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REVIEW ARTICLE

Intracranial Hypertension After Spontaneous Intracerebral Hemorrhage: A Systematic Review and Meta-analysis of Prevalence and Mortality Rate

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Abstract

The objective of this study was to determine the prevalence of intracranial hypertension (IHT) and the associated mortality rate in patients who suffered from primary intracerebral hemorrhage (ICH). A secondary objective was to assess predisposing factors to IHT development. We conducted a systematic literature search of major electronic databases (MEDLINE, EMBASE, and Cochrane Library), for studies that assessed intracranial pressure (ICP) monitoring in patients with acute ICH. Study level and outcome measures were extracted. The meta-analysis was performed using a random-effects model. A total of six studies comprising 381 patients were pooled to estimate the overall prevalence of any episode of IHT (ICP > 20 mmHg) after ICH. The pooled prevalence rate for any episode of IHT after ICH was 67% (95% CI 51–84%). Four studies comprising 239 patients were pooled in order to estimate the overall mortality rate associated with IHT. Pooled mortality rate was 50% (95% CI 24–76%). For both outcomes, heterogeneity was statistically significant, and risk of bias was nonsignificant. Reported variables correlated significantly with increased ICP were lower Glasgow Coma Scale score at admission, midline shift, hemorrhage volume, and hydrocephalus. The prevalence and mortality rates associated with IHT after ICH are high and may be underestimated. Predicting factors for the development of IHT reflect the magnitude of the primary injury. However, the results of present meta-analysis should be interpreted with caution due to methodological limitations such as selection bias of patients who had ICP monitoring, and lack of standardized IHT definition.

Keywords: Intracerebral hemorrhage, Intracranial hypertension, Intracranial pressure, Meta-analysis, Prevalence, Mortality

Introduction

Primary intracerebral hemorrhage (ICH) is defined as the abrupt eruption of blood into the brain parenchyma that may also extend to the intraventricular and subarachnoid space [1, 2]. Arterial hypertension and the use of antithrombotic–anticoagulant agents are the most prominent predisposing factors [1–3]. Morbidity and mortality are high for ICH, with a 30-day mortality rate of about 40% commonly reported [1–3]. The pathophysiology of primary and secondary brain injury from ICH is complex and includes metabolic consequences from the activation of inflammatory and neurotoxic cascades resulting from the degradation of blood components as well as mechanical aspects due to mass effect, herniation, and possibly impaired global perfusion [4–6].

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Intracranial hypertension (IHT) may occur in ICH as a result of mass effect caused by the hematoma, development of surrounding cerebral edema, expansion of the hematoma, or the alteration of cerebrospinal fluid circulation dynamics with subsequent development of hydrocephalus [5, 7–13]. IHT may thereby decrease global cerebral perfusion pressure or be manifested as compression of vital structures [2, 3, 5, 7, 14].

Despite the common concerns of mass effect and hydrocephalus after ICH, there is a paucity of data regarding the frequency and impact on outcome of IHT with most information limited to case series. Therefore, there is limited evidence regarding the role that intracranial pressure (ICP) monitoring and treatment should play in the management of patients with acute ICH. Current American or European guidelines provide some recommendations; however, the strength of these is limited by an inadequate evidence base [1, 15]. The purpose of this study was to conduct a systematic review and meta-analysis addressing the prevalence of IHT after ICH and its associated mortality rate. A secondary objective was to assess predictors of the development of IHT after ICH.

Methods

We conducted a systematic literature search of major electronic databases (MEDLINE, EMBASE, and Cochrane Library) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [16, 17]. The written protocol was registered on January 2018 in PROSPERO, The International Prospective Register of Systematic Reviews (No. CRD42018086016).

Search Strategy

The electronic search strategy is detailed in Supplemental Material. Concepts were created by using a combination of Medical Subject Heading terms and keywords. The search was limited to articles published in English from 1990 to 2018. Literature was presented, classified, and discussed by all authors. Moreover, we reviewed the citations of included references to incorporate relevant studies that were not registered in our initial search (Fig. 1).

Study Identification and Selection

Inclusion Criteria

The inclusion criteria for our study was as follows: (1) adults (>18 years) who suffered from primary ICH; (2) ICP monitoring; (3) IHT prevalence, defined as at least one episode of ICP > 20 mmHg in a patient.

Exclusion Criteria

Our study excluded pediatric patients, traumatic intracerebral hemorrhage, ICH due to secondary bleeding causes (i.e., tumor, hemorrhagic transformation of ischemic infarct or hemorrhagic infarct secondary to venous thrombosis, hemorrhage due to thrombolytics, arteriovenous malformation, aneurysm rupture), animal/in vitro, and experimental studies, as well as studies without data on ICP, or studies that did not estimate prevalence of IHT in ICH.

Data Extraction

Reviews of the literature and data extraction were performed independently. Two authors (R.A.N.P and D.A.G.) ICH screened the titles and abstracts of initial results, read relevant articles that met the inclusion criteria, and assessed the risk of bias according to PRISMA guidelines. When discrepancies in the results were identified, a third investigator was employed as a tiebreaker (J.C.H.). Relevant information was extracted from each article including authors, year of publication, geographic region, type of ICH, sample size, male/female ratio, mean age, mean Glasgow Coma Scale (GCS) score at admission, definition of IHT, number of cases of IHT, mortality in patients with IHT, functional outcome, and time to follow-up.

Definition of Terms

Intracerebral Hemorrhage

Primary non-traumatic ICH and spontaneous ICH.

Intracranial Hypertension Secondary to Intracerebral Hemorrhage

Presence of at least one episode of ICP > 20 mmHg in patients who suffered from ICH and underwent ICP monitoring.

Quality Assessment

The Newcastle–Ottawa Quality Assessment Scale was used [18]. Eight questions were performed, and each satisfactory answer received 1 point; therefore, a maximum score of 8 is defined. Studies with scores of 7 or higher were considered to be of high methodological quality. Those with scores in a range of 4–5 were considered of moderate quality. Studies with a score less than 4 were excluded from the analysis (Table 1).

Statistical Analysis

Qualitative data of nominal variables are presented as percentages. We obtained the pooled prevalence of IHT after ICH by running the commands *metaprop*

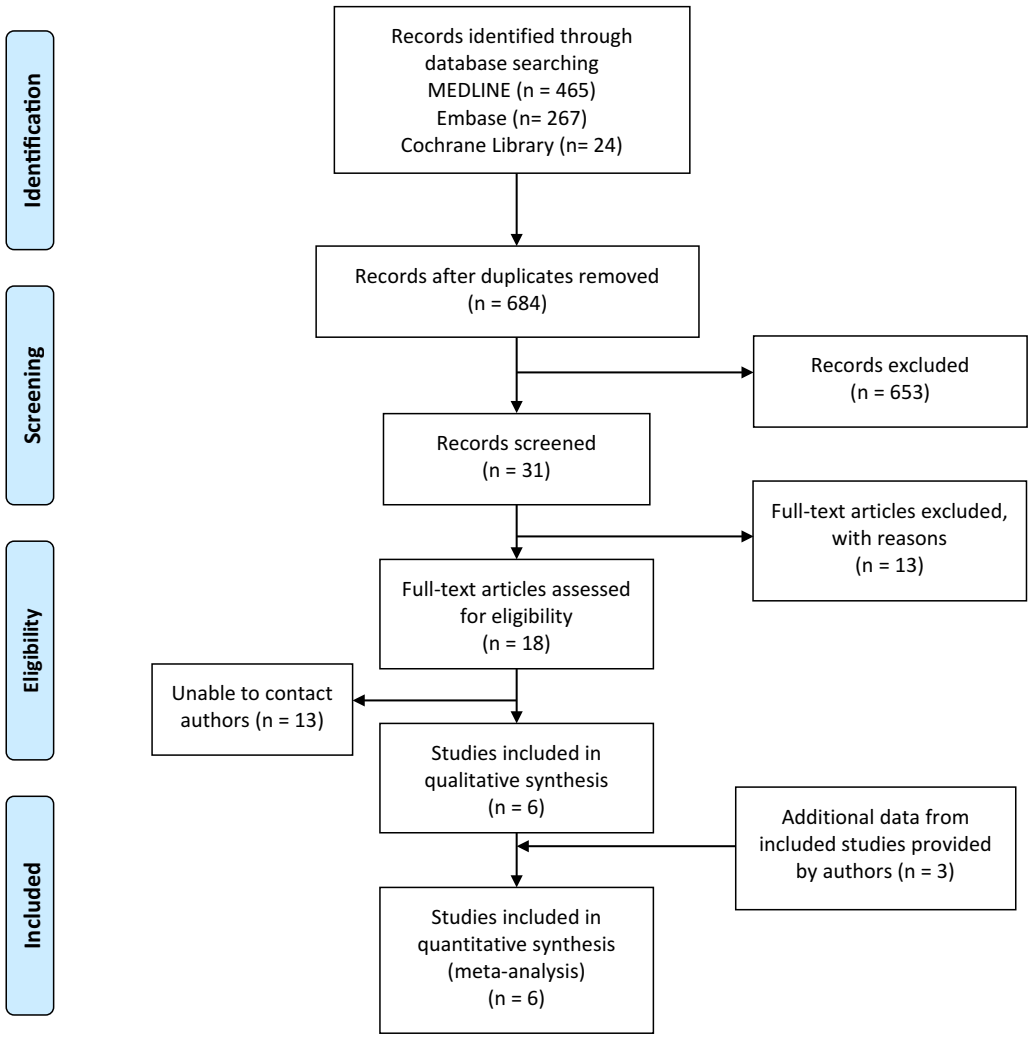

Fig. 1 PRISMA flow diagram

and *metan* in Stata version 13.0 (Stata, College Station, TX), as well as the pooled odds ratio (OR) of mortality risk secondary to IHT. Each meta-analyzed value was measured for heterogeneity and expressed as I^2, which describes the total variation across studies in terms of percentages that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, with the correspondent Chi-squared test ($I^2 < 50\%$ and $I^2 > 50\%$ considered as insignificant and significant heterogeneity, respectively). We carried out the meta-analysis using Stata version 13.0 (Stata, College Station, TX) with a random-effects model (DerSimonian and Laid Method) [19]. Bias was calculated using the *metabias* command by using effect sizes and standard errors [20].

Sensitivity Analysis

We conducted a detailed sensitivity analysis using the one-leave-out method, by sequentially removing each study and its provided prevalence rate. Sensitivity analysis was calculated using the effect size and the standard error of each study, with the *metaninf* command in Stata.

Results

Literature Identification

From the initial literature search, we identified 756 studies based on the inclusion criteria (465 from MEDLINE, 267 from EMBASE, and 24 from the Cochrane Library). After duplicates were removed, 684 potentially relevant articles were screened based on their abstract. Of those, 653 articles did not meet the inclusion criteria and were

Table 1 Newcastle–Ottawa Scale for quality assessment of studies included in this meta-analysis

Study	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at study start	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Adequacy of follow-up cohorts (≥ 5 years)	Enough follow-up period	Overall NOS score
Hara et al. [21]	★		★	★		★			4
Kamel et al. [22]	★	★	★	★	★	★		★	7
Ziai et al. [23]	★	★	★	★	★	★		★	7
Sykora et al. [24]	★	★	★	★		★		★	6
Diedler et al. [25]	★		★	★	★	★			5
Su et al. [26]	★		★	★		★		★	5

NOS Newcastle–Ottawa scale

★ Represents the study according to the item but not has statistical value

removed. The remaining 31 relevant articles were thoroughly reviewed by D.A.G and R.A.N.P. From the 18 full-text articles assessed for eligibility, 15 authors were contacted in order to obtain supplementary information for the qualitative and quantitative synthesis, and only three authors provided supplementary data to complete datasets. After including the data provided by authors, only six studies meet the inclusion criteria. A total of six studies were eligible to be included in the final analysis (Fig. 1).

Study Characteristics

Table 2 summarizes characteristics of the studies included in this meta-analysis including reference, country, baseline characteristics (study, year, type of ICH, sample size, sex, mean age, mean GCS, IHT definition, time assessment, and quality assessment) and outcomes (number of IHT cases, mortality in patients with IHT), time assessment, and quality assessment performed using Newcastle–Ottawa Scale.

Quality Assessment

Only three studies had high methodological quality, while the rest were considered to be of moderate quality. There were no studies with low-quality assessment score.

Meta-analysis

Prevalence

Figure 2a summarizes the results of the meta-analysis of prevalence. A total of six studies [21–26] comprising 381 patients were pooled to estimate the overall prevalence of any episode of IHT after ICH. Pooled prevalence rate of any episode of IHT after ICH was 67% (95% CI 51–84%). The heterogeneity was statistically significant ($I^2 = 93\%$; P for heterogeneity < 0.01) (Table 3)

Mortality Rate

Figure 2b summarizes the results of the meta-analysis of mortality rate associated with IHT. A total of four studies comprising 239 patients were pooled in order to estimate the overall mortality rate associated with IHT. Pooled mortality rate was 50% (95% CI 24–76%). Heterogeneity was statistically significant ($I^2 = 92.4\%$; P for heterogeneity < 0.01).

Qualitative Description of Reported Variables Associated with IHT Development After ICH

With the pooled data, we performed a qualitative description of reported variables of IHT after ICH. We found that some studies reported lower GCS at admission, midline shift, age, hemorrhage volume, and hydrocephalus that were correlated significantly with increased ICP ($P < 0.05$) (Table 4).

Publication Bias and Sensitivity Analysis

In general, the results of this meta-analysis were stable and reliable. Due to the small number of studies included in this meta-analysis, we did not conduct funnel plots to assess publication bias. Publication bias was found as nonsignificant for IHT prevalence (Egger's test = −5.2, P value for bias = 0.37) and IHT mortality (Egger's test = 13.4, P value for bias = 0.34).

In the sensitivity analysis, we found that the study by Diedler et al. [25] influenced the pooled prevalence of ICP after ICH. By omitting this study, we estimated a pooled prevalence of IHT of 60% (CI 95% 52–69%) and a

Table 2 Summary of demographic and baseline characteristics of included studies

Study	Year	Country	Type of ICH	N[a]	Males (%)	Mean age	Mean GCS	Time assessment	Type of monitor	Comments
Hara et al. [21]	1998	Japan	Hypertensive, spontaneous and arteriovenous malformation	21	NR	52	NR	6 h to 14 days (mean 3 days)	Epidural or intraventricular devices	ICP correlated with midline shift, Evan's ratio, ventricular changes and GCS. No correlation between ICP and hematoma volume was found
Kamel [22]	2012	United States	Hypertension (75%), vascular anomaly (11%), coagulopathy (7%), illicit drugs (5%), amyloid angiopathy (2%)	57	27 (47%)	57	10	6–38 h (median 14 h)	EVD	Site of ICH distribution: basal ganglia (30%), lobar (26%), thalamus (35%), cerebellum (9%), brainstem (0%). Radiographic parameters distribution: intraventricular hemorrhage (84%), midline shift > 1 cm (30%), herniation (12%), median hematoma volume (24 ml, IQR 11-48 ml). Median ICH score 2 (IQR 2-3). Patients who underwent surgical hematoma evacuation (19%)
Ziai et al. [23]	2012	United States	Severe intraventricular hemorrhage	100	60 (60%)	55	8	Median duration ICP monitoring 8.6 days (IQR: 7.3)	EVD	Mean IVH Graeb score: 7 (SD 3). Distribution of clot location: caudate (9%), thalamus (43%), putamen (10%), globus pallidus (8%), lobar (8%). Median ICH volume: 6 ml (IQR: 15 ml), Median IVH volume: 35 ml (IQR: 47 ml)
Sykora et al. [24]	2014	Germany	Severe ICH. Etiologies: hypertension (58.7%), coagulopathy including oral anticoagulant treatment (14.9%), AVM (12.4%), cerebral amyloid angiopathy (6.6%).	121	81 (66.9%)	60.9	NR	In-hospital	80 (66.1%) EVD, 11 (9.1%) parenchymal	Location of ICH: deep (80.2%), lobar (19.8%). ICH volume median: 41.7 ml (range: 1-162 ml, IQR: 56 ml). ICH with IVH (83.5%). NIHSS: 28 (IQR: 8-34, 18)

Table 2 (continued)

Study	Year	Country	Type of ICH	N[a]	Males (%)	Mean age	Mean GCS	Time assessment	Type of monitor	Comments
Diedler et al. [25]	2014	Germany	Spontaneous ICH. Etiologies: hypertension (60.5%), coagulopathy (10.5%), other (13.2%), not determined (15.8%)	38	NR	58	NR	Median total monitoring 78 h (IQR: 74 h)	EVD	NIHSS at admission: 30.5 (IQR: 20). Median hematoma size 36 ml (IQR: 50 ml, range: 3 to 144 ml). IVH extension (89.5%). Graeb score: 6.5 (IQR: 5). ICH location distribution: deep (84.2%), lobar (13.2%), brainstem and cerebellar (2.6%). Hematoma evacuation (5.3%)
Su et al. [26]	2017	China	Spontaneous ICH	44	33 (75%)	49.9	6.9	5 days	Parenchymal	Mean hematoma volume: ICP elevated (n = 18): 38.2 ± 3.4 ICP normal (n = 26): 36.1 ± 2.8 Hematoma location distribution (n): basal ganglia 39/44, cerebellum 5/44

AVM arteriovenous malformation, *EVD* external ventricular drain, *GCS* glasgow outcome scale, *ICP* Intracranialpressure, *ICH* Intracerebral hemorrhage, *IQR* Interquartile range, *IVH* intraventricular hemorrhage, *NIHSS* National Institutes of Health Stroke Scale, *NR* not reported

[a] Sample size

lower heterogeneity ($I^2 = 56.3$, P for heterogeneity = 0.06) (Fig. 3). This proportion is substantially different and more stable compared with the overall prevalence (Table 5).

Discussion

In this systematic review and meta-analysis, we found that intracranial hypertension was a common occurrence in patients who underwent ICP monitoring after ICH. IHT can be defined at varying levels; however, a threshold of greater than 20 mmHg is commonly used in neurocritical care and therefore was chosen for this study. At this threshold, about two-thirds of patients who underwent ICP monitoring demonstrated at least one episode of IHT. This strongly suggests that elevated ICP complicates the clinical condition of the majority of ICH patients in whom clinicians choose to use invasive intracranial pressure monitoring.

Only a small number of studies (i.e., case series, cohort studies, and randomized trials of interventions) have been previously published regarding this topic. Two studies of ICH patients with similar sample sizes reported that ICP monitoring was performed in 17% and 24% of patients, respectively [22, 26]. Specific indications for ICP monitoring are not reported in all studies. However, ICP monitoring was likely undertaken in selected populations with features of severe ICH at baseline (i.e., low GCS and serious structural alterations) [21–23, 26–30], as part of management which included surgical hematoma evacuation, or for treatment of hydrocephalus [27, 30–34]. Given the lack of standardized criteria within and across studies, it seems likely that a number of patients did not undergo ICP monitoring in the context of care limitations such as do-not-resuscitate orders or withdrawal of medical support due to perceived poor prognosis [7–11]. A decision to limit or withdraw care would exclude the most critically ill patients. In those patients, larger hematoma volumes and clinical herniation might be expected, leading to an increased theoretical likelihood of IHT. Excluding these patients implies the possibility of both underestimation of the prevalence of IHT and its association with mortality rates in the pooled results.

Current European Stroke Organization evidence-based guidelines for the management of spontaneous ICH used data solely from clinical trials and do not provide criteria for ICP monitoring [15]. American Heart Association guidelines for the management of spontaneous ICH provide a level IIb recommendation that ICP monitoring might be considered in patients with a GCS score of ≤ 8, those with clinical evidence of transtentorial herniation, or those with significant intraventricular hemorrhage or hydrocephalus [1].

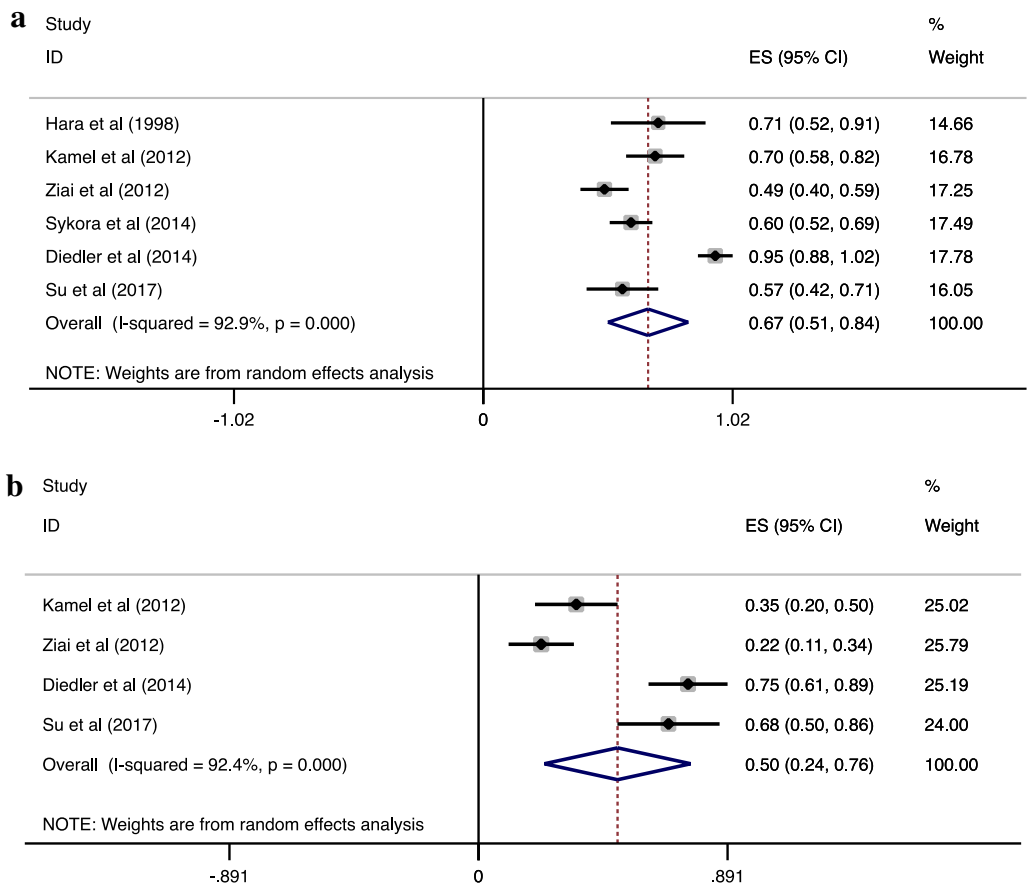

Fig. 2 **a** Forest plot of prevalence of IHT after ICH, **b** forest plot of mortality rate after IHT secondary to ICH

Table 3 Prevalence rates of IHT and associated mortality after ICH

Study	Year	N[a]	IHT cases (%)[b]	IHT mortality
Hara et al. [21]	1998	21	15 (71.43%)	NR
Kamel et al. [22]	2012	57	40 (70.17%)	14 (40%)
Ziai et al. [23]	2012	99	49 (49.49%)	11 (22.45%)
Sykora et al. [24]	2014	121	73 (60.33%)	NR
Diedler et al. [25]	2014	38	36 (94.74%)	27 (75%)
Su et al. [26]	2017	44	25 (56.82%)	17 (38.9%)

ICH intracerebral hemorrhage, *IHT* intracranial hypertension, *NR* not reported

[a] Sample size

[b] Intracranial hypertension cases and percentages

With regard to determinants of IHT after ICH, Hara et al. [21] have reported that lower GCS at admission, midline shift >6 mm, and hydrocephalus (>21% of Evans' index) were correlated significantly with increased ICP. On the other hand, in the studies performed by Kamel and Hemphill [22] and Ziai et al. [23], age, infratentorial localization, and hematoma volume were also significantly correlated with increased ICP.

In the qualitative analysis performed to assess associated factors with IHT development after ICH, we found that GCS at admission, midline shift, hematoma volume, age, and hydrocephalus were implicated with the development of IHT. All these factors clearly reflect the magnitude and severity of the primary injury; however, these findings are not reliable. This fact would be explained due to the inconsistent report of these determinants and the small sample sizes of studies in order to obtain powerful conclusions. Additionally, a common determinant of IHT was not consistently reported across the included studies.

Although this study was not designed to describe temporal profiles of ICP evolution, the exhaustive literature review did not allow us to conclude anything with regard to this matter due to the lack of data about this point and due to the variability of protocols in terms of duration of ICP monitoring in the included studies [21–26].

Table 4 Qualitative description of reported variables associated with IHT development after ICH

Study	Demographic		Clinical			Radiological				
	Sex	Mean age	Cause of ICH	GCS	ICH/ Graeb score	ICH location	Hematoma volume	Ventricular changes[a]	Midline shift	Hydrocephalus/ Evans' index
Hara et al. [21]	–	–	–	IS	–	–	NS	NR	IS (> 6 mm, $P < 0.05$)	IS (> 21%, $P < 0.05$)
Kamel et al. [22]	NS	IS	NS	NS	NS	NS	NS	NS	NS	–
Ziai et al. [23]	–	–	–	NS	NS	NS	IS	NR	–	–
Sykora et al. [24]	–	–	–	–	–	–	–	–	–	–
Diedler et al. [25]	–	–	–	–	–	–	–	–	–	–
Su et al. [26]	NS	NS	–	NS	–	NS	NS	–	–	–

GCS glasgow outcome scale, *ICH* Intracerebral hemorrhage, *IS* included in model, significant ($P < 0.05$), *NS* included in model, not significant, *NR* included in model, significance not reported; – not included in model

[a] Ventricular changes defined by author

Table 5 Sensitivity analysis

Study omitted	Year	Effect size	95% Confidence Interval	
IHT prevalence				
Hara et al. [21]	1998	0.66	0.48	0.85
Kamel et al. [22]	2012	0.67	0.47	0.87
Ziai et al. [23]	2012	0.71	0.54	0.88
Sykora et al. [24]	2014	0.69	0.48	0.89
Diedler et al. [25]	2014	0.60	0.52	0.69
Su et al. [26]	2017	0.69	0.50	0.88
Combined		0.67	0.51	0.84
IHT mortality				
Kamel et al. [22]	2012	0.48	0.40	0.57
Ziai et al. [23]	2012	0.59	0.50	0.68
Diedler et al. [25]	2014	0.35	0.27	0.44
Su et al. [26]	2017	0.41	0.34	0.49
Combined		0.45	0.38	0.52

We were unable to estimate the association between ICP elevation and its duration with relevant clinical outcomes due to the heterogeneous design of the included studies. However, a number of studies have attempted correlating frequency and duration of IHT with clinical endpoints. Ziai et al. reported from a clinical trial population that proportion of ICP readings > 30 mmHg and intraventricular hemorrhage volumes were independent predictors of 30-day mortality and poor functional outcome. In addition, proportion of ICP readings > 20 mmHg were significantly associated with initial intraventricular hemorrhage (IVH) volume [23]. In the study performed by Hara et al. [21], ICP > 20 mmHg was correlated with changes in configuration of the lateral ventricles, intraventricular hemorrhage, and compression of the basal cisterns and cortical sulci. Kamel and Hemphill [22] reported that IHT was not independently associated with functional outcome (modified Rankin Scale score), defining intracranial hypertension as either any ICP > 25 mmHg, the number of ICP elevations, or the area under the curve of ICP elevation. Possible confounders in this study were surgical evacuation in 19% and early "do-not-resuscitate" orders in 25%.

The true impact of IHT on mortality is controversial; a number of studies have found a significant association between IHT and mortality [23, 32, 35–37], while other studies did not show association with final outcome [22, 27, 30–32]. Studies performed during the decade of 1970–1980 reported that more than 65% of the deaths occurred in patients without IHT [27, 30, 31]. Thirty years later, Kamel and Hemphill [22] reported after excluding patients with early do-not-resuscitate orders that IHT should not be considered as an independent factor associated with final outcome. Ziai et al. [23] reported association between IHT and mortality in patients with severe intraventricular hemorrhage and hematomas < 30 cc particularly when ICP readings were > 30 mmHg.

The method used for ICP measurement was variable among authors of the included studies. Four out of six authors reported external ventricular drain (EVD) as method of ICP measurement. Kamel and Hemphill [22] and Sykora et al. [24] did not define an ICP threshold for cerebrospinal fluid (CSF) drainage although the former reported that patients with primarily intraventricular hemorrhage often needed CSF drainage in order to treat hydrocephalus. Diedler et al. [25] reported goals of ICP < 20 mmHg and cerebral profusion pressure > 60 mmHg during EVD use for ICP monitoring. Ziai

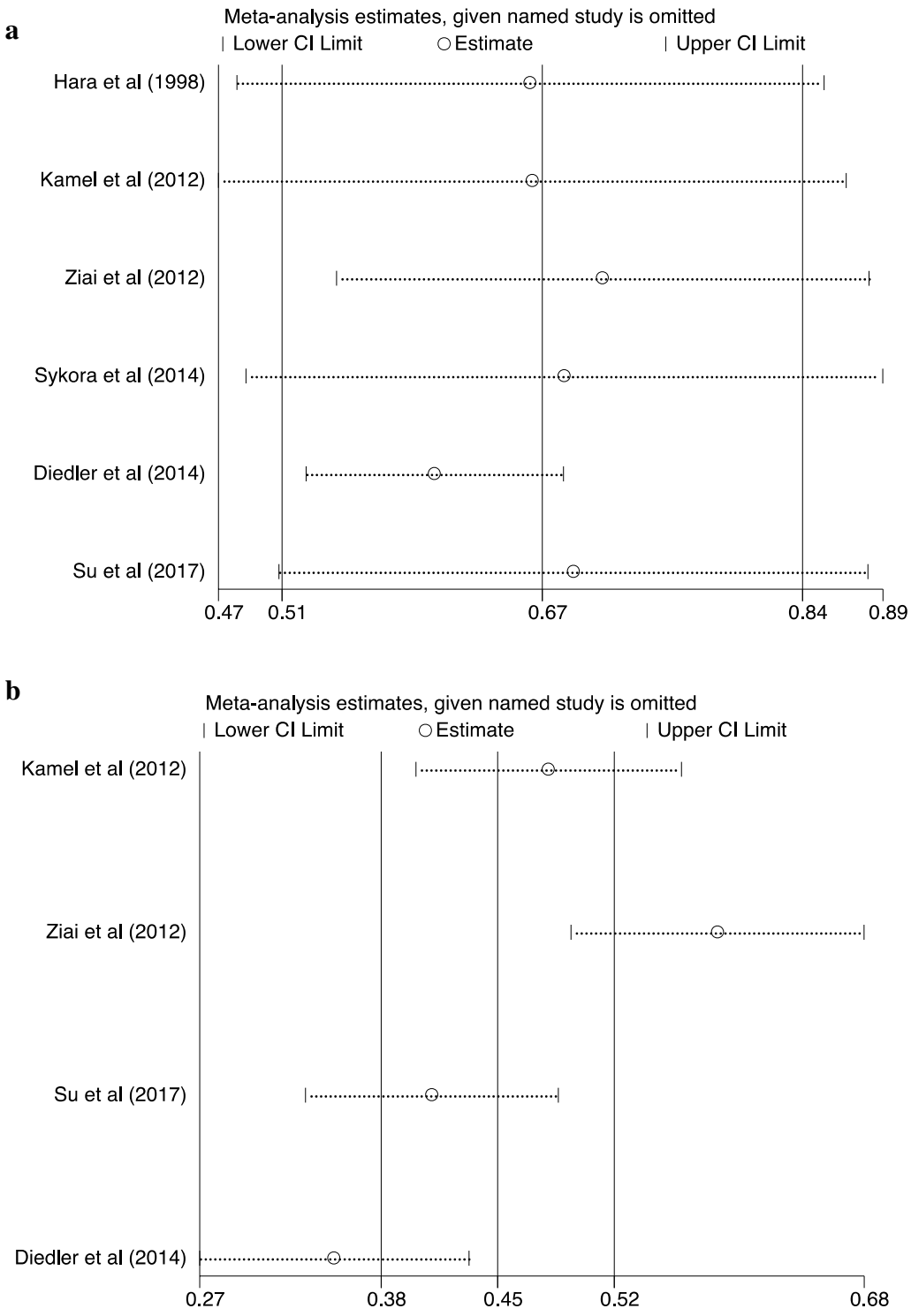

Fig. 3 **a** Sensitivity analysis of IHT prevalence, **b** sensitivity analysis of IHT mortality rate

et al. [23] reported a protocol of continuous CSF drainage with drainage level determined by each site. During monitoring, ICP elevation > 20 mmHg occurred in 8.5% of all *q* 4-h readings after initiation of external CSF drainage for spontaneous IVH with associated hydrocephalus. EVD closure-related ICP elevation, however, was

approximately 25% during protocolized 1-h closure periods, indicating that many patients are highly dependent on CSF drainage to control ICP, or have refractory ICP and that EVDs left open to drain may mask ICP elevations during periods of drainage compared to monitoring. In this scenario, leaving the EVD open, with high dependence on CSF drainage may have underestimated the prevalence of IHT in this study. Recent advances in EVDs allowing simultaneous parenchymal ICP monitoring and CSF drainage were not available during the study period [38].

Our meta-analysis found a high mortality rate (72%) in patients with IHT after ICH, but does not provide clarity on the relative contribution of IHT to patient death. Future studies, likely large prospective cohorts in nature, will be necessary in order to determine whether the treatment of elevated ICP improves patient outcome after ICH.

Limitations and Strengths

This study has several important limitations. A major limitation is confounding by indication to monitor ICP, which could spuriously increase the measured prevalence of intracranial hypertension after ICH. Second, as the protocol for measuring and treating ICP was not standardized across studies, significant heterogeneity exists among patients who were selected for ICP monitoring, treatment protocols, and duration of follow-up. As a consequence, theoretical heterogeneity was high ($I^2 = 93\%$ and 92.4% for IHT prevalence and mortality rate, respectively). These factors along with the fact that moribund patients may not have undergone monitoring, or that some patients who had surgical interventions (clot evacuation or hemicraniectomy) may have had elevated ICP but no monitoring, limit the generalizability of this study. Third, the definition of IHT used does not consider the frequency, depth, and duration of episodes, nor temporal profile or ICP variability. While this definition does allow multiple studies to be pooled for the purpose of meta-analysis, it considers a patient with a single episode of elevated ICP equivalent to one with many episodes or refractory IHT. Likewise, the aggressiveness of treatment to maintain an ICP less than 20 mmHg is not sufficiently captured. It is therefore difficult to isolate the effect of elevated ICP on mortality, given that burden of ICP was not available and that ICP may be a marker of other factors that predict death. Fourth, despite the high occurrence of ICH, the sample size of this meta-analysis is small, owing to the limited number of publications on this topic with sufficient quality and data to be included. Due to lack of sufficient per patient data, we were unable to perform a multivariate analysis which precludes defining a relationship between mortality and elevated ICP based on these data. For standardization purposes in future prospective studies, we consider as a proper definition of intracranial hypertension, ICP > 20 mmHg for more than 30 min of duration [39]. ICP elevations under 30 min of duration should be considered as transient elevations.

Despite these limitations, this study has several strengths. The systematic literature review was detailed and exhaustive. To our knowledge, this is the first meta-analysis aiming to estimate the overall prevalence of IHT and its associated mortality rate as well as associated factors of IHT after ICH. The sensitivity analysis shows that by omitting the study by Diedler et al. the heterogeneity is lower, leading to more reliable results. Despite significant heterogeneity, however, the included studies encompass the full spectrum of severe ICH in terms of hematoma size, location, and inclusion of both parenchymal and intraventricular ICP monitors. All indications for ICP monitoring in ICH are covered by the included studies which cause heterogeneity, but also increase generalizability.

Although this study cannot make treatment recommendations regarding ICP monitoring or management, it is hoped that this study will motivate further prospective research addressing the adverse consequences of elevated ICP and whether ICP is a "modifiable" therapeutic target beyond its current status as a marker of poor outcome. Consideration should be given to study designs such as that used in the BEST TRIP trial [40] which investigated protocols of aggressive treatment of intracranial hypertension, one driven by monitored ICP and the other based on current practices at many centers today, involving serial neurological examination and computed tomography imaging. Only with such prospective investigation can we clarify the impact of IHT and its treatment on outcome after intracerebral hemorrhage.

Conclusions

The prevalence and mortality rates associated with IHT after ICH are high and may be underestimated. The prevalence of IHT in this analysis may be higher than 67% due to the exclusion of outliers such as patients with limitation or withdrawal of active treatment and those who were monitored using an open EVD system. In addition, increased risk of selection bias of patients who had ICP monitoring and lack of standardization of IHT definition in terms of the duration of ICP elevations represent important limitations in this study. We cannot conclude, therefore, that there is a relationship between mortality and elevated ICP based on these data.

Abbreviations
ICH: Intracerebral hemorrhage; ICP: Intracranial pressure; GOS: Glasgow Outcome Scale; IHT: Intracranial hypertension; EVD: External ventricular drain; IVH: Intraventricular hemorrhage; CSF: Cerebrospinal fluid.

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Author Contribution
DAG: design of the study, definition of intellectual content, literature search, data acquisition, data analysis, manuscript editing and manuscript preparation. RAN: design of the study, definition of intellectual content, literature search, data acquisition, data analysis, statistical analyses, manuscript editing and manuscript preparation. AZ: design of the study, data analysis, statistical analyses and manuscript editing. WCZ, JCH: definition of intellectual content, data acquisition, data analysis and manuscript editing.

Source of support
None.

Compliance with ethical standards

Conflict of interest
Daniel A. Godoy, Rafael A. Núñez-Patiño, Andres Zorrilla-Vaca and J. Claude Hemphill declares that they have no conflict of interest and Dr. Ziai reports personal fees from Headsense, Inc., outside the submitted work.

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