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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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.

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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

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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

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).

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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)	

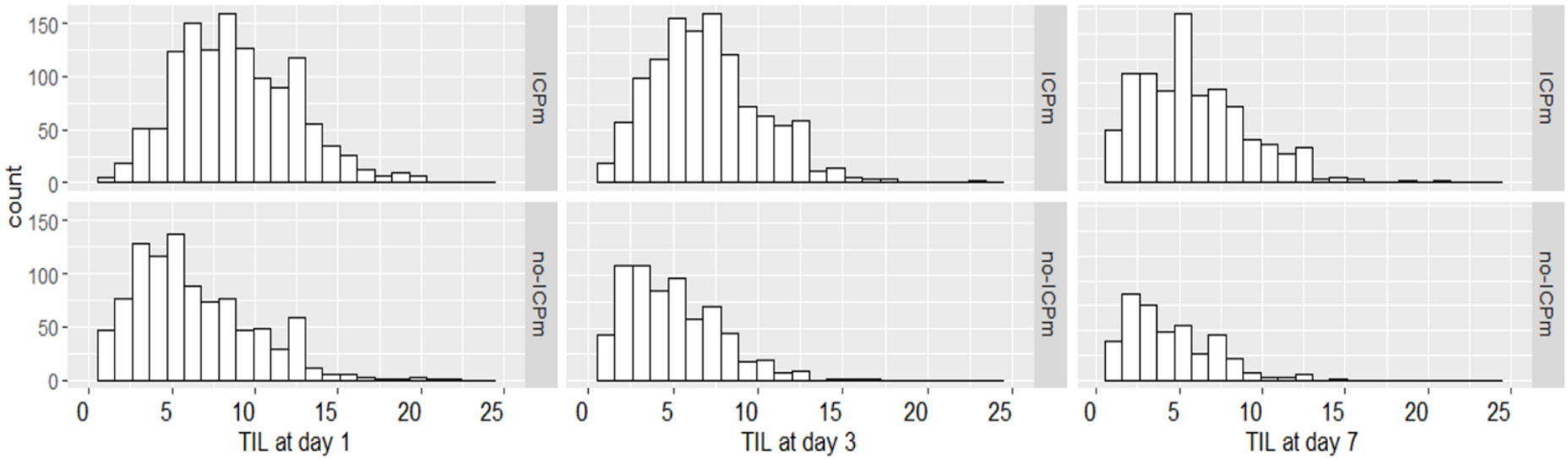
250.000-500.000	23 (16.7)	20 (19.4)	3 (8.6)	
500.000-750.000	20 (14.5)	18 (17.5)	2 (5.7)	
750.000-1.000.000	12 (8.7)	9 (8.7)	3 (8.6)	
> 1.000.000	62 (44.9)	42 (40.8)	20 (57.1)	
N of neuro care beds (mean (SD))	13.30 (10.89)	13.19 (10.29)	13.62 (12.64)	0.845
Nurse:Patient ratio in ICU, n (%)				0.256
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)

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

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Figure 1

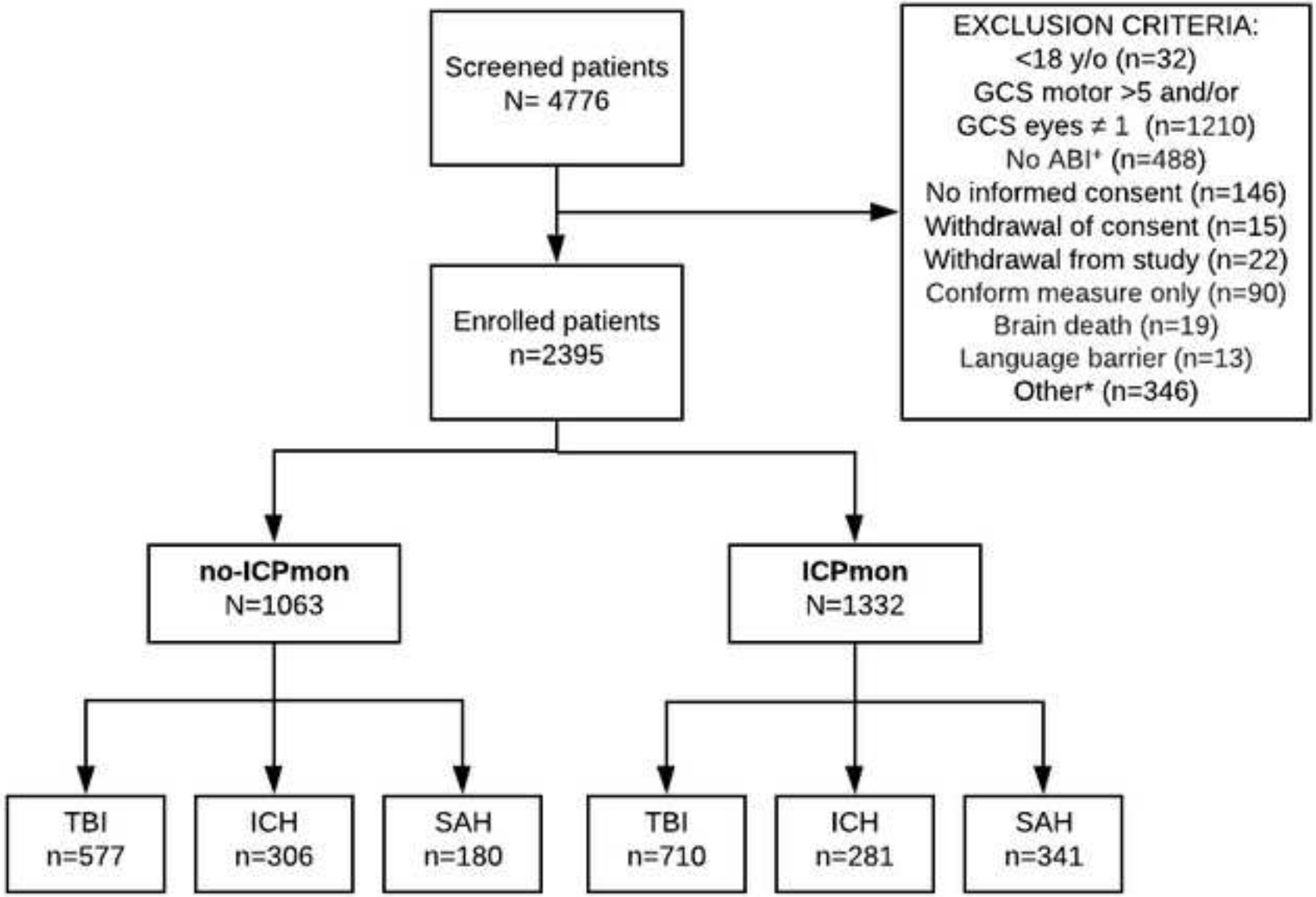

Figure 2 panel A World

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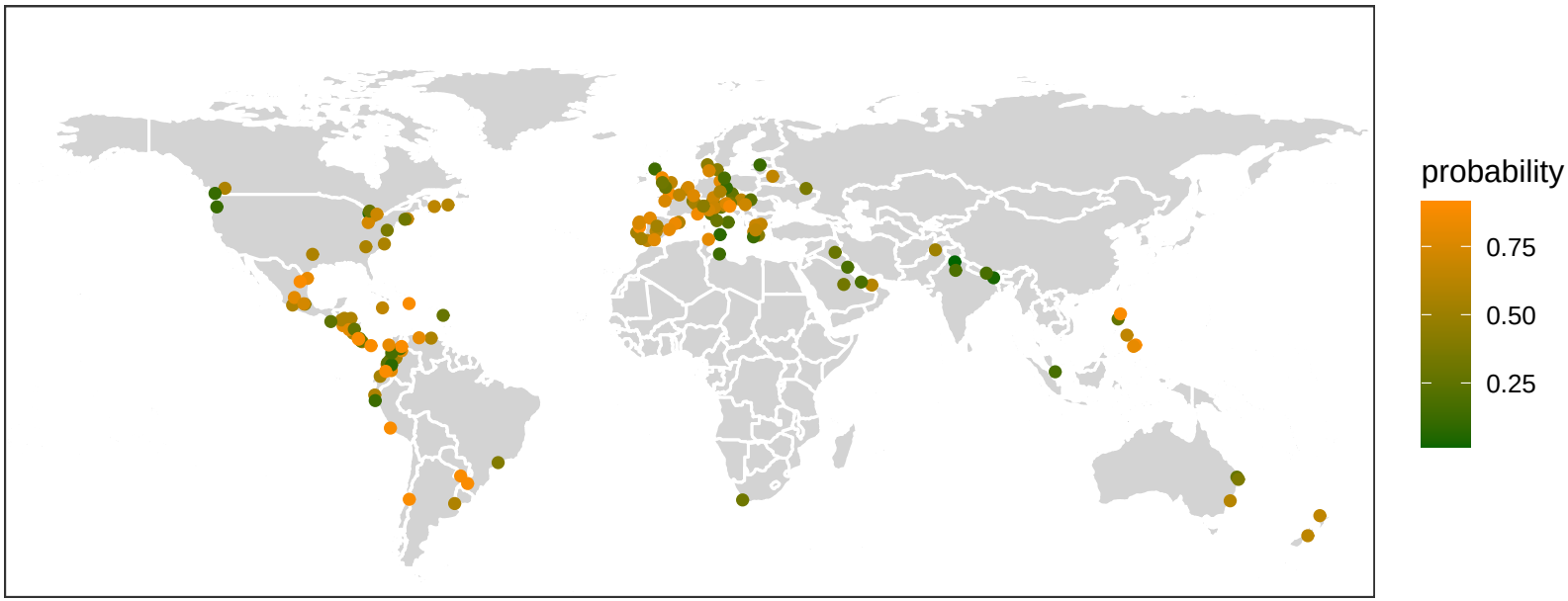

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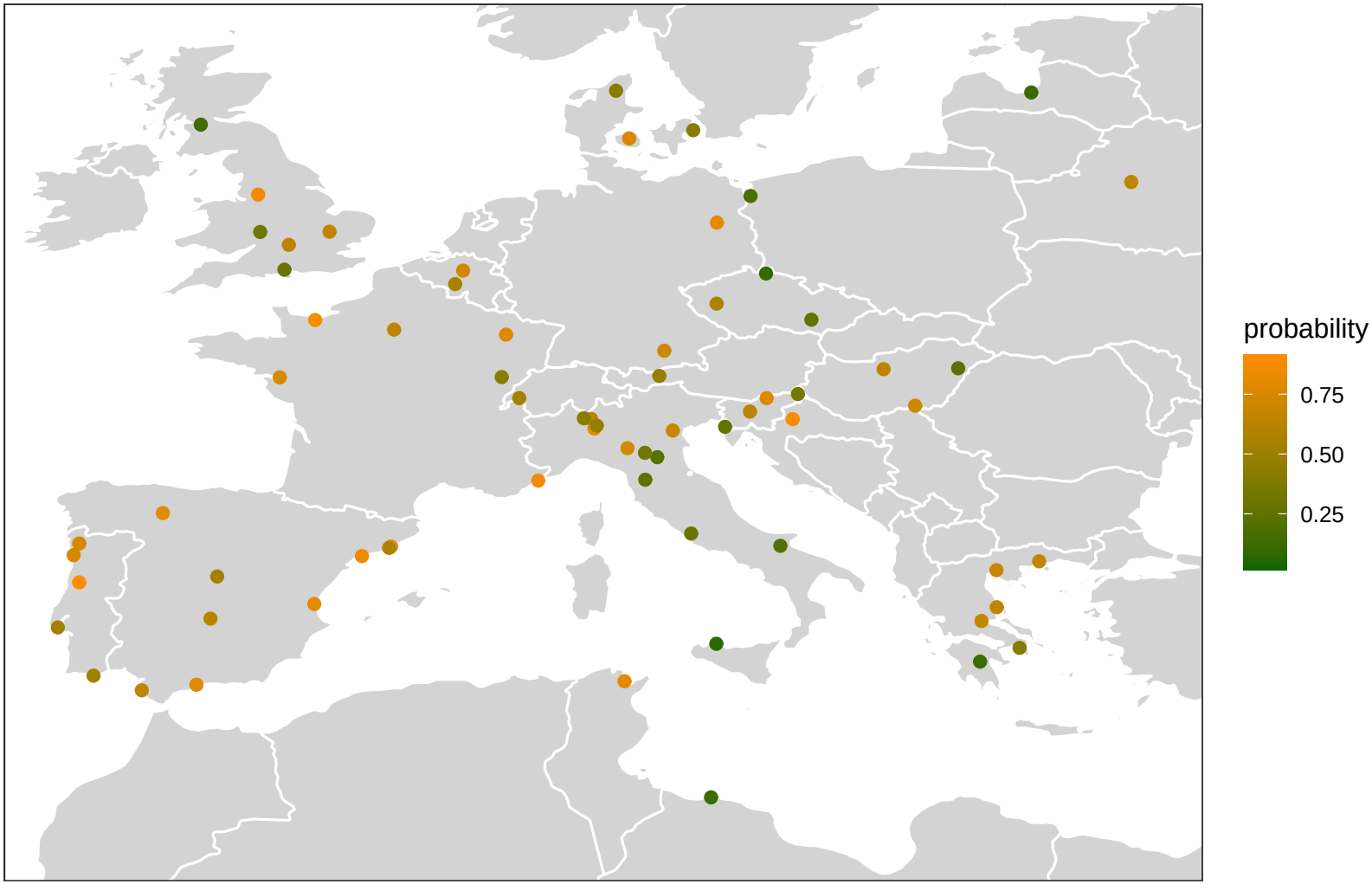

Figure 2 panel A America

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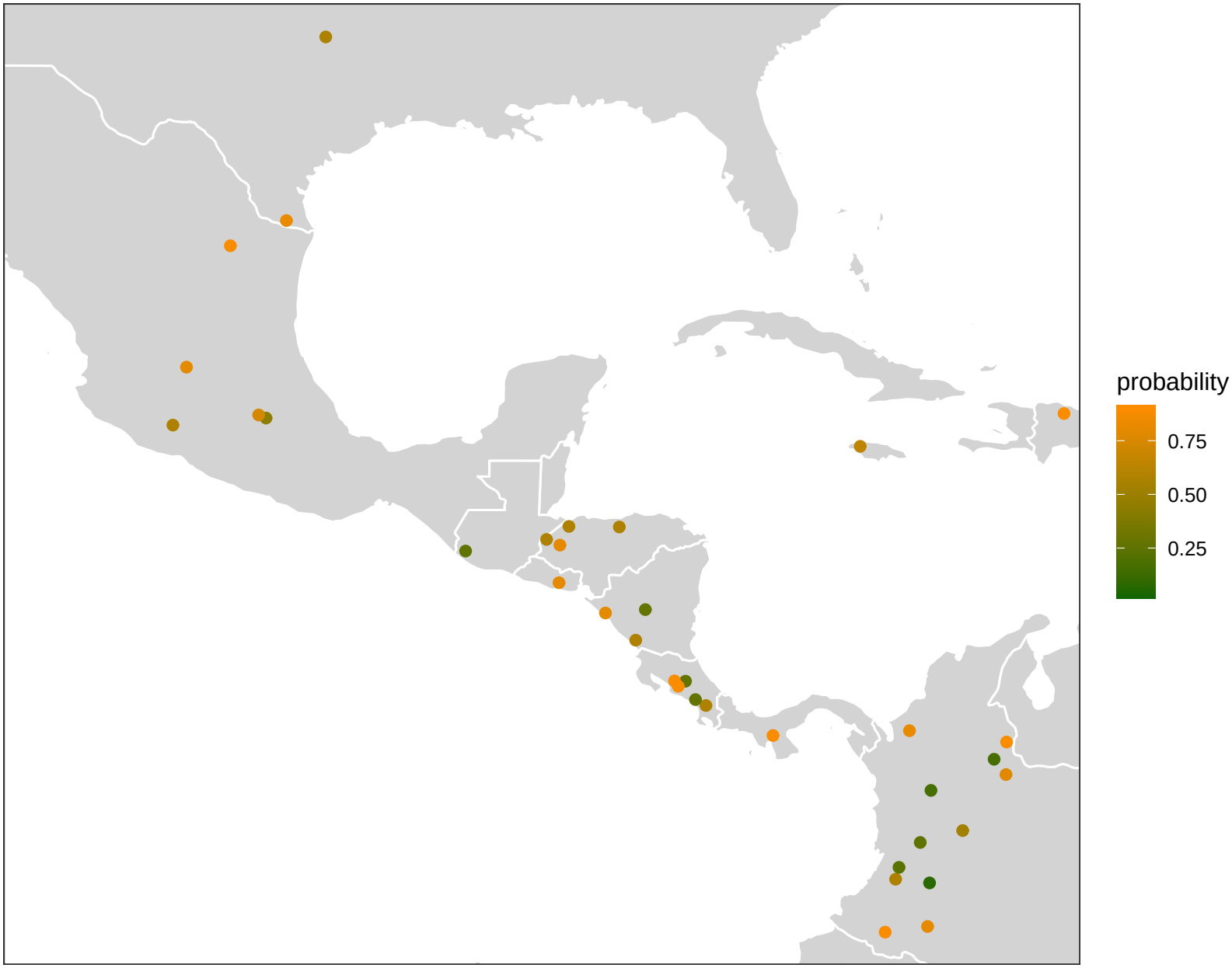

Figure 2 panel orizontal

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