ~~exploring ICPm from the perspective of its~~ to explore ICP monitoring in terms of current use, indications, therapeutic intensity level ~~associated~~ and possible association with ~~ICPm and impact on the~~ outcome. ~~Due to the~~The large sample of patients ~~recruited in the~~, high rates of follow-up for an observational study~~, together with~~ and the inclusion of different types of brain injury ~~and patients~~ from ~~many~~ different countries, mean our results provide a unique and ~~very~~ representative ~~account~~picture of the ~~current~~ status of ~~ICPm~~ ICP monitoring and ~~ICP~~ management. ~~Indeed, the~~The global approach ~~adopted can be considered~~is the main strength and novelty of this study, ~~as it allows~~enabling the exploration of ~~ICPm~~ clinical ICP monitoring practice ~~in~~across different geographical areas.

The main ~~findings~~finding of this study ~~can be summarized as follows:~~

~~- There is great~~is that there is considerable variability in the indications for and ~~management of ICPm~~ use ~~between centers~~of ICP monitoring among centres (MOR=4.50~~) and countries (MOR=3.1). However, clinical~~). Clinical status and results from neuroimaging are the main factors ~~considered~~used by clinicians in ~~the decision~~decisions to insert ~~ICPm. Intraparenchymal probes are more common in TBI patients and EVDs in SAH and ICH.~~

~~- ICPm can~~an ICP monitoring device. Our results suggest that ICP monitoring may lead to a more aggressive therapeutic approach aimed at controlling ~~intracranial pressure.~~

~~- ICPm~~ICP and may be associated with reduced mortality ~~and poor neurological outcome~~ in the most ~~severe cases.~~severely ill patients.

~~ICPm~~Use of ICP monitoring is ~~the~~a cornerstone ~~of~~to guide treatment for severe TBI.[16] ~~-~~Compared with ~~the~~ previous editions,[21,22] the most recent Brain Trauma Foundation guidelines[8] ~~have~~ downgraded the strength of ~~recommendations for ICPm in TBI; this can leave clinicians feeling uncertain regarding the indications,~~recommendation for ICP monitoring in TBI. Indications for monitoring therefore remain unclear and, in clinical practice, the decision to insert an ~~ICPm~~ICP monitoring device seems to be based mainly on experience and local policies.~~-~~[17,23-~~26~~25] The ~~one small randomized~~only published randomised controlled trial ~~published so far, exploring~~to explore the ~~effect~~effects on ~~the outcome~~outcomes of TBI managed ~~with~~using an ~~ICPm~~ICP monitoring-driven protocol vs clinical examination~~,~~ was small and conducted in Latin America~~, where~~ by a group of intensivists, who routinely ~~managed~~manage severe TBI without ~~ICPm~~ICP monitoring.[9]

~~Utilizing a cumbersome scoring system, never used in clinical practice, this~~ This trial found no significant between-group differences in patient functional ~~status and~~or neuropsychological status at 6 months ~~between treatment based on ICPm as opposed to clinical and radiological features. No statistical~~, and no differences in 6-month mortality ~~were found~~ (39% ~~in the ICP monitored group~~ vs 41~~% in the non-monitored group,~~%, p=~~-~~0.60). However, this trial has been ~~broadly~~widely criticized, and several methodological issues have been highlighted ~~which~~that affect ~~its~~ interpretation~~.~~ of its results.[26] These issues include the ~~inappropriate~~inadequate sample size and the specific setting, both of which preclude ~~generalizability~~generalisability to other patient populations; it has also been ~~criticized~~criticised for failing to provide information on the effect~~,~~ on ~~the~~ outcome~~,~~ of the clinical management of ICP, as opposed to the monitoring ~~itself~~. To date, only a few prospective case-control or cohort studies have been conducted in this area, and they support an association between ~~ICPm~~ICP monitoring-based treatment and improved outcomes.~~-~~[2-5]

In the present study, ~~the~~ factors influencing the decision to insert an ~~ICPm~~ICP monitoring device included patients' pre-injury characteristics (~~ICPm~~ICP monitoring was more frequently used in younger patients and in those with ~~a lower number of~~fewer comorbidities), as well as the severity of the injury~~,~~

based on clinical assessment~~,~~ and neuroimaging.

~~However, the~~ The decision not to monitor was often ~~due to~~based on local policies ~~(18.5% of all cases; 21.5% TBI, 22.3% SAH, and 9.2% ICH), a finding which explains~~, which may explain, in part, the large variability ~~between~~in practice across countries and ~~centers~~centres that we observed ~~in our cohort. In fact,~~. Indeed, in Europe and Central/North American countries, ~~ICPm~~ICP monitoring is ~~much~~ more ~~frequently~~widely used.

~~We also found that the~~The probability of ~~receiving ICPm could differ fourfold between centers. This~~patients having ICP monitoring also differed markedly across centres. This observation is probably related to the lack of universal guidelines, but also to differences in ~~the availability of monitoring devices and~~ economic resources in different geographic areas. Compared to ~~HIC, LMIC~~HICs, LMICs have ~~a higher number of~~more non-academic institutions, with smaller hospitals and ~~catchment~~ population catchment areas, and less frequent routine use ~~ICPm routinely~~of ICP monitoring, probably due to a lack of availability of catheters or monitors.

Data on the indications and reasons for performing ~~ICPm~~ICP monitoring were similar across all the types of ABI ~~(including SAH and ICH).~~we studied. This is an ~~extremely~~ important point, given that there is no clearly defined consensus on monitoring (including monitoring duration) or specific ICP thresholds for treatment ~~that may~~to guide clinicians caring for ~~non-TBI ABI~~ patients with non-traumatic ABI.[27-29] In the absence of evidence in these specific subgroups, the indications for ~~ICPm in non-TBI patients~~ICP monitoring are based on those applied in TBI patients and include a state of coma (GCS score ≤8), CT findings suggestive of increased ICP~~,~~ and ~~neuro-worsening. Similarly, extremely~~neuroworsening. In our study, severe clinical status and pathological radiological ~~conditions~~findings were the main ~~reason~~reasons for choosing ~~not~~whether to monitor ICP in patients with SAH and ICH. In contrast with what was observed in TBI patients, the type of device most frequently used in patients with SAH or ICH was the intraventricular catheter, as it allows cerebrospinal fluid drainage, an inherently useful therapeutic option.

~~In contrast~~Patients with ~~what was observed in TBI patients, the type of device most frequently used in SAH and ICH patients was the intraventricular catheter, as it allows cerebrospinal fluid drainage and inherently useful therapeutic option.~~

~~In contrast with the results of Chesnut et al.[9], we found that patients receiving ICPm recorded~~ ICP monitoring had a significantly higher TIL ~~compared with~~ than those ~~who were not monitored, and they also received a higher number of neuroimaging examinations. This was due to a predefined protocol in the Best Trip trial[8] in which patients~~ without ~~ICPm were aggressively treated based on~~. This is in contrast to results from the study by Chesnut et al.[9], which reported a higher TIL in patients who were managed according to clinical status and ~~tomographic~~CT findings~~.~~

~~The finding of longer stays and more aggressive therapies in ICP-monitored TBI cases was reported also~~

~~by Cremer et al.~~ [30] ~~and it~~ compared to those with ICP monitoring. This difference could be ~~linked to the~~a consequence of the study designs (randomised controlled trial vs observational), with different results when patients are managed "real-life" compared to the setting of a randomised controlled trial with prespecified treatment strategies. Longer hospital stays and more aggressive therapy in ICP monitored TBI patients were also reported by Cremer et al.[30] and may be linked to a phenotype of patients who more frequently undergo ~~ICPm~~ICP monitoring, as ~~highlighted~~suggested in our study: severely injured, but still ~~amenable for~~potentially able to benefit from aggressive treatment.

Finally, our results suggest that in patients with more severe neurological ~~conditions~~status (unreactive pupils~~) ICPm, can~~), use of ICP monitoring may be associated with reduced ICU, in-hospital and 6-month mortality rates ~~found on the unadjusted analysis. When~~. After adjusting for confounding factors ~~by weighting for the propensity score, we found an association of ICPm with~~ , ICP monitoring was associated with reduced 6-month mortality in ~~monitored~~ patients with at least one ~~pathologic~~unreactive pupil~~. Although our results do not allow to draw any causality conclusions~~, which was consistent across the subgroups of TBI and SAH. For ICH, this ~~suggests that the association with mortality may be predominant in more severe patients who require aggressive treatment, whereas its~~ effect ~~is more uncertain in less severe cases.~~

~~ICPm was also associated with better GOSE, but its effect on long term neurological outcome is less clear and probably diluted by other factors during the ICU stay and in the rehabilitation phase. This association was not anymore statistically~~was borderline significant, possibly due to the sample size. Moreover, use of therapy in monitored patients was associated with ~~at least~~improved outcome: an increment of one ~~unreactive pupil when excluding extremely severe patients~~point in the TIL was associated with a reduction in the hazard of an unfavourable outcome. Less clear was the effect of ICP monitoring on GOSE, especially after sensitivity analysis~~. OR was higher than 1 in less severe patients~~.

~~These~~Our results highlight the importance not only of ~~ICPm itself~~ICP monitoring, but of aggressive ~~ICPm~~ICP monitoring-driven treatment, which can effectively ~~reduce early deaths~~ improve mortality in more severe patients with clinical signs of intracranial hypertension ~~but might have a less strong effect on neurological outcome and disability, which are influenced not only by high ICP, but by many other factors. Moreover, aggressive ICP treatment can lead to a reduction of deaths, but at the expenses of a higher number of severe disabilities~~, but potentially leading to higher rate of unfavourable neurological outcomes.

~~*Limitations of the study*~~

The main limitation ~~of our results~~ lies in the observational nature of the study, which makes it impossible to draw causal inferences ~~reliably. However, ICPm is nowadays~~. Nevertheless, ICP monitoring is currently considered a standard of care ~~and a fundamental component of the~~

~~neurocritical care~~ in the management of ABI ~~patients[8].~~patients in many centres.[16]~~, and therefore ethical~~ Ethical constraints ~~preclude the conducting of~~would therefore make it difficult to conduct large ~~multicenter randomized controlled trials~~multicentre RCTs involving non-monitored ~~controls.~~control patients. We tried to overcome this limitation ~~with~~by having a ~~preplanned~~pre-planned statistical plan~~, involving also causal inference approach by the~~ and using a propensity score ~~use, and~~analysis with a rigorous analysis of the findings.

Other ~~than the observational design of this study, there are further~~ limitations ~~that need to~~should also be mentioned. ~~First~~Firstly, we decided ~~at the beginning of the study to evaluate the effect of high ICP on acute brain damage and we analysed~~ to select patients with ABI and thus grouped together patients with three different pathologies, ~~grouped~~all characterised by ~~an increase in~~increased intracranial volume, but with different trajectories and predictors.

~~Second~~[31] To overcome this limitation, we provide some analyses in the three subgroups (TBI, SAH and ICH). Secondly, neurological severity ~~has been~~was evaluated on admission. We ~~didn't~~did not insert ~~in any model~~ information on ~~the acute~~disease trajectories ~~in intensive care, along with~~or complications during the ICU stay~~. We found a potential beneficial effect of ICPm monitoring and treatment in the sickest patients. The association of a poorer outcome in patients with both reactive pupils on admission~~ into our models. In addition, the presence of unmeasured confounders could ~~be due to confounding factors not collected during the study.~~

~~Third, due to~~affect our results, however we performed sensitivity analysis simulating a latent confounder and we found that our results were robust needing a confounder strongly associated with mortality (I.e.HR=6.5) to lose statistical significance in patients with at least one unreactive pupil. Thirdly, because of funding constraints, we were unable to provide on-site monitoring ~~of~~for all the source documents used to gather the data entered into the database. However, we did monitor for outlier or incongruent data and the study coordinator had ~~an extensive exchange~~regular contact with the ~~centers for improving~~centres to try and maximise data quality.

~~Fourth~~ Fourthly, we did not include ~~the~~ withdrawal of life-sustaining measures in our analysis, ~~even though~~although it is conceivable that there were differences between the groups that may have altered the results. ~~For limiting the influence of withdrawal of life-sustaining, in~~To address this limitation, we performed a sensitivity analysis ~~we excluded patients~~, excluding in both groups ~~with a very~~patients who had severe neurological ~~presentation~~status on admission and those who died within 48 hours~~ and the findings, i.e., the beneficial effect of ICPm in the sickest, were confirmed.~~; this analysis supported our original results. Finally, although we collected a large amount of data, additional information could have been useful, including data on temperature instability, the daily volume of cerebrospinal fluid drainage, and the patient's neurocritical trajectory during the ICU stay.

Conclusions

In conclusion, the results ~~emerging~~ from the present ~~large database analysis allowed us to better specify the~~ study suggest a phenotype of patients ~~undergoing ICPm.~~ in whom ICP monitoring may be associated with improved 6-month outcome. The use of ~~ICPm~~ICP monitoring is more frequent in ~~severe ABI~~ patients with severe ABI with specific pre-injury (age, comorbidities) and injury-related (CT findings, clinical status on admission) characteristics. Monitoring of ICP is ~~related to~~associated with a more aggressive therapeutic approach and a higher TIL in the ICU~~,~~ and ~~it~~ may have a protective effect on 6-month mortality in more severe cases.

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Declarations

Ethical approval

The study was approved at the sponsor site by the Ethics Committee 'Brianza'~~,~~ ASST-Monza~~,~~ on November 21st, 2017 and ~~it has been~~was performed according to the Helsinki Declaration and the International Conference on Harmonization for Good Clinical Practice.

Since comatose patients could not provide informed consent at the time of study recruitment, each ~~center~~centre referred to local/national law on the issue of lack of capacity. If the patients regained capacity at the follow-up visit, they were required either to provide informed consent to the use of the acute and follow-up data or to refuse to participate in the research.

National/local approvals at the international study sites were obtained by the National Coordinators and local PIs according to the local regulations.

~~**Availability of data and materials**~~

Data sharing statements

The data supporting the findings of the study are available upon reasonable request after approval of a proposal from the ~~senior~~corresponding author (GC). Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, will be made available to others. Related documents will also be available, such as the study protocol, statistical analysis plan, informed consent form.

Competing interests

GC reports grants, personal fees as Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics, all outside the submitted work. FST received lecture fees from BD and ZOLL and personal fees as Advisory Board Member from Nihon Khoden and Neuroptics, all outside the submitted work. RH received speakers' fees from BARD Medical, ZOLL Medical and Integra, and an Advisory Board fee for the Bard Medical INTREPID trial, all outside the submitted work. NS received personal fees from Integra. MO received grants from the Swiss National Science Foundation, and he is a consultant and member of the Scientific Advisory Board of Neuroptics. JIS is Chair of the DSMB for the Bard Medical INTREPID trial outside the submitted work. The other authors ~~do not~~ declare no competing interests.

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Authors' contributions

Chiara Robba: drafting the manuscript, participation in data interpretation, critical revision of the manuscript, final approval of the version to be published.

Paola Rebora and Francesca Graziano: data analysis and verification of the data, interpretation, drafting the manuscript, critical revision of the manuscript, final approval of the version to be published.

Francesca Elli: data collection management, data quality check, drafting the manuscript, critical revision of the article, final approval of the version to be published.

Carlo Giussani, Mauro Oddo, Geert Meyfroidt, Raimund Helbok, Fabio Taccone, Lara Prisco, Jean-Louis Vincent, Jose Suarez, Nino Stocchetti: participation in the definition of the protocol, critical revision of the manuscript, final approval of the version to be published

Giuseppe Citerio: conception of the work (PI), funding application, enrolment of the participants ~~centers~~centres, supervision of the data collection, participation in data analysis verification of the data and interpretation, drafting the manuscript, critical revision of the manuscript, final approval of the version to be published. GC is the guarantor of the entire manuscript~~.~~ and responsible for the decision to submit the manuscript.

All the authors have seen and approved the final text.

The SYNAPSE-ICU investigators (listed in the electronic supplementary material) participated ~~at~~in the data collection and they are non-author contributors.

Table 1 - Characteristics of the study cohort, divided by use/non-use of intracranial pressure (ICP) monitoring and by type of underlying brain injury

	~~Overall~~Total	no ICP monitoring	ICP monitoring	P value[+]	TBI	SAH	ICH	~~p~~
N (%)	2395	1063 (44)	1332 (56)		1287 (54)	521 (22)		587 (25)
Age (median [IQR])	55 [39, 69]	58 [40, 73]	53 [39, 65]	<0.0001	47 [31, 65]	57 [48, 66]		64 [52, 74]
Male	1567 (65)	701 (66)	866 (65)	0.665	1026 (80)	194 (37)		347 (59)
High-income country	1954 (82)	769 (72)	1185 (89)	<0.0001	977 (76)	452(87)		525(89)
History of cardiovascular disease[a]	992 (43)	489 (48)	503 (39)	<0.0001	353 (29)	253 (50)		386 (67)
History of neurological disease[a]	285 (12)	145 (14)	140 (11)	0.014	117 (10)	47 (9)		121 (21)
Pupils[b]				<0.0001				
• Both reactive	1491 (66)	620 (62)	871 (70)		804 (66)	352 (71)		335 (61)
• One unreactive	273 (12)	110 (11)	163 (13)		162 (13)	39 (8)		72 (13)
• Both unreactive	494 (22)	274 (27)	220 (18)		246 (20)	105 (21)		143 (26)
GCS score on admission[a]				0.001				

• n3-5	13321197 (52)	527 (51)	670 (52)		633 (51)	710267 (53.3%))	341 (25.6%)297 (53)	281 (21.1%)
• 6-8	776 (34)	378 (37)	398 (31)		450 (36)	139 (28)		187 (33)
• 9-15	339 (15)	126 (12)	213 (17)		163 (13)	95 (19)		81 (14)
Highly pathological CT scan[c]	1535 (64)	670 (63)	865 (65)	0.355	666 (52)	472 (91)		397 (68)
Neuroworsening[d]	842 (37)	354 (34)	488 (39)	0.037	381 (31)	222 (44)		239 (42)

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Tables

Table 1 - Characteristics of the study cohort, divided by use/non-use of ICPm and by underlying brain injury.

	Overall	no-ICPm	ICPm	p	TBI	SAH	ICH
N (%)	2395	1063 (44.4)	1332 (55.6)		1287 (53.7)	521 (21.8)	587 (24.5)
Age (median [IQR])	55 [39, 69]	58 [40, 73]	53 [39, 65]	<0.001	47 [31, 65]	57 [48, 66]	64 [52, 74]
Male gender, n(%)	1567 (65.4)	701 (65.9)	866 (65)	0.665	1026 (79.7)	194 (37.2)	347 (59.1)

Country economic level = HICs (%)	1954 (81.6)	769 (72.3)	1185 (88.9)	<0.001	977 (75.9)	452(86.8)	525(89.4)
Cardiovascular history (%)[a]	992 (42.9)	489 (47.9)	503 (39)	<0.001	353 (28.7)	253 (50)	386 (67)
Neurological history (%)[a]	285 (12.3)	145 (14.3)	140 (10.8)	0.014	117 (9.5)	47 (9.3)	121 (21.2)
Pupils (%)[b]				<0.001			
Both reactive	1491 (66)	620 (61.8)	871 (69.5)		804 (66.3)	352 (71)	335 (60.9)
One reactive	273 (12.1)	110 (11)	163 (13)		162 (13.4)	39 (7.9)	72 (13.1)
Both unreactive	494 (21.9)	274 (27.3)	220 (17.5)		246 (20.3)	105 (21.2)	143 (26)
GCS score on admission (%)[a]				0.001			
3-5	1197 (51.8)	527 (51.1)	670 (52.3)		633 (50.8)	267 (53.3)	297 (52.6)
6-8	776 (33.6)	378 (36.7)	398 (31.1)		450 (36.1)	139 (27.7)	187 (33.1)
9-15	339 (14.7)	126 (12.2)	213 (16.6)		163 (13.1)	95 (19)	81 (14.3)

~~**Highly pathologic CT scan (%)[e]**~~	~~1535 (64.1)~~	~~670 (63)~~	~~865 (64.9)~~	~~0.355~~	~~666 (51.7)~~	~~472 (90.6)~~	~~397 (67.6)~~
~~**Neuro worsening (%)[d]**~~	~~842 (36.6)~~	~~354 (34.2)~~	~~488 (38.5)~~	~~0.037~~	~~381 (31)~~	~~222 (44)~~	~~239 (42.2)~~

[a] 83 patients with missing data

[b] 137 patients with missing data

[e] ~~Highly pathologic CT scan was~~[c] defined as Marshall classification ≥ 3 (in TBI) Fisher grade ≥ 3 (in SAH) or ICH size ≥ 30mL (in ICH~~).~~)

[d] 95 patients with missing data

Abbreviations: GCS = Glasgow Coma Scale; TBI = traumatic brain injury; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; ~~IQR = interquartile range; HIC = high-income country; CT, Computed Tomography~~CT = computed tomography

~~**Table 2 – ICPm patient's characteristics**~~

Data are n(%), mean (SD) or median [IQR].

[+]Mann-Whitney U test and chi-squared test for the comparison of ICP monitoring and no ICP monitoring groups

Table 2 – Characteristics of patients with intracranial pressure (ICP) monitoring by type of underlying brain injury

	~~Overall~~Total	TBI	SAH	ICH	~~p~~P value
~~n~~N (%)	1332	710 (53.~~3~~%)	341 (~~25.6~~26%)	281 (21.~~1~~%)	
Insertion ~~Location, n (%)~~[a] **location**[a]					<0.~~001~~0001
• ~~1~~ ICU	359 (28.~~4~~)	221 (33.~~0~~)	82 (25.~~1~~)	56 (21.~~0~~)	
• ~~2~~ Emergency department	78 (6.~~2~~)	43 (6.~~4~~)	27 (8.~~3~~)	8 (3.~~0~~)	
• ~~3~~ Operating theatre	820 (~~64.9~~65)	400 (~~59.8~~60)	218 (~~66.7~~67)	202 (~~75.7~~76)	
• ~~4~~ Other	6 (~~0.5~~1)	5 (~~0.7~~1)	0 (0.0)	1 (~~<~~<0.~~4~~5)	
~~**Insertion Staff,n (%)**~~[a] **Inserted by**[a]					0.524
• ~~1~~ Neurosurgeon	1227 (97.~~1~~)	652 (~~97.5~~98)	319 (~~97.6~~98)	256 (~~95.9~~96)	
• ~~2~~ Neurointensivist	26 (2.~~1~~)	11 (~~1.6~~2)	7 (2.~~1~~)	8 (3.~~0~~)	
• ~~3~~ Other	10 (~~0.8~~1)	6 (~~0.9~~1)	1 (~~<~~0.~~3~~5)	3 (1.~~1~~)	
~~**InsertionType,n (%)**~~[b] **Catheter type**[b]					<0.~~001~~0001
• ~~1~~ Parenchymal	767 (59.~~1~~)	505 (73.~~2~~)	143 (43.~~1~~)	119 (43.~~1~~)	
• ~~2~~ Subdural	61 (~~4.7~~5)	40 (~~5.8~~6)	13 (~~3.9~~4)	8 (~~2.9~~3)	
• ~~3~~ Epidural	5 (~~<~~<0.~~4~~5)	4 (~~0.6~~1)	0 (0.0)	1 (~~<~~<0.~~4~~5)	
• ~~4~~ Intraventricular	465 (~~35.8~~36)	141 (20.~~4~~)	176 (53.~~0~~)	148 (~~53.6~~54)	
Antimicrobial ~~prophylaxis, n (%)~~[c] **prophylaxis**[c]	763 (64.~~0~~)	440 (69.~~0~~)	166 (~~54.6~~55)	157 (~~62.8~~63)	<0.~~001~~0001
~~**Change, n (%)**~~ **Catheter changed**	272 (20.~~4~~)	132 (~~18.6~~19)	77 (~~22.6~~23)	63 (22.~~4~~)	0.209
~~**Change**~~ **Reason~~, n (%)~~ for change**					0.209
• ~~1~~ catheter mispositioned	46 (~~12.6~~13)	27 (~~14.6~~15)	11 (~~10.9~~11)	8 (10.~~0~~)	

• 2 catheter misplaced/accidentally removed	31 (8.59)	13 (7.0)	9 (8.9)	9 (11.2)	
• 3 catheter faulty/broken	41 (11.2)	21 (11.4)	13 (12.913)	7 (8.89)	
• 4 site infection	8 (2.2)	1 (0.51)	6 (5.96)	1 (1.2)	
• 5 neurosurgery	54 (14.815)	27 (14.615)	16 (15.816)	11 (13.814)	
• 6 other	186 (50.851)	96 (51.952)	46 (45.546)	44 (55.0)	
ICPm insertionInsertion time (days)					0.570
• day 0 (pre-ICU admission in ICU)	69 (5.2)	35 (4.95)	22 (6.57)	12 (4.3)	
• day 1 (at ICU admission in ICU)	1079 (81.0)	570 (80.3)	271 (79.580)	238 (84.785)	
• day 2	143 (10.711)	80 (11.3)	39 (11.4)	24 (8.59)	
• day ≥3	41 (3.1)	25 (3.54)	9 (2.63)	7 (2.53)	
LengthMean duration of ICPm (mean (SD))[d] ICP monitoring[d]	10.18 (9.36)	8.04 (8.82)	14.32 (10.28)	10.60 (7.65)	<0.0010001
Median ICP max value during the 1st week median [I-III quartile]	22 ([15-30)]	22 ([16-30)]	21 ([16-30)]	19 ([14-26)]	0.005
Median daily ICP at 8 AM during the 1st week	10.67 [7.33-14.33]	11.5 [8.00-15.00]	10.00 [6.67-14.08]	9.67 [7.00-13.33]	<0.0001

[a] 69 patients with missing data

[b] 34 patients with missing data

[c] 140 patients with missing data

[d] 85 patients with missing data

Data are n(%), mean (SD) or median [IQR].

Abbreviations: ICU= intensive care unit; TBI = traumatic brain injury; SAH = subarachnoid ~~hemorrhage~~haemorrhage; ICH = intracranial ~~hemorrhage; ICPm= intracranial pressure monitoring~~haemorrhage

Table 3. ~~**Results on the association**~~Association between ~~**ICPm**~~ICP monitoring (yes versus no) and 6 ~~**months**~~-month outcomes (mortality and unfavourable outcome) weighted by the propensity score~~.~~ with random effect of centres overall and stratified by diagnosis.

	6 ~~months~~ month mortality [a]		**unfavourable outcome at 6 months (GOSE < 5)** [b]	
Strata~~:~~	**N deaths**	**HR (CI95%)**	**N events**	**OR (~~CI95%)~~ CI 95%)**
Pupils both reactive	428	1.~~04~~02 (0.~~84~~78-1.~~28~~34)	683	1.~~39~~34 (1.~~01~~11-1.~~91~~63)
~~Pupils~~At least one ~~or both~~ unreactive pupil	408	0.~~37~~35 (0.~~28~~26-0.~~50~~47)	518	0.~~53~~38 (0.~~33~~ 26 0.~~84~~56)
Sensitivity ~~*analysis*~~analyses: excluding ~~*extremely severe*~~severely ill patients, [c] **and patients who died within 48 hours**				
Pupils both reactive	398	0.93 (0.72-1.~~26(1.00 1.57~~20)	633	1.~~52~~51 (1.~~10 2.10~~24-1.85)
At least one unreactive pupil	185	0.35 (0.23 0.52)	233	0.85 (0.48-1.45)
By diagnosis				
TBI				
Pupils both reactive	192	1.27 (0.87-1.85)	311	1.67 (1.27-2.20)
~~Pupils~~At least one ~~or both~~ unreactive pupil	~~185~~184	0.~~51~~31 (0.~~27~~20-0.~~95~~47)	~~233~~249	0.~~92~~53 (0.~~50 1.72~~30-0.93)
SAH				
Pupils both reactive	99	0.64 (0.36-1.16)	164	1.19 (0.71-2.03)
At least one unreactive pupil	74	0.25 (0.13-0.47)	94	0.15 (0.05-0.39)
ICH				
Pupils both reactive	137	0.57 (0.38-0.87)	208	0.83 (0.49-1.39)
At least one unreactive pupil	150	0.34 (0.22-0.53)	175	0.23 (0.04-1.00)

[a] outcome missing in 28 subjects

[b] 6-month GOSE missing in 193 subjects

[c] patients with admission GCS score ~~on admission~~= 3 and unreactive pupils

~~**Figures' legend**~~

Abbreviations: TBI = traumatic brain injury; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; N = number of; HR = hazard ratio; GOSE: Glasgow Outcome Scale Extended

Figure legends

Figure 1 - Flow-chart of the study population.

~~*Language barrier~~

~~Patient with brain death~~

~~Confort measure only~~

*Other: patient death after ICU admission; patient transfer to other ward/hospital; patient participation in other clinical trials; recruitment of the max n. of patients for each primary diagnosis; not known

[+] No ABI: ABI different from TBI/SAH/ICH (encephalitis, epilepsy, stroke, post-surgery haemorrhage, brain tumour haemorrhage).

Abbreviations: ABI = acute brain injury; mGCS= motor component of Glasgow Coma Scale; IC = informed consent; ICH = intracerebral ~~hemorrhage~~haemorrhage; TBI = traumatic brain injury; SAH = subarachnoid ~~hemorrhage;~~haemorrhage

Figure 2 - Variability in use of ICP monitoring among countries.

Panel A) world map of unadjusted ~~ICPm use~~ probability ~~for centers~~ of ICP monitoring use (logistic regression model with the ~~center~~centre as a random effect).

Panel B) caterpillar plot of predicted random intercept for each centre corresponding to the adjusted log odds of ~~ICPm~~ICP monitoring use ~~for centers~~ (logistic regression model with ~~the center~~centre as a random effect adjusted for sex, age, pupillary reactivity, diagnosis, country ~~economic~~income level, GCS and ~~highly pathologic~~pathological CT- scan, MOR = 4.50). Predicted random intercepts with corresponding prediction intervals (higher values indicate higher propensity to use ICP monitoring) are given on the horizontal axis; centres are given on the vertical axis.

73.3% of the patients were in Europe, 14.0% in America, 9.7% in Asia, 2.3% in Africa and 0.7% in Oceania.

Appendix. Pdf

Electronic Supplementary Material –ESM

-Data collection management and statistical analysis

-STROBE Statement

-Supplementary Tables and analysis

Giuseppe Citerio
Professor of Anesthesia and Intensive Care
School of Medicine and
Surgery

University Milano Bicocca
giuseppe.citerio@unimib.it
Office (+39) 0392334316, Mobile (+39) 3490956697

Monza, 30/03/2021

Response to reviewers.

Dear Dr Lynskey,

Thank you for the sincere interest you have shown in our manuscript, by allowing us to revise the last version we sent. We are grateful to the reviewers for their detailed assessment of our work. Therefore, we have incorporated all their points into our revision. A professional medical writer (Karen Pickett) has extensively reviewed the manuscript, as requested. We have highlighted the changes to the manuscript, and below we provide a line-by-line response to the reviewers' comments.

Thank you for considering our revised manuscript.

Kind regards,

Prof Giuseppe Citerio, on behalf of the other authors

Reviewers' Comments:

Reviewer #1:

This is useful multicenter, observational study conducted with primary aim to observe relationship between ICP monitoring and outcome in patients suffering from brain injury.

Study is well conducted and described. Discussion is somehow minimalistic.

Answer: We thank the reviewer for his/her thoughtful suggestions. We agree with the concerns raised, and we have substantially modified the manuscript, accordingly, including the discussion (page 11).

Few points deserve to be discussed more precisely:

In their analysis investigators mixed traumatic brain injury, SAH and ICH. This is a risky tactics as pathophysiology between at least TBI and SAH is rather different, therefore keeping these cases in common pot may produce misinterpretation.

Thank you for pointing this out. We agree that the inclusion of different pathologies may lead to misleading conclusions, and this is now clearly stated in the limitations section (page 12, line 6-10). On the other hand, this could provide an idea of the overall clinical and epidemiological characteristics of acute brain-injured patients. As for the reviewers' comments, we performed further sub-analysis especially regarding the outcomes, by considering the different subgroups. These can be found in new Table 3 and the Supplementary materials, and in the Results section and in the discussion (page 11, line 4-8).

Reasons for ICP monitoring are more or less precisely described in guidelines. Different point how clinics around the world stick to them. There are obvious differences in age and comorbidities between monitoring and no-monitoring groups. Therefore, if monitoring is compared to outcome, we really do not know if differences are related to outcome or rather age or comorbidities.

Although we recognize the possibility of a bias related to age and comorbidities, as mentioned in the limitations section, we accounted for that in the models on outcomes by including adjustments for confounding factors through a propensity score. This approach should minimize the risk of bias. This is now specifically described in the statistical methods section (in the main manuscript page 6-7 and in the Suppl materials).

Maximum ICP over a week is very poor descriptor of intracranial hypertension. If the authors have an information about mean ICP from monitoring interval, these values should be compared to outcome. Although such a comparison is not a new concept, it would serve as a good indicator of data quality.

Thank you for this suggestion. We agree with the reviewer, and we therefore added new analysis including the values of daily mean ICP measure at 8 AM in the manuscript and their effect on outcome. These results are presented in Table 2 and in the results section, page 9.

	Overall	**TBI**	**SAH**	**ICH**	**p**
Daily ICP value at 8 AM (median [I-III quartile])	10.67 [7.33-14.33]	11.50 [8-15]	10 [6.67-14.08]	9.67 [7-13.33]	<0.0001

	GOSE unfavorable OR CI 95%
ICPm at 8:00am	1.01 (1.00-1.01)

Figure 2b is really poorly described. What are values along y axis and how to interpret data along x axis?

We have implemented the description of Figure 2b, and in particular regarding the values in the y axis and the interpretation of the x axis.

Reviewer #2:

This paper reports on variation in ICP monitoring and the relationship between ICPm and 6 month outcomes from over 2300 patients with acute brain injury ; approximately half underwent ICP m and half did not. Main findings are: large variation in ICP m use, escalation of care by TIL with ICPm use, and improved outcomes among the sickest patients.

Overall, the paper is well written, the hypothesis is clear, the conclusions reflect the results.

We would like to thank the reviewer for these positive comments.

Specific comments:

1. Please clarify outcomes by different disease types (TBI, ICH etc). Outcomes are currently combined for these conditions

As for the reviewer comments, we added further analysis regarding the outcomes of the different subgroups of acute brain injured patients in Table 3.

2. Please comment on timing of ICP m placement and variation among centers

As suggested, we calculated the timing of ICP monitoring and found that 1148 (86%) patients inserted ICP monitoring within the first day of admission. No important differences among centres were found, in fact the mean of insertion time of ICP monitoring was within day 2 after ICU admission in 141 (97%) centres

3. Are outcomes clustered or crude ? please justify

Outcomes displayed in Table S2 are crude, apologies for this inaccuracy. We added this detail in the table legend.

4. Please describe outcomes by ICP for TBI by HIC status.

Thank you for this suggestion. As for the reviewer's comments, we added the requested data/analysis regarding HIC in the results section page 9, line 3-12.

TBI	**High Income Countries**		**Low-Middle Income Countries**	
	No-ICP monitoring	**ICP monitoring**	**No-ICP monitoring**	**ICP monitoring**
n	375	602	202	108
Early death (≤48hrs), n (%)	58 (15.5)	21 (3.5)	14 (7.0)	2 (1.9)

GOSE<5 at ICU, n (%)	271 (73.2)	440 (74.7)	84 (42.9)	47 (43.9)
ICU Mortality, n (%)	113 (30.5)	111 (18.8)	38 (19.4)	19 (17.8)
GOSE<5 at hospital, n (%)	253 (68.4)	396 (67.7)	80 (40.6)	40 (39.6)
In hospital mortality, n (%)	129 (34.9)	138 (23.6)	43 (21.8)	25 (24.8)
6 months mortality, n (%)	159 (42.6)	174 (29.1)	55 (27.6)	31 (29.0)
GOSE at 6 months<5, n (%)	211 (59.8)	313 (56.8)	69 (38.5)	36 (40.0)

Reviewer #3:

SUMMARY

Controversy exists on the value of intracranial pressure (ICP) monitoring in neurocritical care (NCC), most notably in severe traumatic brain injury (TBI). Given that nearly all the current therapy used to treat brain swelling is based on findings learned from the effect of each therapy on ICP and given that ICP monitoring is standard of care and/or integrated into care in different manners across various centers, it is difficult to define its optimal use. The only RCT addressing this question compared severe TBI management with and without ICP monitoring in a resource limited setting where many caregivers had little experience with ICP monitoring. That study had other flaws and thus advanced the field in a limited manner. Many centers/investigators do not have equipoise to participate in an RCT—when brain swelling is being treated. This controversy on ICP monitoring in severe TBI is also unfolding at a time when the need to better endophenotype patients is emerging as vital to optimal management and advances. This study thus comes at an important juncture in the field. In this study, Robba et al., perform a prospective, multinational one-year analysis of adult patients with acute brain injury (ABI) secondary to hemorrhagic stroke (subarachnoid hemorrhage [SAH] or intracranial hemorrhage [ICH]) or TBI with a GCS motor score ≤ 5 and GCS eye score of 1 at presentation or within 48 h. In addition to demographic data, they collected data on the use of ICP monitors, therapeutic intensity level (TIL), neuroimaging findings, and 6-mo survival and Glasgow Outcome Scale Extended (GOSE). They find that 1) ICP monitoring is heavily variable across centers, with a median odds ratio of 4.50 after adjustment for available covariates, 2) that ICP monitoring is associated with a higher TIL, and 3) that ICP monitoring was associated with significantly reduced 6-mo mortality and improved GOSE in patients with unresponsive pupils, but (marginally) higher mortality and worsened GOSE in patients with reactive pupils.

Thank you for the thorough revision of our manuscript and for the suggestions provided that have significantly improved our work.

CRITIQUE

As a large multicenter, international, prospective, observational investigation of 2395 patients with TBI, SAH and ICH from 42 countries it provides new insight on ICP monitoring and TIL that could

influence care and trial design. The findings that ICP monitoring across diagnoses was associated with higher TIL, reduced mortality and improved 6-mo outcome are of interest to the field. After propensity matching, the differences in mortality and outcome based on the use of ICP monitoring were limited to patients with at least one un-reactive pupil—suggesting that it is the sicker patients who benefit. These are logical conclusions and provide some balance to the aforementioned RCT and will be of interest across the field of NCC. The finding of marked variability in ICP monitor use is valuable alone, and without substantial limitations. That said, there are some important limitations that threaten the validity of findings 2 and 3 above.

Thank you for these comments. In general, we agree with the limitations mentioned by the reviewer and we provide a point-by point response and additional analysis/changes with the aim to address the reviewer's concerns.

Research in Context

1. The Implications of the available evidence are overstated given the observational nature of the study. Stating that the study has better specified a phenotype of patients "requiring" ICP monitoring is not supported—in contrast to stating that the study suggests the phenotypes of patients in whom ICP monitoring may be associated with improved 6-month outcome.

We agree with the reviewer's comments. We have modified the "Research in context" section (page 2), particularly aiming to avoid any overstatement and clearly highlighting the limitations of the observational nature of our study.

Methods

2. The authors identify important differences between the monitored and non-monitored groups (the monitored group is younger, has fewer comorbidities, and is more distributed in high-income countries), which almost certainly contributed to the improved outcomes in Table S2. They then use propensity-score matching to attempt to address these differences (Table S3). However, given the handful of presenting characteristics and treatment factors provided (i.e., there is no severity of illness score, no assessment for coagulopathy, hypotension, second insults, polytrauma, etc.), and the fact that treatment is rolled up into a TIL, there is a high probability of residual confounding. It would have been preferable if they had built out the CRF to capture a much broader array of data given that it spread across three distinct diseases. This is not addressed by a single sensitivity analysis simply excluding patients with unreactive pupils. There was no sensitivity analysis for lurking confounders to indicate how brittle are findings and what effect size and prevalence of an unmeasured confounder is needed to fail to reject the null hypothesis in this cohort and the studied strata. Given that they used R, they should use the obsSens package.

Thank you for this suggestion. We have added the factors in the Tables 1,2, which were available from the Synapse eCRF, acknowledging in the limitations section (page 12) those which were not available. We agree with the reviewer that a wider number of data would have strengthened our results;

however, we built a eCRF with a large number of data, but trying to keep it feasible for the recruiting centres, in order to avoid overwork and encourage the centres to enroll patients. As suggested by the reviewer, we performed further sensitivity analysis including the mentioned confounders and taking in consideration the diseases. Of note, results were confirmed by accounting for an unmeasured confounder. We would need a confounder with an OR of 6-months unfavorable outcome of 5 (or HR of mortality 6.5) and prevalence 30% to fail to reject the null hypothesis of absence of association between ICP monitoring and outcome in patients with one or both unreactive pupils.

3. Given that ICP monitoring may have been chosen differently across diseases (and might have variable effects in each cohort), they should conduct sub-analyses of each disease.

Thank you, we agree with the reviewer. We therefore performed further analysis regarding the outcome by dividing the cohort in subgroups of acute brain injured patients (TBI, SAH and ICH). Results are presented in Table 3.

4. Please reword the description of propensity matching. Referring to propensity matching as creating a pseudo-population similar to an RCT is misleading to the reader—given the inability of propensity matching to control for unknown confounders.

We have reworded as suggested the description of the propensity weighting as suggested by the reviewer.

5. It was unclear in the Methods what was meant by the statement "...The decision not to insert an ICP monitor was taken…because of the characteristics of the neuroimaging (24.7%)." Is the supposition that the imaging was not felt to be sufficiently severe, too severe/hopeless, etc? How was this term defined for data collection?

We agree and we have better specified the meaning of “characteristics of the neuroimaging”, page 8, line 1-2.

6. If data exist, an additional exploratory analysis is warranted examining whether there were any differences in patients with and without CSF drainage and whether the volume of drainage was associated with outcome.

We agree with this suggestion. Further analysis regarding the presence or not of CSF drainage are now presented in the results section. We do not have detailed data on the volume of CSF drainage in the SYNAPSE eCRF, but only general definition of mild and moderate CSF drainage. The results are presented below. We did not feel that these general results would improve our manuscript, and we did not include them in the current form. However, we leave the final decision to the reviewer/editor.

	Favourable Outcome	Unfavourable Outcome
N	487	733
CSF at day 1, n(%)		
no CSF drainage	319 (68.6)	391 (54.8)
Mild CSF drainage	50 (10.8)	125 (17.5)
Moderate CSF drainage	96 (20.6)	197 (27.6)
CSF at day 3, n(%)		
no CSF drainage	304 (67.6)	369 (54.9)
Mild CSF drainage	43 (9.6)	96 (14.3)
Moderate CSF drainage	103 (22.9)	207 (30.8)
CSF at day 7, n(%)		
no CSF drainage	284 (71.4)	332 (58.3)
Mild CSF drainage	36 (9.0)	67 (11.8)
Moderate CSF drainage	78 (19.6)	170 (29.9)

mildCSF = CSF drainage < 120 ml/day (<5 ml/hour)
moderateCSF= CSF drainage > 120 ml/day (>5 ml/hour)

Results

7. Characteristics of the propensity score seem to be missing and score diagnostics need to be included. The authors should at least present the standardized differences of the included variables (according to the supplemental methods this step was performed, just not presented).

We added more information on the propensity score results as suggested in the supplementary material. Standardized differences for both groups are presented in Table S4.

8. Please clarify the statement, "No ICPm was due to local policy in 18.1% of cases." Were there sites in the cohort that did not insert ICP monitors under any circumstance? If so, were these sites used in the propensity matching group? A sensitivity analysis excluding patients from sites that did not place any ICP monitors should be performed.

As this is an observational- non interventional study- we thought it would be important to take in consideration the different policies across the countries included; that in some cases, local policies are importantly different (for example, in the lack of guidelines some centres do not insert an ICP monitoring in ICH). Only 2 centres that declared local policy as reason for no-ICP monitoring actually did not insert ICP monitoring in any patient included in the study. Nevertheless, we performed a sensitivity analysis excluding the centres who did not place any ICP monitor within the study and results were consistent. We included the following analysis as supplementary material.

	Unfavourable Outcome	
OVERALL	**N events**	**OR (CI 95%)**
strata		
Pupils both reactive	650	1.45 (1.19-1.75)
Pupils one or both unreactive	485	0.53 (0.37-0.74)

9. Treatment data are rolled into a TIL, but it would have been more interesting to examine the components of the scale alongside the aggregate score. Similarly, more detail in the NCC course, such as the prevalence of seizures, hypotension, and temperature instability, would be valuable to describe in this cohort.

We agree with the reviewer's suggestion; we added a supplementary table describing the single treatments included in the TIL, and second tier therapies (Table S3). Some further data requested (such as hypotension) were included, some more specific data were not available and this was reported in the limitations section.

10. The section on "Variability in ICP monitoring between countries and centers" is poorly worded. On page 8, the sentence "This variability, although lower, was still substantial after adjustment for the patient- and practice-level variables when randomly picking out two centers, the variability in ICPm use between them was MOR=4.5" is unclear and needs to be revised.

This sentence has been reworded, and the entire manuscript revised by a medical mother tongue writer (Prof Karen Picket, Bruxelles).

11. It unnecessarily complicated the results and tables when the investigators shift from describing patients with "at least one unreactive pupil" to "pupils one or both unreactive." Please maintain a singular terminology.

This has been made consistent through the manuscript.

12. In the second paragraph on page 9, the investigators never clearly indicate that it is the use (or not) of an ICP monitor that is impacting the magnitude and directionality of the findings being described—in the entire paragraph. It is implied and only becomes clear when simultaneously viewing Table 3. This should be clarified in the text.

We have specified in this paragraph that we refer to the "use of ICP monitoring".

Discussion

13. As stated in the Research in Context section, the sentence on page 11 "These results highlight the importance not only of ICP monitoring itself, but of aggressive ICP monitoring-driven treatment which can effectively reduce early deaths in more severe patients with clinical signs of intracranial hypertension…" overstates the findings given the observational nature of the study. It is surprising, given both the more guarded statements in other places in the manuscript and the experience on the authorship team, that there would be such an uneven nature to the approach to data interpretation.

We have importantly modified the section as suggested.

14. Concerns related to unmeasured confounders need to be discussed in the limitations.

This has been added in the limitations section, page 12.

15. In the limitations section, it would be more appropriate to state "However ICP monitoring is currently considered a standard of care and a fundamental component of the neurocritical care management of ABI patients in some centers, and therefore ethical constraints hinder the ability to conduct large multicenter RCTs involving non-monitored control." This same conundrum (high level standard of care use in some centers unable to randomize vs other centers without use) has been raised in pediatric TBI (see Bennett et al, JAMA Pediatr, 2017), so greater balance on this issue is needed from the authors—given an apparent position in the pro ICP monitoring camp.

Thank you, this has been added in the limitations section, page 12, as suggested.

16. You reported that across conditions, TIL was greater (highly significantly—$p < 0.001$) in patients managed using ICP monitoring vs no ICP monitoring. As you indicate, however, it contrasts the BEST-TRIP RCT on management of patients with severe TBI with and without monitoring (your ref. #9). The magnitude of difference in the findings between these two studies merits greater emphasis. BEST-TRIP reported less hypertonic saline and hyperventilation—two of the most common therapies they used--in the patients with ICP monitoring—again showing difference at highly significant, $p < 0.008$ and <0.003, respectively). You briefly discuss this, but to this reviewer it suggests, possibly a very fundamental difference when comparing two monitoring-based management strategies in real-world use vs. in the setting of an RCT.

We would like to thank the reviewer for this important comment. We agree that these results should deserve more space and attention. And we also agree that the differences regarding the TIL levels between the two studies rely on the structure and settings of the studies. We tried to highlight this important concept in the discussion section.

17. There is other recent investigation of ICP monitoring across NCC (beyond just TBI) that provide support for the concept that ICP management needs to be investigated across conditions and nuances regarding ICP-directed care may need to differ across conditions (i.e., even the ICP threshold related to outcome or intervention; see Woods et al., Pediatr Crit Care Med, 2021). That is another useful message of your observational study.

This reference has been added and the issue discussed in the limitations section, page 12.

Minor

18. The writing is often sloppy grammatically and informal in places with use of contractions, remnant multi-color edits, lack of consistency in abbreviation use, etc., which detracted from the findings and quality of the work.

A professional medical writer has revised the manuscript. We hope that the writing has improved.

19. The abbreviation ICPm for ICP monitoring is unconventional and should be eliminated.

We have modified through the manuscript, and in particular we removed “ICPm” using a non abbreviated form, maintaining it as “ICPmon”only in the figures.

20. In the Abstract, please use "Glasgow Outcome Scale Extended" rather than "GOSE".

This has been corrected.

21. In the Methods, please provide the choice of statistical software (and packages, if used), as well as the prespecified alpha value.

This has been added.

22. Also, the imaging definitions should be placed in the text proper, rather than only found in a figure legend.

This has been added.

23. Figure 1: 699 patients were excluded from the study for "other" reasons. Please provide a more detailed (i.e. numeric) summary of these reasons in the figure legend.

This has been added.

24. Figure 2A: Please provide additional clarity on this figure in the legend. The figure legend states that a logistic regression model with a random intercept for center was used to generate the probability. Given that the model is otherwise empty (contains no fixed-effect variables) is this graph simply showing the proportion of included patients at each center who received an ICP monitor? If not, please explain how these values differ.

We have reworded and clarified the figure legends.

Reviewer #5:

This large, observational, multicenter, international, and prospective study aims to describe the current practice of ICPm in ABI patients and to assess the variations in ICPm indications and management by analysing adult patients admitted to the intensive care unit for haemorrhagic stroke or traumatic brain injury, with altered consciousness at admission or within the first 48 hours.

Answer: Thank you for the thorough revision of our manuscript and for the suggestions provided that have significantly improved our work.

Comments:

The authors state that part of the study aims are to assess: "ICPm...effect on long term patients'

outcome" and "... to evaluate the impact of ICPm on patient outcomes."
This study aim (using language such as 'effect on' and 'impact of') is not achievable here, due to the observational study design limiting the ability to infer causality.
The authors do acknowledge in the article that inferring causality is not possible given the observational study design. In line with this, they should be careful of their wording throughout the manuscript in order to avoid implying otherwise.
Thank you, we totally agree with the reviewer. We have reviewed the entire manuscript aiming to avoid any infer causality message.

"The use of ICPm can lead to a more aggressive therapeutic approach and may be associated with lower 6-months mortality in more severe cases, whereas the effect on GOSE is less clear. "Please can the authors ensure they define all acronyms before first use (in the above example, this is the first use of the GOSE abbreviation).
Of note, the list of abbreviations provided by the authors is a useful resource.
We have checked all the acronyms and abbreviations, an English mothertongue and professional medical writer has reviewed the manuscript.

"The protocol has already been published elsewhere and details of the study are available via open access.19 This study was reported as for The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines (Electronic Supplementary Material, ESM). "
Can the authors please provide a copy of the study protocol in the supplementary material?
Thank you, we have added the reference of the protocol and the online link to access the open access manuscript.

"Details regarding data collection management, definitions and detailed statistical analysis are reported in ESM, File 1."
The methods have been described in a clear and concise way.
Thank you for this comment.

The authors transparently describe how reasons for ICPm are clincally led: "The main reason for placing an ICPm device was clinical status (low GCS score) both in the overall population (70.7%) and in each primary diagnosis group (74.4% of TBI, 68.8% of SAH and 63.6% of ICH patients). The decision not to insert an ICPm device was taken either because the patient, according to clinician's judgment, presented with too severe clinical conditions (25%), or because of the characteristics of the neuroimaging (24.7%). No ICPm was due to local policy in 18.1% of cases. ICPm was more frequently inserted in the operating theatre (64.9% of cases), and mainly by the 8 neurosurgeons (97.1%). A parenchymal probe was inserted in 767 (59.1%) patients, whereas 465 (35.8%) received an intraventricular catheter."

This causes potential issues of bias, sampling misrepresentation, and confounding when attempting to compare ICPm and non-ICPm groups.

In an attempt to account for these issues in the data, the authors have applied inverse probability modelling in order to compute relevant weights for variables that were shown to be associated with ICPm.

We agree with the reviewer, who highlights the need for advanced statistical analysis to reduce the risk of bias and misinterpretation. We have highlighted this potential limitation in the limitations section, explaining the statistical analysis that we used to try to overcome this issue.

"This pseudo-population was created using inverse probability of ICPm weights computed by a multivariable Cox model (accounting for the insertion time) on the propensity to undergo ICPm in which the variables included were age, sex, GCS, primary diagnosis, highly pathologic CT scan, cardiovascular and neurological history, center and country economic level and the interaction term between GCS and country economic level."

Can the authors please confirm whether these variables were also associated with the 6-month outcome (and therefore, can be considered as confounders within the analysis)?

Yes, the variables included in the model were associated with 6-month outcome. We have provided a more specific description of the choice of the variables in the statistical method section in the Supplementary material and association with outcome are also shown below.

	Favourable Outcome	**Unfavourable Outcome**	**p**
N	836	1366	
age (mean SD))	45.65 (16.80)	59.32 (17.82)	<0.0001
GCS score on admission (mean(SD))	6.37 (3.04)	5.23 (2.75)	<0.0001
Country economic level = Low-Middle, n(%)	205 (24.5)	165 (12.1)	<0.0001
Diagnosis, n(%)			<0.0001
ICH	105 (12.6)	439 (32.1)	
SAH	187 (22.4)	298 (21.8)	
TBI	544 (65.1)	629 (46.0)	
Highly pathologic CT scan, n(%)	446 (53.3)	988 (72.3)	<0.0001
Cardiovascular history, n(%)	216 (26.8)	706 (53.3)	<0.0001
Neurological history, n(%)	74 (9.2)	195 (14.7)	<0.0001
Female gender, n(%)	272 (32.5)	499 (36.5)	0.063

"Between-center differences in the use of ICPm were quantified by the median odds ratio (MOR) after

unadjusted and adjusted generalized linear mixed modeling with 'center' included as random effect, respectively. Centers with fewer than 10 enrolled patients were codified as "Other". Similar analyses were conducted including 'country' as random effect."

The authors have appropriately applied a multilevel modelling technique with random effects in order to assess the between-center and between-country differences.

Can the authors clarify if they developed a multilevel model with more levels, to allow for center and country clustering within the same analysis?

When we included centre and country within the same hierarchical model, variability among countries, after accounting for centeres, was limited (variance of country: site random effect 0.2283567, variance of site effect 2.2632981). As the inclusion of an additional level for country did not substantially modify the MOR of centres in adjusted analysis (from 4.5 to 4.33) we decided to keep the simpler analysis with centre as random effect (also to avoid complication in MOR interpretation).

Given the observed variability in ICPm use between countries and centers, did the authors consider applying hierarchical modelling, accounting for center and country as different levels within the model, for other analyses?

For all the analysis we consider centre as random effect due to the low variability among countries after accounting for centre's effect. We better specified this in the statistical methods section (page 6-7) of the manuscript and in the Supplementary material.

Currently: "Weighted regression models with robust standard error were applied to the pseudo-population to assess the impact of ICPm on 6-months outcome. When dealing with mortality up to 6 months, we applied a weighted time-dependent Cox model in which subjects enter in the ICPm group at the actual insertion day, accounting for a potential survival time bias. For neurological outcome at 6 months, we applied a weighted logistic regression model."

One consequence of not including hierarchical structures within the analytical model, when they exist in the data, is that standard errors of regression coefficients will be underestimated, leading to an overstatement of statistical significance.

In previous analysis we included centres in the propensity score to account for the different propensities of centres in ICP monitoring. As suggested by the reviewer we now included centres as random effect in the model on outcome obtaining consistent results. Country was included in the propensity score model getting a good balance among the two treatment groups. We modified statistical methods section (page 6-7) and results accordingly. We thank the reviewer for these suggestions that we believe improved our results.

"We performed a sensitivity analysis excluding extremely severe patients (with both unreactive pupils

and GSC=3) and patients died within 48 hours."

The authors have undertaken valuable sensitivity analyses that help to demonstrate the robustness of the study findings.

"The ICPm technique used varied according to the primary diagnosis. In TBI patients, the intraparenchymal device was the most frequently used (73.2%), whereas SAH and ICH patients more commonly had an intraventricular catheter inserted (53% and 53.6%, respectively). The mean duration of ICPm was 8 (SD 8.8) days in TBI, 14.3 (SD 10.3) in SAH and 10.6 (SD 7.7) in ICH, and ICPm maximum value recorded during the first week was 22 mmHg (SD 15-30). "

Did the authors consider completing sub-group analyses by the above noted variations in ICPm (e.g. by ICPm technique or duration)?

Thank you for this comment. As suggested, we have added in this revised version new models regarding the effect on 6 months outcome considering different subgroups of acute brain injured patients (Table 3), as well as more data regarding the type of ICP monitoring technique, with specific focus on the use of EVD (Results section, page 7,8).

"In patients with at least one unreactive pupil, ICPm was associated with significantly lower 6 months mortality (Hazard Ratio, HR=0.37, 95% CI: 0.28-0.50), and better neurological outcome (Odds Ratio OR=0.53, 95% CI:0.33- 0.84), but not in patients with normal pupillary reactivity."

The authors comment that the use of ICPm can lead to a more aggressive therapeutic approach. Might this be confounding the study outcomes? Or, would the authors consider such therapies to be on the causal pathway between ICPm and 6-month outcome? For instance, can the authors please comment on whether these more aggressive therapeutic approaches are only feasible if ICPm has been performed first?

If not, did the authors consider including therapy type and treatments as covariates within the analyses in an attempt to account for possible confounding? For example, can the authors include therapy intensity level (TIL) in the model?

Thank you for this comment. The issue of the TIL related to ICP monitoring is of great importance, and we agree with the reviewer that it should deserve more importance in the manuscript. The presence of ICP monitoring itself can lead to more aggressive treatment, as therapies aimed to manage ICP- especially second-line therapies- are more likely to be applied under neuromonitoring and therefore be on the causal pathway between ICP monitoring and outcome. However, Chesnut et al. demonstrated in their RCT that patients treated without ICP monitoring underwent higher TIL. This could be related to several factors and differences between the 2 studies, for example the settings (limited to South America for the trial by Chesnut and more heterogeneous for our study), and for the different design (RCT, where management is influenced by the context of the randomization vs observational study, which just describes the clinical practice). We have added in the discussion a paragraph discussing and clarifying this issue (page 11). Furthermore, we added a new Table representing the single components of the TIL as additional material (Table S2).

By considering TIL on the causal pathway between ICP monitoring and 6-month outcome we did not include it in the outcome model, however when we did it results were consistent (see table below). We added a sentence in the results (page 9, line 17-20).

	Unfavourable Outcome		**6 months mortality**	
OVERALL	**N events**	**OR (CI 95%)**	**N events**	**HR (CI 95%)**
Pupils both reactive	683	1.34 (1.11-1.63)	428	1.02 (0.78-1.34)
Pupils one or both unreactive	518	0.38 (0.26-0.56)	408	0.35 (0.26-0.47)
Pupils both reactive				
ICP monitoring		0.97 (0.79-1.20)		0.86 (0.64-1.15)
Max TIL during the week		1.074 (1.05-1.10)		1.01 (0.97-1.05)
Pupils one or both unreactive				
ICP monitoring		0.37 (0.25-0.54)		0.28 (0.20-0.38)
Max TIL during the week		1.02 (0.98-1.07)		0.94 (0.91-0.98)

"The median value of the maximum TIL score calculated during the first week of ICU stay in the overall population was 7 [IQR 5,10]; distribution by day is reported in Figure S1. In the ICPmonitoring group- compared to no-ICPmonitoring group the median value of TIL score was higher; in particular, the median (IQR) of maximum TIL was 9 [7-12] vs 5 [3-8] (p<0,001); at day 1 was 8 [6-11] vs 5 [3-8] (p<0,001); at day 3 was 6 [4-8] vs 4 [2-6] and at day 7 was 5 [3-7] vs 3 [2-5], p<0,001. "

There are some typos in the manuscript that need rectifying and grammatical improvements are required, in particular towards the end of the results section.

The manuscript has been revised by a mother tongue medical writer from the University of Brussels (Karen Pickett).

"Results weighted by propensity score with multiple imputations for missing covariates confirmed the results and are presented in Table S4".

The authors have included a rigorous sensitivity analysis of missing values.

The main study limitations have been suitably acknowledged within the discussion section.

Thank you for these comments

Electronic Supplementary Material – ESM

Intracranial pressure monitoring in the intensive care unit: An international prospective observational StudY on iNtrAcranial PreSsurE in intensive care (SYNAPSE-ICU)

Data collection and management

The recruitment period officially started on March 15th, 2018 and ended on April 30th, 2019. Due to unexpected delays linked to ethics committee approval procedures and regulatory issues, in a few selected centers the recruitment deadline was extended until June 30th, 2019. Each center was required to enroll a maximum of 90 patients over a period of 12 weeks. For feasibility and to balance the number of patients included among different centers, each center could recruit up to 30 patients for each form of ABI. De-identified data were collected in a web-based electronic Case Report Form (Clinfile platform, https://synapse-icu.clinfile.com/). Data were securely stored at the University of Milano-Bicocca and all the procedures complied with the European Union Regulation 2016/679 on the protection of natural persons regarding personal data processing and movement. The primary diagnosis (e.g., TBI, SAH or ICH), clinical neurological parameters, laboratory profile and ICP interventions (i.e. therapy intensity level (TIL), calculated according to[1]) were monitored on hospital admission and at days 1, 3, and 7 of ICU stay.

LMICs and HICs were defined according to the World Bank criteria.[2]

Neuroimaging was performed on admission and thereafter whenever needed, based on the clinical situation. "Highly pathologic" CT scans were defined according to the primary diagnosis, and thus corresponded to a Marshall classification ≥ 3 in TBI[4], a modified Fisher grade ≥ 3 in SAH[5] or a hemorrhage volume ≥ 30mL in ICH[6]. Patients were classified according to their primary diagnosis and the use/non-use of an ICPmonitoring device. In the ICPmonitoring group, information about ICP monitoring and management was collected.

Statistical methods

Given the exploratory nature of the study, a formal sample size calculation was not done,[7] but a target sample of >2000 patients was planned. Continuous variables were described with median and interquartile range (IQR), and categorical data were expressed as frequency and percentage values. Comorbid conditions, neurological assessment on admission, and type and severity of head injury were compared between the two study groups (no-ICPmonitoring and ICPmonitoring) by Mann-Whitney U test and chi-squared test for continuous and categorical data, respectively.

Between-center differences in the use of ICPmonitoring were quantified by the median odds ratio (MOR) after unadjusted and adjusted generalized linear mixed modeling with 'center' included as random effect. Centers with fewer than 10 enrolled patients were codified as "Other". Separate analyses were conducted including 'country' as random effect.

To estimate the association between use of ICP monitoring and 6-month outcome independently of measured baseline covariates, we used a propensity score method with inverse probability of treatment weighting.[8,9] Pupil reactivity modified the association between receipt of ICP monitoring and outcome, so we divided the cohort into two groups: patients in whom both pupils were reactive and patients with at least one unreactive pupil. For each

group, we created a pseudo-population to mitigate the selection bias in the decision to use ICP monitoring. These pseudo-populations were created using inverse probability of ICP monitoring weights computed from a multivariable Cox model (accounting for the insertion time) on the propensity to undergo ICP monitoring. The variables included in the model were age, sex, GCS, primary diagnosis, highly pathological CT scan (defined as Marshall classification ≥ 3 in TBI, Fisher grade ≥ 3 in SAH, and ICH size ≥ 30 ml in ICH), history of cardiovascular or neurological disease, country and country economic level (defined according to the World bank criteria), and the interaction term between GCS and country economic level. These variables were chosen on the basis of clinical relevance and statistical association with ICPmonitoring and with 6 –month outcome (if $p<0.1$). Statistically significant interactions were also included. The assumption of overlapping of the distribution of propensity scores in the no-ICPmonitoring and ICPmonitoring groups was fulfilled. The covariate balance between ICPmonitoring and no-ICPmonitoring in the pseudo-population was checked by standardized differences. Weighted regression models with robust standard error were applied to the pseudo-populatiosn to assess the association of ICP monitoring with 6-month mortality and GOSE. For the association with 6-month mortality, we applied a weighted, time-dependent, Cox model in which subjects entered the ICP monitoring group on the actual day of insertion of the ICP monitor to account for a potential survival time bias. For the association with 6-month neurological outcome, we applied a weighted logistic regression model. Center was included as random effect in both models to account for variability among centers. In order to assess the impact of extremely severely injured patients considered not suitable for ICPmonitoring, we performed a sensitivity analysis excluding extremely severe patients (with both unreactive pupils and GSC=3) and patients died within 48 hours.

Due to missing values in predictors, both complete case analysis and multiple imputation were performed. We assumed data were missing at random and we combined multiple imputation, using the multivariate imputation by chained equations (MICE) algorithm, which uses the chained equation method, and the missing indicator method.[10] Ten imputed datasets were created using all the variables that were used in the propensity score analysis as well as the outcomes. Sub-analyses stratifying for disease (TBI, SAH, ICH) were also performed using the same methodology as that used in the overall sample. The results are shown as hazard ratio (HR) and odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). All data analyses and data visualization were done using R software (version 4.0.3, packages survey, ipw, survival, obsSens dplyr, Hmisc, ggplot).

References

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	"Intracranial pressure monitoring in the intensive care unit : an international prospective observational study on intracranial pressure in intensive care(SYNAPSE-ICU)"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	**Main outcomes and measures:** Primary endpoints were 6-month mortality ɔnth neurological outcome as assessed using the Glasgow Outcome Scale Extended (GOSE). ry endpoints were mortality and GOSE score at ICU and hospital discharge. **Results*:*** 2395 patients were included in the analysis (53.7% TBI; 24.5% :% SAH). They had a median age of 55 years and 65.4% were male. The patients :ived ICPmon (1332, 55.6%) were younger, had a lower prevalence of cardiovascular and ;ical comorbidities, and more often presented episodes of neuro-worsening (38.5% vs. 34.2%, p=0.037). ı reasons for ICPmon were clinical indications (70.7%) and pathological findings on cerebral :d Tomography scan (15.4%). Considerable variability in ICPmon use was observed between

				s and centers. 6-month mortality was lower in the ICPmon than the no-ICPmon group (441 /s 512 (52.1%), p<0.001). In patients in whom one or both pupils were unreactive, ICPmon use was dently associated with lower mortality (OR=0.38, 95%CI: 0.24-0.59), but no effect on neurological (OR=0.72, 95%CI: 0.41-1.28). In patients with both pupils reactive no difference on mortality was d, while ICPmon showed a higher odds of poor neurological outcome (OR=1.34, 95%CI 1.04-1.75).
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	Elevated intracranial pressure (ICP) is one of the major clinical complications of acute brain injury (ABI), and large cohort studies have shown it to be independently associated with a higher risk of death and poor outcome after ABI. Although ICP monitoring (ICPmon) is widely used and considered a fundamental component of the management of ABI patients admitted to intensive care units (ICUs),several uncertainties remain.
Objectives	3	State specific objectives,	5	To address these issues, we designed a study, SYNAPSE-ICU, which aims to

		including any prespecified hypotheses		describe current practice regarding the use of ICPmon in ABI, to assess the variability in ICPmon use between centers and countries, and to evaluate the impact of ICPmon on patient outcomes.
Methods				
Study design	4	Present key elements of study design early in the paper	5	SYNAPSE-ICU (NCT03257904) is an international, prospective, observational, cohort study. The protocol has already been published elsewhere and details of the study are available via open access
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	SYNAPSE-ICU (NCT03257904) is an international, prospective, observational, cohort study. The protocol has already been published elsewhere and details of the study are available via open access
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of	5-6	The inclusion criteria were: age ≥18 years; a diagnosis of ABI following TBI, ICH or SAH; altered consciousness defined as a Glasgow Coma Scale (GCS) eye response score of 1 (no eye opening) and a GCS motor response score ≤5 (not obeying commands) either on ICU admission

		selection of participants. Describe methods of follow-up		or subsequently due to neuro-worsening (defined as a spontaneous GCS motor score decrease of 2 points or more compared with the previous examination and/or a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2mm and/or deterioration in neurological or Computed Tomography (CT) status sufficient to warrant immediate medical or surgical intervention during first the first week of the ICU stay). Patients not admitted to the ICU and/or presenting other forms of ABI (e.g. infections of the central nervous system, ischemic stroke) were excluded from the study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	The overall goals of the study were to outline important aspects of ICPmon use, namely: - current ICPmon practice in a large number of centers worldwide, - reasons for inserting an ICPmon device, - variability between countries and centers, - treatment intensity in ICPmon and no-ICPmon groups, - association with patient outcomes.
Data sources/ measurement	8*	For each variable of	*6-*	Data were collected in a web-based electronic Case Report Form (Clinfile

		interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*ESM*	platform, https://synapse-icu.clinfile.com/). Data were securely stored at the University of Milano-Bicocca and all the procedures complied with the European Union Regulation 2016/679 on the protection of natural persons regarding personal data processing and movement. The primary diagnosis (e.g. TBI, SAH or ICH), clinical neurological parameters, laboratory profile and ICP interventions (i.e. TIL, therapy intensity level, defined according to the Common Data Elements principles, www.tbi-impact.org) were monitored on hospital admission and at days 1, 3, and 7 of ICU stay.
Bias	9	Describe any efforts to address potential sources of bias	ESM	Each center was required to enroll a maximum of 90 patients over a period of 12 weeks. To avoid sampling or selection bias, each center could recruit up to 30 patients for each form of ABI. De-identified data were collected in a web-based electronic Case Report Form (Clinfile platform, https://synapse-icu.clinfile.com/).
Study size	10	Explain how the study size was arrived at	ESM	Given the exploratory nature of the study, a formal sample size calculation was not done, [16] but a target sample of >2000 patients was planned.

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	ESM	Continuous variables were described with median and interquartile range (IQR), and categorical data were expressed as frequency and percentage values. Comorbid conditions, neurological assessment on admission, and type and severity of head injury were compared between the two study groups (no-ICPmon and ICPmon) by Mann-Whitney U test and chi-squared test for continuous and categorical data, respectively
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,ESM	Between-center and between-country differences in the use of ICPmon were quantified by the median odds ratio (MOR) after unadjusted and adjusted generalized linear mixed modeling with 'center' or 'country' included as random effect, respectively. Countries and centers with fewer than 5 and 10 enrolled patients, respectively, were codified as "Other". The covariate balance between ICPmon and no-ICPmon in the pseudo-population was checked by standardized differences. The weighted logistic regression model with robust standard error was applied to the pseudo-population to assess the impact of ICPmon on 6-month outcome. In order to assess the impact of unsalvageable patients on the results we performed a sensitivity analysis excluding patients with a very severe condition (unreactive pupils and GSC=3).
		(*b*) Describe any methods used to examine subgroups and interactions	ESM	To estimate the effect of ICPmon on 6-month outcome independently of measured baseline covariates, the propensity score method was used.As we found that pupil reactivity modified the association between ICPmon and outcome, we divided the cohort into two strata: patients in whom both pupils were reactive and patients with at least one unreactive pupil. For each stratum, we created a pseudo-population (that mimics a randomized trial) to mitigate the selection bias in ICPmon assignment.
		(*c*) Explain how missing data were addressed	6,ESM	Due to missing values in predictors, both complete case analysis and multiple imputation were performed. We assumed data were missing at random and we combined multiple imputation, using the MICE algorithm, which uses the chained equation method, and the missing indicator method
		(		
		(*e*) Describe any sensitivity analyses	6,ESM	In order to assess the impact of unsalvageable patients on the results we performed a sensitivity analysis excluding patients with a very severe condition (unreactive pupils and GSC=3)
Results				
Participants	13*	(a) Report numbers of individuals at each stage		Figure 1

		of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage		Figure 1
		(c) Consider use of a flow diagram		Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7	Table 1
		(b) Indicate number of participants with missing data for each variable of interest		Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-9	Table 1-3 ESM
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-9	age, gender, GCS, primary diagnosis, highly pathologic CT scan, cardiovascular and neurological history, country and countr economic level, and the interaction term between GCS and country economic level. These variables were chosen on the ba of clinical relevance and statistical association with ICPmon (if $p<0.1$).
		(*b*) Report category boundaries when		Table 1-2

		continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		NA
Continued on next page				
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	ESM	
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	1. The frequency of ICPmon use varies greatly between centers (MOR=4.50) and countries (MOR=3.1) . 2. ICPmon can lead to a more aggressive therapeutic approach aimed at controlling intracranial pressure. 3. ICPmon can have a beneficial effect on mortality in the most severe cases.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	The main limitation of our results lies in the observational nature of the study, which makes it difficult to draw causal inferences reliably. However, ICPmon is nowadays considered a standard of care and a fundamental component of the neurocritical care management of ABI patients, [1,13,28-30] and therefore ethical constraints actually preclude the conducting of large multicenter randomized controlled trials involving non-monitored controls. Other than the observational design of this study, there are further limitations that need to be mentioned. First, due to funding constraints, we were unable to provide on-site monitoring of all the source documents used to gather the data entered into the database. However, we did monitor for outlier or incongruent data. Second, we did not include withdrawal of life-sustaining measures in our analysis, even though it is conceivable that there were differences between the groups that may have altered the results. Third, because of the lack of reliable preliminary data, we were unable to calculate a priori the adequate sample size and power.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	10-11	. our results suggest that in patients with severe neurological conditions (unreactive pupils) who underwent ICPmon, this might have a beneficial impact on outcome, with lower ICU, in-hospital and 6-month mortality rates found on the unadjusted

		analyses, results from similar studies, and other relevant evidence		analysis. When adjusting for confounding factors by weighting for the propensity score, we found a beneficial effect of ICPmon on 6-month mortality in monitored patients with at least one pathologic pupil. This suggests that the beneficial effect on outcome is particularly marked in more severe patients and more uncertain in less severe cases. These results confirm the importance of ICPmon and ICPmon-driven treatment, and the need to select, on the basis of the type of brain injury and the clinical assessment, the patients who might benefit from aggressive ICP management.
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11	In the present study, the factors influencing the decision to insert an ICPmon device included patients' pre-injury characteristics (ICPmon was more frequently used in younger patients and those with a lower number of comorbidities), as well as severity of injury, clinical assessment and neuroimaging. In particular, the main reasons for inserting an ICPmon device were poor neurological conditions on admission (low GCS score) and a highly pathologic head CT scan. By contrast, the main reasons for not inserting an ICPmon device were a negative CT scan, good neurological status at presentation, or extremely severe clinical conditions (patient considered unsalvageable). However, the decision not to monitor was often due to local policies (18.5% of all cases; 21.5% TBI, 22.3% SAH, and 9.2% ICH), a finding which explains the large variability between countries and centers observed in our cohort.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16	University Milano-Bicocca is the study's sponsor. The study was endorsed and funded by the European Society of Intensive Care Medicine (ESICM) on January 31st, 2017. T the design and testing of the electronic Case Report From (eCRF).

Table S1 - Characteristics of the participating sites.

	Overall	HICs	LMICs	p
n	138*	103	35	
Low/Middle income countries, n (%)	35 (25.4)			
Institution Type, n (%)				<0.0001
Academic/teaching hospital	102 (73.9)	79 (76.7)	23 (65.7)	
Non-teaching hospital	8 (5.8)	7 (6.8)	1 (2.9)	
Private non-academic	12 (8.7)	2 (1.9)	10 (28.6)	
Public non-academic	15 (10.9)	14 (13.6)	1 (2.9)	
District/peripheral hospital	1 (0.7)	1 (1.0)	0 (0.0)	
Institution n. of beds, n (%)				<0.0001
< 250	17 (12.3)	1 (1.0)	16 (45.7)	
250-500	25 (18.1)	20 (19.4)	5 (14.3)	
500-750	29 (21.0)	22 (21.4)	7 (20.0)	
750-1000	24 (17.4)	23 (22.3)	1 (2.9)	
> 1000	43 (31.2)	37 (35.9)	6 (17.1)	
Catchment Area population, n (%)				0.124
< 100.000	3 (2.2)	1 (1.0)	2 (5.7)	
100.000-250.000	18 (13.0)	13 (12.6)	5 (14.3)	

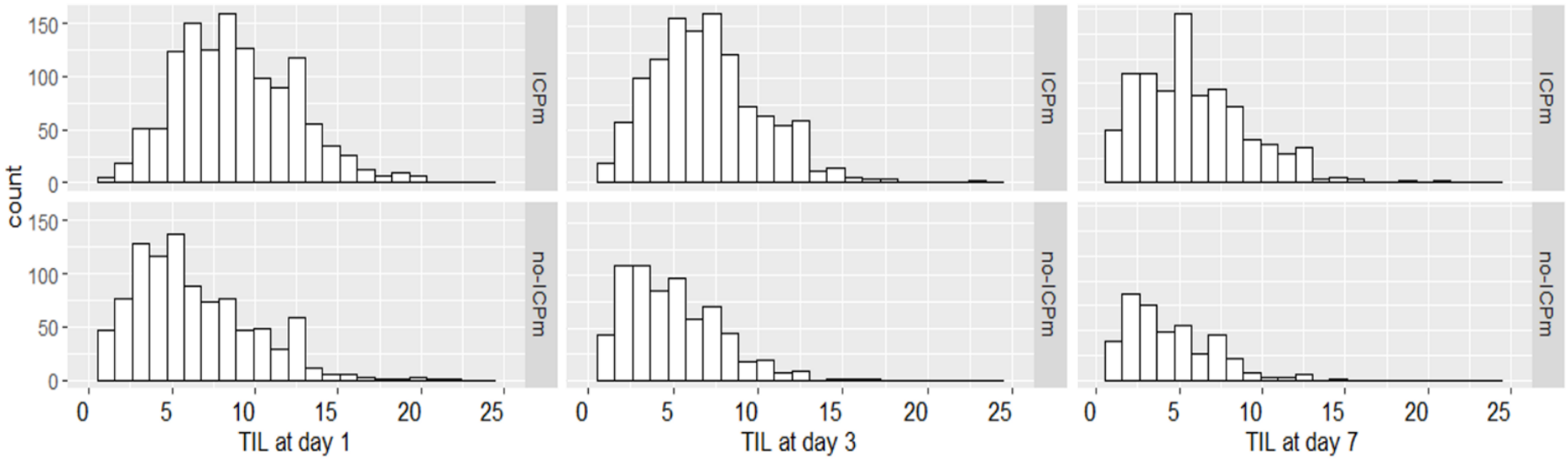
250.000-500.000	23 (16.7)	20 (19.4)	3 (8.6)	
500.000-750.000	20 (14.5)	18 (17.5)	2 (5.7)	
750.000-1.000.000	12 (8.7)	9 (8.7)	3 (8.6)	
> 1.000.000	62 (44.9)	42 (40.8)	20 (57.1)	
N of neuro care beds (mean (SD))	13.30 (10.89)	13.19 (10.29)	13.62 (12.64)	0.845
Nurse:Patient ratio in ICU, n (%)				0.256
1:1	28 (20.3)	20 (19.4)	8 (22.9)	
1:2	77 (55.8)	61 (59.2)	16 (45.7)	
1:3	30 (21.7)	21 (20.4)	9 (25.7)	
1:4	3 (2.2)	1 (1.0)	2 (5.7)	
Nurse:Patient Ratio HDU, n (%)				0.501
1:1	9 (6.8)	5 (5.1)	4 (11.8)	
1:2	54 (40.9)	40 (40.8)	14 (41.2)	
1:3	34 (25.8)	24 (24.5)	10 (29.4)	
1:4	20 (15.2)	17 (17.3)	3 (8.8)	
More	15 (11.4)	12 (12.2)	3 (8.8)	
ICP USE (routine use and presence of local protocol)				
ICP Routinely Use TBI, n (%)	104 (75.4)	88 (85.4)	16 (45.7)	<0.0001
ICP Protocol TBI, n (%)	92 (66.7)	71 (68.9)	21 (60.0)	0.447
ICP Routinely Use SAH, n (%)	78 (56.9)	68 (66.7)	10 (28.6)	<0.0001

ICP Protocol SAH, n (%)	73 (53.3)	58 (56.9)	15 (42.9)	0.216
ICP Routinely Use ICH, n (%)	76 (55.1)	65 (63.1)	11 (31.4)	0.002
ICP Protocol ICH, n (%)	69 (50.0)	54 (52.4)	15 (42.9)	0.434
THRESOLD FOR STARTING TREATMENT AND FOR HOW LONG				
TBI (mean (SD)) mmHg	20.67 (2.80)	20.85 (2.08)	20.10 (4.39)	0.192
TBI (mean (SD)) minutes	12.43 (10.03)	11.12 (9.08)	16.48 (11.79)	0.009
SAH (mean (SD)) mmHg	19.96 (3.72)	20.39 (2.86)	18.52 (5.56)	0.017
SAH (mean (SD)) minutes	11.82 (9.84)	10.92 (9.16)	14.70 (11.46)	0.066
ICH (mean (SD)) mmHg	19.84 (4.10)	20.24 (3.49)	18.52 (5.56)	0.047
ICH (mean (SD)) minutes	11.77 (9.91)	10.83 (9.23)	14.70 (11.46)	0.062

*the center form was not returned by 8 centers.

Abbreviations: HIC, high income countries; LMIC, low/middle income countries; N= number; SD, standard deviation; HDU, high dependency unit; ICP, intracranial pressure; TBI, traumatic brain injury; SAH, subarachnoid haemorrhage; ICH, intracranial haemorrhage.

Figure S1 – Distribution of Therapy Intensive Level (TIL) score, in no-ICPmonitoring and ICPmonitoring patients at day 1, 3 and 7



Abbreviations: TIL= therapy intensity level; ICPm= intracranial pressure monitoring

Table S2. Details of Therapy Intensive Level (TIL) overall, in no-ICPmonitoring and ICPmonitoring patients at day 1, 3 and 7.

	Day 1				Day 3				Day 7			
	Overall	no-ICPmon	ICPmon	p	Overall	no-ICPmon	ICPmon	p	Overall	no-ICPmon	ICPmon	p
N	2395	1063	1332		2395	1063	1332		2395	1063	1332	
No therapy, n(%)	580 (24.7)	436 (41.1)	144 (11.2)	<0.0001	547 (27.6)	321 (42.7)	226 (18.4)	<0.0001	538 (35.1)	234 (48.5)	304 (28.9)	<0.0001
Basic sedation, n(%)	1008 (42.9)	484 (45.6)	524 (40.7)	0.018	723 (36.5)	279 (37.1)	444 (36.2)	0.717	475 (30.9)	145 (30.1)	330 (31.3)	0.664
Basic volume, n(%)	480 (20.4)	224 (21.1)	256 (19.8)	0.481	304 (15.4)	88 (11.7)	216 (17.6)	0.001	204 (13.3)	53 (11)	151 (14.3)	0.087
Basic head up, n(%)	2112 (89.8)	888 (83.6)	1224 (94.8)	<0.0001	1718 (86.8)	615 (81.8)	1103 (89.9)	<0.0001	1259 (82)	383 (79.5)	876 (83.2)	0.090
Basic normocapnia, n(%)	1005 (42.7)	454 (42.7)	551 (42.7)	1.000	945 (47.8)	362 (48.3)	583 (47.6)	0.793	689 (44.9)	209 (43.5)	480 (45.6)	0.490
Mild sedation, n(%)	795 (33.8)	215 (20.2)	580 (44.9)	<0.0001	579 (29.3)	129 (17.2)	450 (36.7)	<0.0001	304 (19.8)	65 (13.5)	239 (22.7)	<0.0001
Mild volume, n(%)	1123 (47.7)	281 (26.5)	842 (65.2)	<0.0001	855 (43.2)	181 (24.1)	674 (54.9)	<0.0001	379 (24.7)	75 (15.6)	304 (28.9)	<0.0001
Mild osmotic, n(%)	578 (24.6)	226 (21.3)	352 (27.3)	0.001	400 (20.2)	156 (20.7)	244 (19.9)	0.686	245 (16)	82 (17)	163 (15.5)	0.493
Mild hypocapnia, n(%)	710 (30.2)	250 (23.5)	460 (35.6)	<0.0001	531 (26.9)	169 (22.5)	362 (29.5)	0.001	342 (22.3)	93 (19.4)	249 (23.6)	0.072
Mild CSF, n(%)	234 (10)	46 (4.3)	188 (14.6)	<0.0001	184 (9.3)	35 (4.7)	149 (12.1)	<0.0001	138 (9)	24 (5)	114 (10.8)	<0.0001
Moderate osmotic, n(%)	351 (14.9)	118 (11.1)	233 (18)	<0.0001	249 (12.6)	79 (10.5)	170 (13.9)	0.035	121(7.9)	37(7.7)	84(8)	0.920
Moderate hypocapnia, n(%)	234 (9.9)	103 (9.7)	131 (10.1)	0.776	171 (8.7)	56 (7.5)	115 (9.4)	0.166	138 (9)	47 (9.8)	91 (8.6)	0.527
Moderate hypothermia, n(%)	348 14.8)	117 (11)	231 (17.9)	<0.0001	255 (12.9)	80 (10.6)	175 (14.3)	0.023	168 (10.9)	36 (7.5)	132 (12.5)	0.004
Moderate CSF, n(%)	355 (15.1)	46 (4.3)	309 (24)	<0.0001	376 (19)	49 (6.5)	327 (26.7)	<0.0001	295 (19.2)	33 (6.9)	262 (24.9)	<0.0001

Extreme hypocapnia, n(%)	62 (2.6)	20 (1.9)	42 (3.3)	0.053	38 (1.9)	9 (1.2)	29 (2.4)	0.097	31 (2)	4 (0.8)	27 (2.6)	0.042
Extreme hypothermia, n(%)	33 (1.4)	12 (1.1)	21 (1.6)	0.399	18 (0.9)	2 (0.3)	16 (1.3)	0.034	14 (0.9)	1 (0.2)	13 (1.2)	0.094
Extreme suppression, n(%)	72 3.1)	16 (1.5)	56 (4.3)	<0.0001	49 (2.5)	5 (0.7)	44 (3.6)	<0.0001	33 (2.1)	3 (0.6)	30 (2.8)	0.009
Decompression, n(%)	354 (15)	138 (13)	216 (16.7)	0.014	63 (3.2)	15 (2)	48 (3.9)	0.026	21 (1.4)	5 (1)	16 (1.5)	0.604

Basic sedation (sedation for ventilator/endotracheal tube tolerance); Basic volume (vasopressors/volume for non-CNS cause, e.g. sepsis, myocardial injury); Normocapnia (PaCO2≥40mmHg); Mild sedation (higher level of sedation); Mild volume (vasopressors/volume for CPP support); Mild osmotic (low dose osmotic therapy: hyperosmolar therapy with mannitol up to 2g/kg/24h; hyperosmolar therapy with hypertonic saline up to 0.3g/kg/24h); Mild hypocapnia (PaCO2 35-40mmHg); Mild CSF (CSF drainage<120ml/day (<5ml/h)); Moderate Osmotic (higher dose of osmotic therapy; hyperosmolar therapy with mannitol>2g/kg/24h); hyperosmolar therapy with hypertonic saline>0.3g/kg/24h); Moderate hypocapnia (PaCO2 30-35mmHg); Moderate hypothermia (T>35°C); Moderate CSF (CSF drainage≥120ml/day (>5ml/h); Extreme hypocapnia (PaCO2<30mmHg); Extreme Hypothermia (T<35°C); Extreme Suppression (metabolic suppression for ICP control).

Abbreviations: CSF = Cerebrospinal Fluid; CPP = Cerebral Perfusion Pressure; ICPmon= intracranial pressure monitoring

Table S3 – At hospital and 6-months crude outcomes in ICPmonitoring and no-ICPmonitoring patients

	Overall	Missing values	no-ICPmon	ICPmon	p
n	2395		1063	1332	
Early death (≤48hrs), n(%)	218 (9.2)	22	177 (16.8)	41 (3.1)	<0.0001
GOSE <5 at ICU, n(%)	1734 (73.9)	48	751 (72.1)	983 (75.3)	0.083

ICU Mortality, n(%)	680 (29.0)		391 (37.5)	289 (22.1)	<0.0001
GOSE <5 at hospital, n(%)	1618 (69.4)	65	719 (69.1)	899 (69.7)	0.759
In hospital mortality, n(%)	793 (34.0)		436 (41.9)	357 (27.7)	<0.0001
GOSE at 6 months<5, n(%)	1366 (62.0)	193	633 (64.5)	733 (60.1)	0.039
6 months mortality, n(%)	958 (40.5)	28	517 (49.3)	441 (33.5)	<0.0001
ICU LOS (median[IQR])	11[5,21]	29	6[2,13]	16[9,24]	<0.0001
In hospital LOS (median[IQR])	19[8,37]	46	11[3,24]	26[13,47]	<0.0001
ICU LOS of alive subjects (median[IQR])	15 [8, 24]		9[4,17]	18 [11, 26]	<0.0001
In hospital LOS of alive subjects (median[IQR])	27 [16, 47]		19[10,33]	33 [21,53]	<0.0001

Abbreviations: GOSE, Extended Glasgow Outcome Scale; LOS, Length of stay; ICU, Intensive Care Unit; IQR, Interquartile Range; ICPmon, intracranial pressure monitoring.

Table S4 - Baseline characteristics of the pseudo-population weighted for the propensity score (to mitigate the selection bias in ICP monitoring) stratified for pupils' reactivity using complete data.

	Strata 1: weighted pseudo-population of patients with both reactive pupils				Strata 2: weighted pseudo-population of patients with one or both unreactive pupils			
	no-ICPmon	ICPmon	p	SMD	no-ICPmon	ICPmon	p	SMD
age (median [IQR])	54 [40, 69]	55 [40, 69]	0.873	0.006	54 [34, 71]	56 [39, 68]	0.854	0.029
GCS (median [IQR])	7 [4, 8]	6 [3, 8]	0.360	0.039	3 [3, 6]	4 [3, 6]	0.895	0.040
Country Level = LMIC, n (%)	233.2 (18.9)	214.7 (17.4)	0.638	0.040	102.5 (14.9)	82.6 (13.1)	0.729	0.053
diagnosis n(%)			0.940	0.024			0.986	0.016
TBI	659.8 (53.5)	670.4 (54.3)			378.5 (55.0)	343.1 (54.3)		
SAH	295.0 (23.9)	299.0 (24.2)			121.7 (17.7)	115.1 (18.2)		
ICH	277.9 (22.5)	266.2 (21.5)			187.6 (27.3)	173.6 (27.5)		
CT-scan = highly pathologic, n(%)	720.3 (58.4)	718.6 (58.2)	0.937	0.006	508.3 (73.9)	447.9 (70.9)	0.610	0.067
Sex = Female, n (%)	435.8 (35.4)	438.2 (35.5)	0.976	0.002	239.1 (34.8)	199.9 (31.6)	0.524	0.066
Cardiovascular history, n(%)	517.2 (42.0)	501.7 (40.6)	0.693	0.027	289.0 (42.0)	268.9 (42.6)	0.914	0.011
Neurologic history, n(%)	139.4 (11.3)	131.2 (10.6)	0.732	0.022	91.7 (13.3)	95.3 (15.1)	0.573	0.050

Abbreviations: SMD, standardized mean difference; TBI, Traumatic Brain Injury; SAH, subarachnoid haemorrhage; ICH, intracerebral haemorrhage; GCS, Glasgow Coma Scale; LMIC, low/middle income countries

Table S5. Results on the association between ICPmonitoring (yes versus no) and 6-months outcomes (mortality and unfavorable outcome) weighted by propensity score with multiple imputation (MI) for missing covariates.

	6 months mortality	unfavorable outcome at 6 months (GOSE < 5)
Strata:	HR (CI95%)	OR (CI 95%)
Pupils both reactive	0.81 (0.65-1.01)	1.37 (1.15-1.63)
Pupils one or both unreactive	0.24 (0.18- 0.31)	0.46 (0.33 -0.65)
Sensitivity analysis excluding extremely severe patients[a] and patients died within 48 hours:		
Pupils both reactive	0.87 (0.68-1.09)	1.27 (1.05-1.54)
Pupils one or both unreactive	0.35 (0.24-0.51)	0.49 (0.34- 0.71)

[a] patients with GCS score on admission 3 and both unreactive pupils

Abbreviations: HR, hazard ratio; OR, odds ratio; GOSE, extended Glasgow outcome score; multiple imputation, MI

Table S6. Sensitivity analysis excluding centers that did not insert ICP monitoring (22 centers).

	unfavorable outcome at 6 months (GOSE < 5)	
OVERALL	N events	OR (CI95%)
Pupils both reactive	650	1.45 (1.19-1.75)
Pupils one or both unreactive	485	0.53 (0.37-0.74)

File 2. SYNAPSE-ICU Investigators

The numbers in the list refer to the enrolled patients by each centre.

Argentina (National Coordinator, Videtta Walter)

Sanatorio De La Trinidad San Isidro, San Isidro, Argentina (4, Domeniconi Gustavo)

Higa Dr Oscar Alende, Mar Del Plata, Argentina (8, Giménez María Estrella)

Hospital Castro Rendon, Neuquen, Argentina (1, Fumale Mariela)

Hospital El Cruce, Florencio Varela, Argentina (11, Amundarain Edgar Daniel)

Centro Medico Integral Fitz Roy, Buenos Aires, Argentina (14, Casanova Matias)

Australia (National Coordinator, Reade Michael)

Royal Brisbane And Women's Hospital, Brisbane, Australia (4, Hallt Elizabeth)

Gold Coast University Hospital, Gold Coast, Australia (7, Pearson David)

Nepean Hospital, Penrith, Australia (7, Seppelt Ian)

Austria (National Coordinator, Helbok Raimund)

Medical University Innsbruck, Innsbruck, Austria (23, Helbok Raimund, Lindner Anna)

Belarus (National Coordinator, Davidovich Valery)

5th City Clinical Hospital, Minsk, Belarus (1, Davidovich Valery)

Belgium (National Coordinator, Meyfroidt Geert)

Hopital Erasme, Bruxelles, Belgium (19, Crippa Ilaria Alice)

University Hospitals Leuven, Leuven, Belgium (22, Mebis Liese)

Chu Charleroi, Lodelinsart, Belgium (3, Biston Patrick)

Az Maria Middelares, Gent, Belgium (1, Van De Velde Stijn)

Grand Hopital De Charleroi, Charleroi, Belgium (6, Denis Glorieux)

Brazil (National Coordinator, Kurtz Pedro)

Instituto Estadual Do Cerebro, Rio De Janeiro, Brazil (6, Kurtz Pedro)

Das Clinicas Hospital University of Sao Paulo, Sao Paulo, Brazil (19, Yasin Wayhs Samia)

Canada (National Coordinator, Sekhon Mypinder)

Vancouver General Hospital University of British Columbia, Vancouver, Canada (80, Sekhon Mypinder, Griesdale Donald)

St Michael's Hospital, Toronto, Canada (6, Rigamonti Andrea)

Chile (National Coordinator, Montes José Miguel)

Clinica Alemana De Santiago, Santiago, Chile (12, Pérez-Araos Rodrigo)

Colombia (National Coordinator, Mejia-Mantilla Jorge H)

Fundacion Valle Del Lili, Cali, Colombia (31, Mejia-Mantilla Jorge H, Gempeler Andrés)

Hospital San Vicente Rionegro, Rionegro, Colombia (3, Mendoza Ray)

Croatia (National Coordinator, Kovac Natasa)

University Hospital Centre Zagreb, Zagreb, Croatia (10, Kovac Natasa)

Cuba (National Coordinator, Berty Gutiérrez Hedgar)

Hospital Dr Miguel Enríquez, La Habana, Cuba (18, Berty Gutiérrez Hedgar)

Czech Republic (National Coordinator, Spatenkova Vera)

St Anne's University Hospital, Brno, Czech Republic (10, Fencl Marek)

Hospital Brno, Brno, Czech Republic (47, Gal Roman, Hrdy Ondrej, Vrbica Kamil)

Masaryk Hospital in Usti Nad Labem, Usti Nad Labem, Czech Republic (33, Skola Josef, Provaznikova Eva)

University Hospital Plzen, Plzen, Czech Republic (38, Kletecka Jakub, Lavicka Pavel)

Regional Hospital Czech Republic, Liberec, Czech Republic (12, Spatenkova Vera)

Denmark (National Coordinator, Bresil Piergiorgio)

Aalborg University Hospital, Aalborg, Denmark (6, Levin Marianne)

Odense University Hospital, Odense, Denmark (87, Bresil Piergiorgio, Thomsen Josefine, Egmose Larsen Thomas, Westy Hoffmeyer Henrik, Olskjaer Holm Morten)

Rigshospitalet, Copenhagen, Denmark (62, Andersen Jesper Borg, Majholm Birgitte, Smitt Margit, Eddelien Heidi Shil)

Ecuador (National Coordinator, Jibaja Manuel)

Hospital De Especialidades Eugenio Espejo, Quito, Ecuador (9, Jibaja Manuel)

Carlos Andrade Marin Hospital, Quito, Ecuador (22, Maldonado Freddy)

Clinica La Merced, Quito, Ecuador (17, García María Fernanda)

France (National Coordinator, Asehnoune Karim)

Chu Pointe-À-Pitre Abymes, Pointe-À-Pitre Cedex, France (12, Pons Bertrand)

Hôpital Central, Nancy, France (33, Audibert Gérard, Lucca Manon)

Chu Besancon, Besancon, France (20, Besch Guillaume)

Grenoble University Hospital, Grenoble, France (17, Banco Pierluigi)

Chu De Nantes, Nantes, France (35, Asehnoune Karim, Cinotti Raphael)

Pasteur 2 Chu Nice, Nice, France (8, Quintard Hervé)

Hôpital Lariboisière, Aphp, Paris, France (33, Soyer Benjamin, Caillard Anais)

Caen University Hospital, Caen, France (11, Gakuba Clement)

Bichat Claude Bernard University Hospital, Paris, France (3, Sonneville Romain)

Germany (National Coordinator, Wolf Stefan)

Klinikum Rechts Der Isar, Munich, Germany (89, Fuest Kristina, Albrecht Lea, Grotheer Sarah, Krieg Sandro M, Schaller Stefan J)

Charité University Medicine Berlin, Berlin, Germany (11, Wolf Stefan)

Greece (National Coordinator, Vrettou Charikleia)

General Hospital of Chania, Chania, Greece (3, Kontoudaki Eftychia)

Saint Savvas Hospital, Athens, Greece (25, Efthymiou Anna)

University Hospital Larissa, Larissa, Greece (32, Palli Elena, Makris Demosthenes)

Attikon University Hospital, Chaidari, Greece (21, Diakaki Chrysi)

G. Papanikolaou General Hospital, Thessaloniki, Greece (14, Iasonidou Christina)

Asklipieio Voulas General Hospital, Voula, Greece (6, Dimoula Aikaterini)

General Hospital of Athens G. Gennimatas, Athens, Greece (2, Koukoulitsios Georgios)

Lamia General Hospital, Lamia, Greece (24, Kyriazopoulos George)

General Hospital of Tripolis, Tripolis, Greece (5, Pantelas Nikolas)

Achillopoulio General Hospital, Volos, Greece (1, Tsikriki Syragoula)

General Hospital of Kavala, Kavala, Greece (5, Stamou Electra Eleni)

Evaggelismos General Hospital, Athens, Greece (32, Vrettou Charikleia, Giannopoulos Achileas)

Public General Hospital Hippokratio of Thessaloniki, Thessaloniki, Greece (12, Mouloudi Eleni)

Hong Kong (National Coordinator, Shum Hoi Ping)

Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong (4, Shum Hoi Ping)

Tuen Mun Hospital, Tuen Mun, Hong Kong (6, Chan Cheuk Yan)

Princess Margaret Hospital, Kwai Chung, Hong Kong (10, Kandamby Darshana Hewa)

Hungary (National Coordinator, Tánczos Krisztián)

Peterfy Hospital and Trauma Centre, Budapest, Hungary (15, Nardai Gabor)

University of Szeged, Szeged, Hungary (6, Tánczos Krisztián)

Kenezy University Hospital, Debrecen, Hungary (8, Szentkereszty Zoltan)

India (National Coordinator, Sapra Harsh)

All India Institute of Medical Sciences, Delhi, India (30, Gupta Deepak, Sharma Kaveri)

Medanta Medicity Gurgaon, Gurgaon, India (21, Sapra Harsh)

Artemis Hospital, Gurgaon, India (2, Anand Saurabh)

Post Graduate Institute of Medical Education And Research Chandigarh, Chandigarh, India (76, Luthra Ankur, Bloria Summit, Chauhan Rajeev, Panda Nidhi)

King George's Medical University, Uttar Pradesh, India (16, Ozair Ahmad)

Indonesia (National Coordinator, Kilapong Bram)

Awal Bros Hospital, Batam, Indonesia (3, Kilapong Bram)

Iraq (National Coordinator, Alsudani Anass)

Neurosurgery Teaching Hospital, Baghdad, Iraq (1, Alsudani Anass)

Italy (National Coordinator, Citerio Giuseppe)

Ospedale Dell'angelo, Zelarino, Italy (9, Soragni Alessandra)

Asst Settelaghi Varese, Varese, Italy (6, Motta Alessandro)

Aou Modena, Modena, Italy (37, Marudi Andrea, Bertellini Elisabetta)

Policlinico A. Gemelli, Roma, Italy (75, Caricato Anselmo, Gelormini Camilla, Ioannoni Eleonora, Stival Eleonora, Silva Serena)

Asst Grande Ospedale Metropolitano Niguarda, Milano, Italy (14, Pozzi Federico)

Policlinico San Martino, Genova, Italy (23, Brunetti Iole)

Policlinico Paolo Giaccone University of Palermo, Palermo, Italy (18, Cortegiani Andrea)

Azienda Ospedaliero Universitaria Di Parma, Parma, Italy (12, Picetti Edoardo)

Humanitas, Rozzano, Italy (16, Villa Federico)

Asl Toscana Centro Ospedale San Giuseppe Empoli, Empoli, Italy (17, Calamai Italo)

Irccs Bellaria Hospital Ausl Bologna, Bologna, Italy (2, Casadio Maria Chiara)

Ospedali Riuniti, Livorno, Italy (28, Quartarone Maria Concetta)

Azienda Ospedaliera Universitaria Padova, Padova, Italy (22, Grandis Marzia)

Ospedale San Gerardo, Monza, Italy (51, Magni Federico, Del Bianco Silvia, Bonetti Claudia)

Ospedale Maggiore, Bologna, Italy (34, Buldini Virginia, Giugni Aimone)

Asst Lariana Ospedale Sant'Anna Di Como, San Fermo Della Battaglia, Italy (11, Zerbi Simone Maria)

Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy (4, Carbonara Marco)

Azienda Universitario Ospedaliera O.O.R.R. Foggia, Foggia, Italy (34, Cotoia Antonella, Izzi Antonio)

Latvia (National Coordinator, Sabelnikovs Olegs)

Paul Stradins Clinical University Hospital, Riga, Latvia (5, Sabelnikovs Olegs)

Libya (National Coordinator, Elhadi Muhammed)

Seoul Clinic, Tripoli, Libya (10, Elhadi Muhammed)

Abo Selim Trauma Hospital, Tripoli, Libya (6, Ahmed Hazem)

Mexico (National Coordinator, Ñamendys Silva Silvio A)

Fundacion Clinica Medica Sur, Mexico City, Mexico (7, Ñamendys Silva Silvio A)

Hospital Regional De Alta Especialidad De Ixtapaluca, Ixtapaluca, Mexico (4, Gasca López Gilberto Adrian)

Nepal (National Coordinator, Shrestha Gentle S)

Tribhuvan University Teaching Hosptial, Kathmandu, Nepal (8, Shrestha Gentle S)

Grande International Hospital, Kathmandu, Nepal (4, Maskey Shirish)

B&B Hospital, Kathmandu, Nepal (1, Bajracharya Tamanna)

National Trauma Center, Kathmandu, Nepal (3, Nilam Khadka)

Nobel Hospital, Kathmandu, Nepal (15, Kafle Prakash)

Birat Medical College, Tankisinuwari, Nepal (3, Rajbanshi Laleet)

Neuro Cardio & Multispecialty Hospital, Biratnagar, Nepal (2, Bahadur Roka Yam)

Nigeria (National Coordinator, Idowu Olufemi)

Lagos State University Teaching Hospital Ikeja, Lagos, Nigeria (7, Idowu Olufemi)

Pakistan (National Coordinator, Muhammad Mukhtar Khan)

Northwest General Hospital & Research Centre, Peshawar, Pakistan (5, Muhammad Mukhtar Khan)

Peru' (National Coordinator, Pinedo Portilla Juan Luis)

Clinica Del Pacifico, Chiclayo, Perù (10, Pinedo Portilla Juan Luis)

Poland (National Coordinator, Kojder Klaudyna)

University Hospital No. 1, Pomeranian Medical University, Szczecin, Poland (3, Kojder Klaudyna)

Portugal (National Coordinator, Aragao Irene)

Hospital Santo Antonio, Porto, Portugal (23, Aragao Irene)

Centro Hospitalar e Universitario De Coimbra, Coimbra, Portugal (32, Freitas Ricardo, Simoes Marco)

Hospital Garcia De Orta, Almada, Portugal (13, Batista Dario)

Hospital De Braga, Braga, Portugal (51, Pacheco Cecília, Assunção Fátima, Lencastre Luís)

Centro Hospitalar Universitário Do Algarve - Unidade De Faro, Faro, Portugal (8, Cavaleiro Pedro)

Qatar (National Coordinator, Abdelaty Mohamed)

Hamad Medical Corporation, Doha, Qatar (7, Abdelaty Mohamed)

Russian Federation (National Coordinator, Gritsan Alex)

Belgorod Regional Clinical Hospital of St. Ioasaph, Belgorod, Russian Federation (5, Khomiakov Sergey)

Krasnoyarsk Regional Clinical Hospital, Krasnoyarsk, Russian Federation (7, Gritsan Alex, Nikolay Dovbysh)

Saudi Arabia (National Coordinator, Arabi Yaseen)

King Abdulaziz Medical City, Riyadh, Saudi Arabia (8, Arabi Yaseen)

Slovenia (National Coordinator, Gradisek Primoz)

Splosna Bolnisnica Murska Sobota, Murska Sobota, Slovenia (3, Forjan Petra)

Izola General Hospital, Isola, Slovenia (4, Škoti Mara)

University Medical Centre Ljubljana, Ljubljana, Slovenia (57, Filekovic Ribaric Suada, Gradisek Primoz, Milivojevic Nataša)

Slovenj Gradec General Hospital, Slovenj Gradec, Slovenia (3, Kozar Sergeja)

Spain (National Coordinator, Badenes Rafael)

Hospital Universitario Ramòn Y Cajal, Madrid, Spain (3, Blandino Ortiz Aaron)

Hospital Universitario Puerta Del Mar, Cadiz, Spain (1, Celaya Lopez Mikel)

Hospital General Universitario De Castellon, Castellon De La Plana, Spain (8, Galarza Laura)

Hospital Universitari De Bellvitge, Hospitalet De Llobregat, Spain (81, Corral Luisa, Lores Africa, Soley Ricard, Pariente Laura, López Ojeda Pablo)

Hospital Regional Universitario Carlos Haya, Malaga, Spain (22, Arias Verdu Maria Dolores)

Hospital General Universitario De Ciudad Real, Ciudad Real, Spain (4, Yuste Dominguez Luis Javier)

Complejo Hospitalario De Leon, Leon, Spain (4, Gonzalez Perez Maria Isabel)

Hospital Germans Trias I Pujol, Badalona, Spain (9, Anglada Mireia)

Gregorio Maranon Hospital, Madrid, Spain (5, Duque Patricia)

Hospital Clinic Universitari De Valencia, Valencia, Spain (33, Serrano Ainhoa, Monleon Berta)

Joan Xxiii University Hospital, Tarragona, Spain (6, Blazquez Vanessa)

Switzerland (National Coordinator, Oddo Mauro)

Chuv Lausanne University Hospital, Lausanne, Switzerland (46, Abed Maillard Samia, Morelli Paola, Miroz John-Paul, Favre Eva)

Tunisia (National Coordinator, Sellami Walid)

Military Hospital of Tunis, Tunis, Tunisia (31, Sellami Walid)

United Arab Emirates (UAE) (National Coordinator, Lamperti Massimo)

Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates (7, Dibu Jamil)

United Kingdom (UK) (National Coordinator, Siviter Richard)

Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom of Great Britain and Northern Ireland (1, Kolias Angelos)

University Hospitals of North Midlands NHS Trust, Stoke on Trent Staffordshire, United Kingdom of Great Britain and Northern Ireland (4, Thompson Chris)

NHS Greater Glasgow and Clyde, Glasgow, United Kingdom of Great Britain and Northern Ireland (4, Hawthorne Christopher)

Salford Royal NHS Foundation Trust, Salford, United Kingdom of Great Britain and Northern Ireland (8, Roberts Justin)

University of Oxford Hospitals NHS Foundation Trust, Oxford, United Kingdom of Great Britain and Northern Ireland (25, Prisco Lara)

University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom of Great Britain and Northern Ireland (1, Lightfoot Roger)

United States of America (USA) (National Coordinator, Suarez I Josè)

The Johns Hopkins University, Baltimore, United States of America (5, Rivera-Lara Luci)

University of Massachusetts Medical School, Worcester, United States of America (26, Muehlschlegel Susanne)

Doctors Hospital Renaissance, Edinburg, United States of America (5, Padilla Juan)

Greenville Health System, University of South Carolina, Greenville, United States of America (6, Sivakumar Sanjeev)

University of Texas Southwestern Medical Center, Dallas, United States of America (12, Olson Daiwai)

Group collaborators

First and Middle name initials	Surname
M.	Abdelaty
S.	Abed Maillard
H.	Ahmed
L.	Albrecht
A.	Alsudani
E.D.	Amundarain
S.	Anand
J.B.	Andersen
M.	Anglada
Y	Arabi
I.	Aragao
M.D.	Arias Verdu
K.	Asehnoune
F.	Assunção
G.	Audibert
R.	Badenes
T.	Bajracharya
P.	Banco
D.	Batista
E.	Bertellini
H.	Berty Gutiérrez
G.	Besch
P.	Biston
A.	Blandino Ortiz
V.	Blazquez
S.	Bloria
C.	Bonetti
P.	Bresil
I.	Brunetti
V.	Buldini
A.	Caillard
I.	Calamai
M.	Carbonara
A.	Caricato
M.C.	Casadio
M.	Casanova
P.	Cavaleiro
M.	Celaya Lopez
C.Y.	Chan
R.	Chauhan
R.	Cinotti
L.	Corral
A.	Cortegiani
A.	Cotoia
I.A.	Crippa
V.	Davidovich
S.	Del Bianco
C.	Diakaki
J.	Dibu
A.	Dimoula
G.	Domeniconi
L.J.Y.	Dominguez
N.	Dovbysh
P.	Duque
H.S.	Eddelien

A.	Efthymiou
T.	Egmose Larsen
M.	Elhadi
E.	Favre Eva
M.	Fencl
P.	Forjan
R.	Freitas
K.	Fuest
M.	Fumale
C.	Gakuba
L.	Galarza
M.F.	García
G.A.	Gasca López
C.	Gelormini
A.	Gempeler
A.	Giannopoulos
M.E.	Giménez
A.	Giugni
D.	Glorieux
M.I.	Gonzalez Perez
P.	Gradisek
M.	Grandis
D.	Griesdale
A.	Gritsan
S.	Grotheer
D.	Gupta
E.D.	Hallt
C.	Hawthorne
R.	Helbok
M.O.	Holm
C.	Iasonidou
O.	Idowu
E.	Ioannoni
A.	Izzi
M.	Jibaja
P.	Kafle
D.H.	Kandamby
M.M.	Khan
S.	Khomiakov
B.	Kilapong
J.	Kletecka
K.	Kojder
A.	Kolias
E.	Kontoudaki
G.	Koukoulitsios
N.	Kovac
S.	Kozar
S.M.	Krieg
P.	Kurtz
G.	Kyriazopoulos
M.	Lamperti
P.	Lavicka
L.	Lencastre
M.	Levin
R.	Lightfoot
A.	Lindner
P.	López Ojeda

A.	Lores
M.	Lucca
A.	Luthra
F.	Magni
B.	Majholm
D.	Makris
F.	Maldonado
A.	Marudi
S.	Maskey
L.	Mebis
J.H.	Mejia-Mantilla
R.	Mendoza
N.	Milivojevic
J.P.	Miroz
B.	Monleon
J.M.	Montes
P.	Morelli
A.	Motta
E.	Mouloudi
S.	Muehlschlegel
S.A.	Ñamendys Silva
G.	Nardai
K.	Nilam
D.	Olson
A.	Ozair
C.	Pacheco
J.	Padilla Juan
E.	Palli
N.	Panda
N.	Pantelas
L.	Pariente
D.	Pearson
R.	Pérez-Araos
E.	Picetti
J.L.	Pinedo Portilla
B.	Pons
F.	Pozzi
E.	Provaznikova
M.C.	Quartarone
H.	Quintard
L.	Rajbanshi
M.	Reade
S.F.	Ribaric
A.	Rigamonti
L.L.	Rivera
J.	Roberts
Y.B.	Roka
O.	Sabelnikovs
H.	Sapra
S.J.	Schaller
M.	Sekhon
W.	Sellami
I.	Seppelt
A.	Serrano
K.	Sharma
G.S.	Shrestha
H.P.	Shum

S.	Silva
M.	Simoes
S.	Sivakumar
R.	Siviter
J.	Skola
M.	Škoti
M.	Smitt
R.	Soley
R.	Sonneville
A.	Soragni
B.	Soyer
V.	Spatenkova
E.E.	Stamou
E.	Stival
Z.	Olson
K.	Tánczos
C.	Thompson
J.	Thomsen
S.	Tsikriki
S.	Van De Velde
W.	Videtta
F.	Villa
K.	Vrbica
C.	Vrettou
H.	Westy Hoffmeyer
S.	Wolf
S.	Wolf
S.	Yasin Wayhs
S.M.	Zerbi

Figure 1

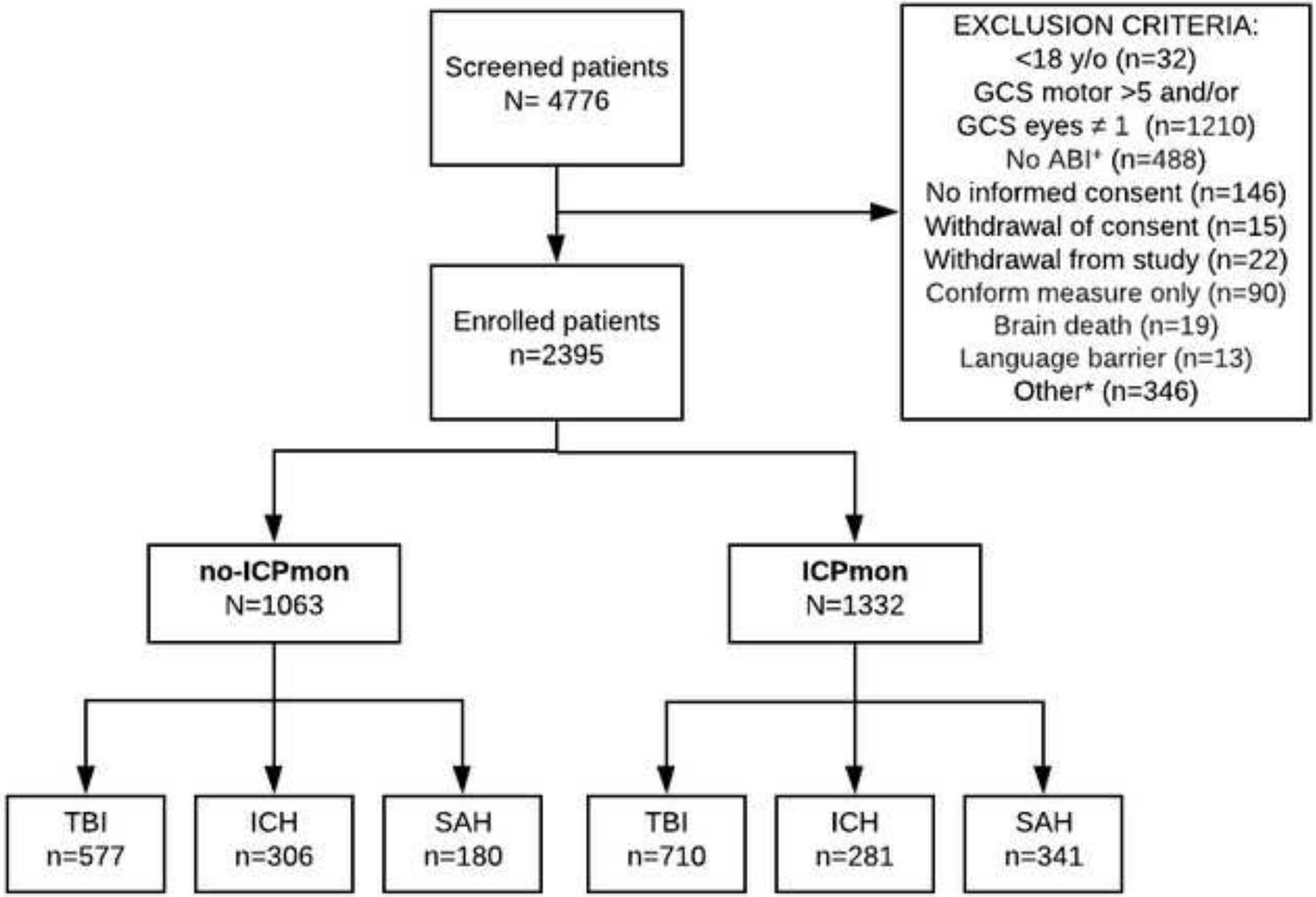


Figure 2 panel A World

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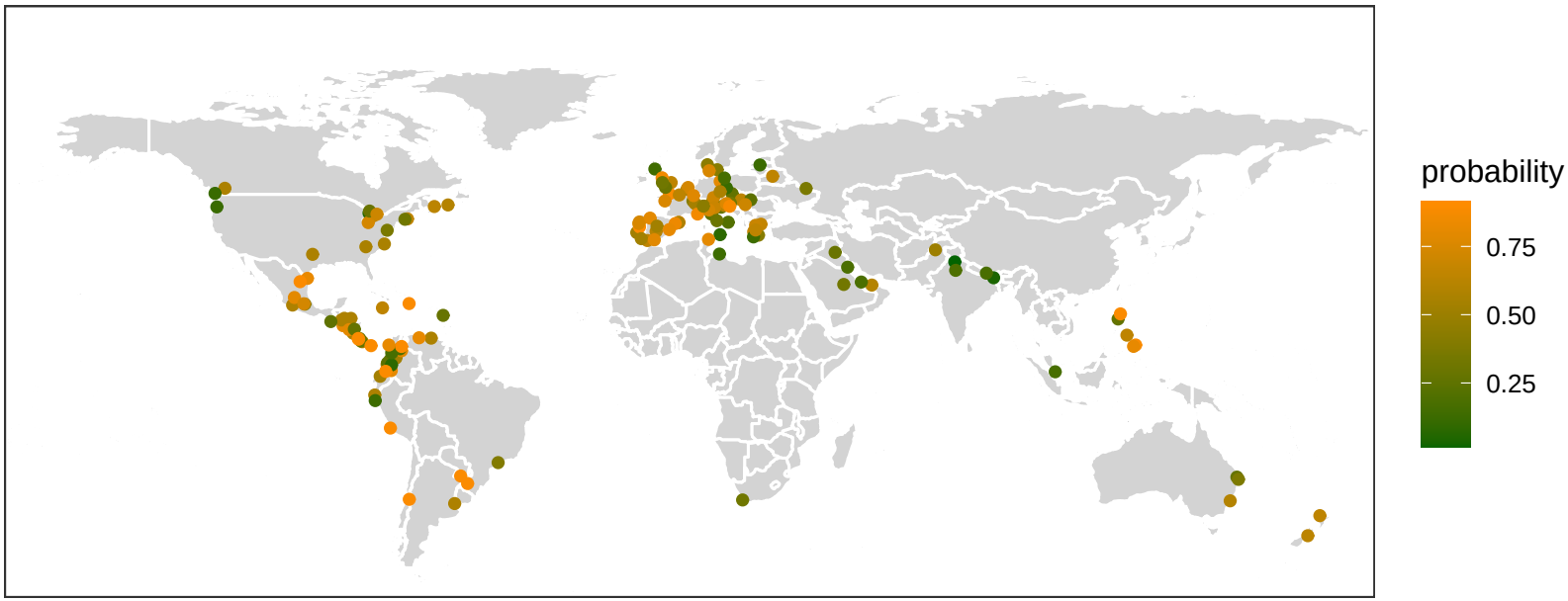

Figure 2 panel A Europe

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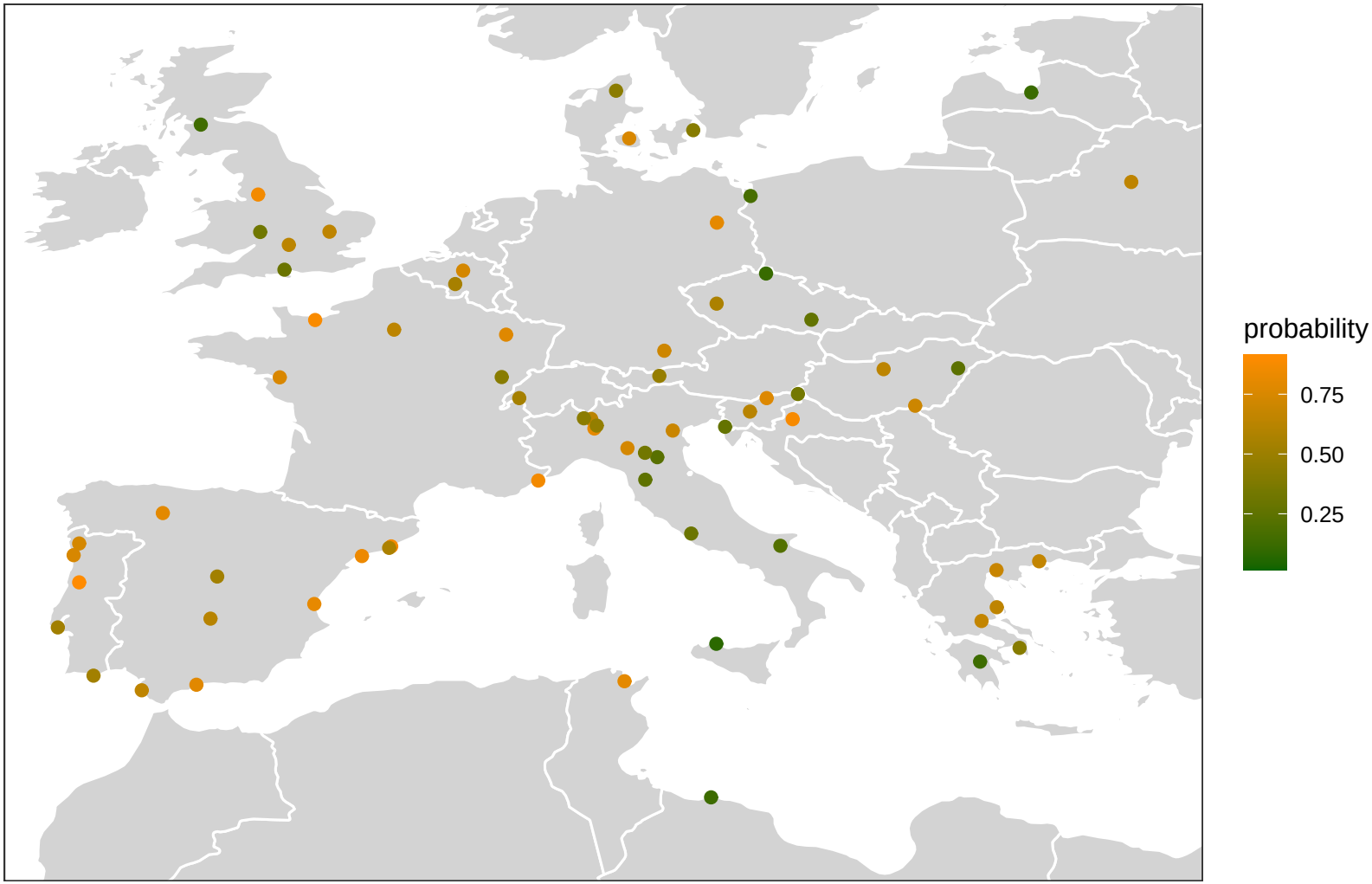

Figure 2 panel A America

Click here to access/download;Figure;Figure2PanelA_America.eps

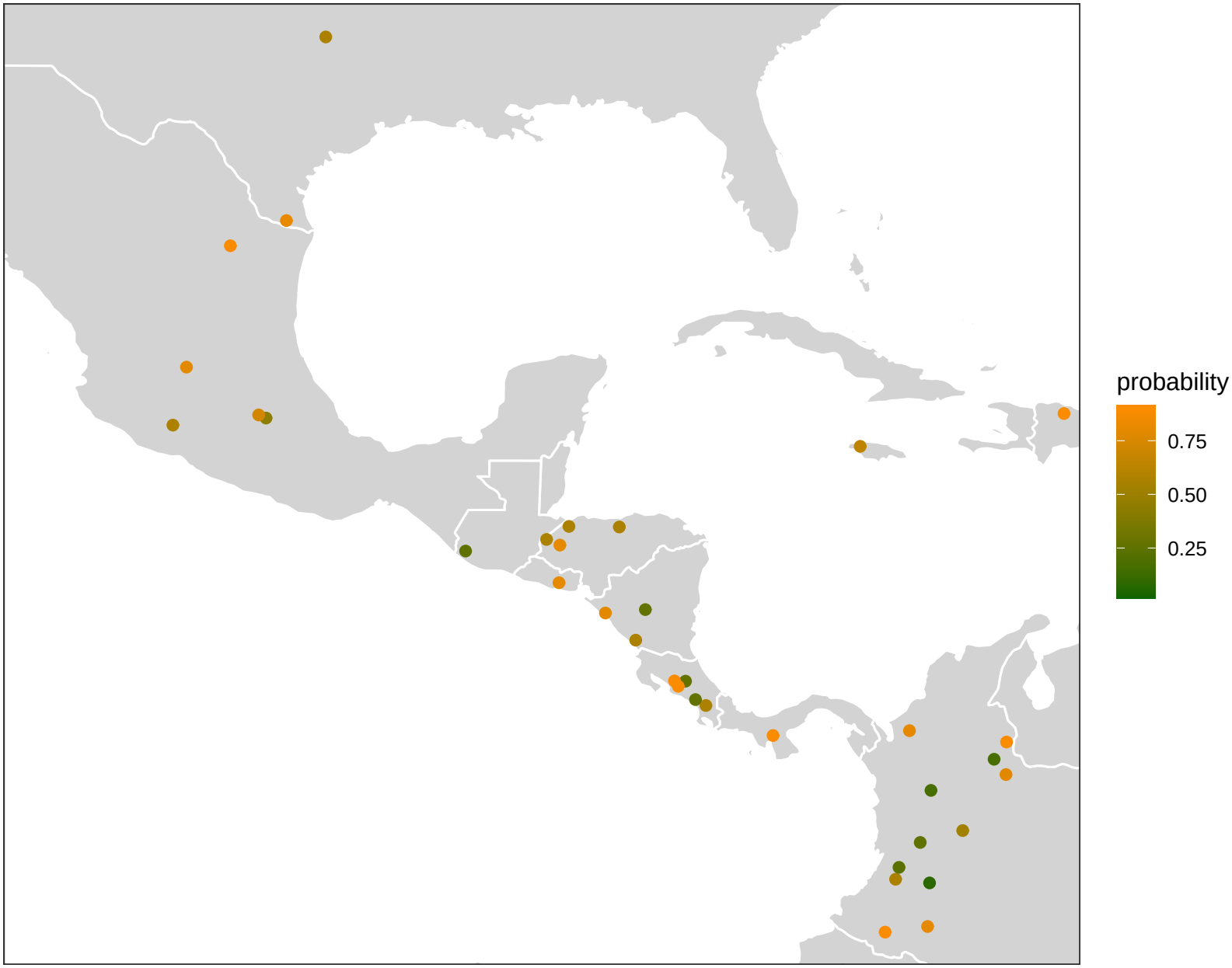

Figure 2 panel orizontal

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