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ORIGINAL ARTICLE

Intracerebral Hemorrhage Location and Functional Outcomes of Patients: A Systematic Literature Review and Meta-Analysis

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Abstract

Background and Purpose Intracerebral hemorrhage (ICH) has the highest mortality rate among all strokes. While ICH location, lobar versus non-lobar, has been established as a predictor of mortality, less is known regarding the relationship between more specific ICH locations and functional outcome. This review summarizes current work studying how ICH location affects outcome, with an emphasis on how studies designate regions of interest.

Methods A systematic search of the OVID database for relevant studies was conducted during August 2015. Studies containing an analysis of functional outcome by ICH location or laterality were included. As permitted, the effect size of individual studies was standardized within a meta-analysis.

Results Thirty-seven studies met the inclusion criteria, the majority of which followed outcome at 3 months. Most studies found better outcomes on the Modified Rankin Scale (mRS) or Glasgow Outcome Score (GOS) with lobar compared to deep ICHs. While most aggregated deep structures for analysis, some studies found poorer outcomes for thalamic ICH in particular. Over half of the studies did not have specific methodological considerations for location designations, including blinding or validation.

Conclusions Multiple studies have examined motor-centric outcomes, with few studies examining quality of life (QoL) or cognition. Better functional outcomes have been suggested for lobar versus non-lobar ICH; few studies attempted finer topographic comparisons. This study highlights the need for improved reporting in ICH outcomes research, including a detailed description of hemorrhage location, reporting of the full range of functional outcome scales, and inclusion of cognitive and QoL outcomes.

Keywords Intracranial hemorrhage · Meta-analysis · Quality and outcomes · Activities of daily living

Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15 % of all strokes but is associated with the highest mortality rate (40–50 %) [1, 2] of all subtypes. However, compared to ischemic stroke, ICH survivors may exhibit greater improvement in short- [3] and long-term recovery [4]. Injury location is an established outcome predictor in both ischemic stroke [5] and ICH [6, 7], but the extent to which it is categorized varies. While ischemic stroke research commonly utilizes specific topographic schema [5] (e.g., globus pallidus versus putamen), most ICH studies focus on differences between lobar and non-lobar hemorrhage [6, 7]. This discrepancy has started to bring attention to ICH studies attempting finer neuroanatomic comparisons [8–10], which have not been reviewed in the literature.

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Most prediction tools that utilize ICH location [6, 7] have based their outcomes on mortality or the Modified Rankin Scale (mRS). While prevalent, the mRS is biased toward motor disability [5], neglecting cognitive, emotional, and psychosocial domains. Since these additional domains can also be localized to regions of interest, more precise ICH locations may provide valuable insight on overall prognosis. This descriptive review compiles all studies that evaluated functional outcome by ICH location and considers different location classification schemes. The purpose of this analysis is to (1) enumerate differences in location comparisons and outcome measures, (2) compile our understanding of how ICH location influences prognosis, and (3) discuss shortcomings of current work and future avenues of research.

Methods

Literature Search

A systematic review was undertaken using PRISMA guidelines. A search of the OVID MEDLINE Database (1946–2015) using both MeSH terms and unindexed studies was conducted on August 7, 2015. To ensure the parameters were sensitive enough to capture all studies of interest, 13 studies from a previous preliminary search were used to validate the literature review. Keywords and filters were adjusted until all 13 studies were captured within the final search. The search criteria are outlined in the online supplement (Table I).

Evaluation of Studies

The evaluation of the studies was completed by A.S. and summarized in Fig. 1. Inclusion criteria included any study on the outcome of nontraumatic ICH patients. The exclusion criteria were (1) case reports or meta-analyses, (2) studies exclusively on pregnant or pediatric subjects, (3) inclusion of other neurovascular diseases within the analysis (e.g., ischemic stroke, subarachnoid hemorrhage, vascular malformation, etc.), or (4) outcome limited to mortality or complication (e.g., repeat hemorrhage, seizure, etc.). The methods of the remaining studies were reviewed to ensure that they included a location classification scheme and a statistical analysis that compared outcome by location category. Only studies reporting a statistical analysis were considered for further review.

Details regarding abstracted variables from individual studies are provided in the online supplement (Table II). Due to the fact that studies utilizing the Glasgow Outcome Scale (GOS) employed different numerical designations for outcomes, the numbers were standardized to allow for comparisons across papers (1 = death, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = good recovery).

Statistical Analysis

A meta-analysis was conducted for a subset of studies within the review that utilized similar outcome scales, mRS or GOS. Odd ratios were calculated using the most common designation of location (i.e., lobar versus deep or non-lobar). As in previous meta-analyses [11], the mRS and GOS cutoffs of the original studies were utilized and matched to compare between scales (i.e., mRS 3 equivalent to GOS 4). Three studies [1, 12, 13] were excluded because location designation did not match the meta-analysis, and six studies [6, 8, 9, 14–16] did not provide the primary data required for the analysis. Odds ratios, weighted odds ratios (Mantel–Haenszel method [17]), 95 % confidence intervals (CI), and p values of the remaining studies were calculated using Microsoft Excel for Mac 2011 Version 14.1.0 (Microsoft Corporation, Redmond, WA, USA).

Results

Location Designations and Outcome Measures

The location comparisons used for analysis of the 37 studies are detailed in Table 1; the predominant categorization was lobar versus deep or non-lobar ICH. Seventeen unique outcome measures were employed across all studies, summarized in Table 2. The majority utilized the mRS or GOS, with operational definitions of "good" outcome varying between studies. Study design, methodological considerations, and conclusions of all 37 studies are summarized in the online supplement (Table III; Table IV). Methodological considerations to control biases included obtaining location via chart review [18], blinding the abstractors [1, 6, 19–25], calculating interobserver agreement [21], or providing neuroanatomical definitions for location designation [13, 19, 25–29].

Outcomes: Lobar ICH

Lobar ICH was associated with better functional outcomes at 3, 6, and 12 months on the GOS [6, 24, 27] and the mRS [20, 26, 30–32] ($p < 0.05$ for all studies). Additionally, lobar ICH was associated with better quality of life at 3 months [16] (OR 3.05, $p = 0.003$). Conversely, one study [33] suggested worse outcomes (OR 2.2, $p = 0.028$) for lobar ICH at 1 year. Lobar ICH was also associated with greater cognitive impairment (OR 14.1, $p = 0.016$) in

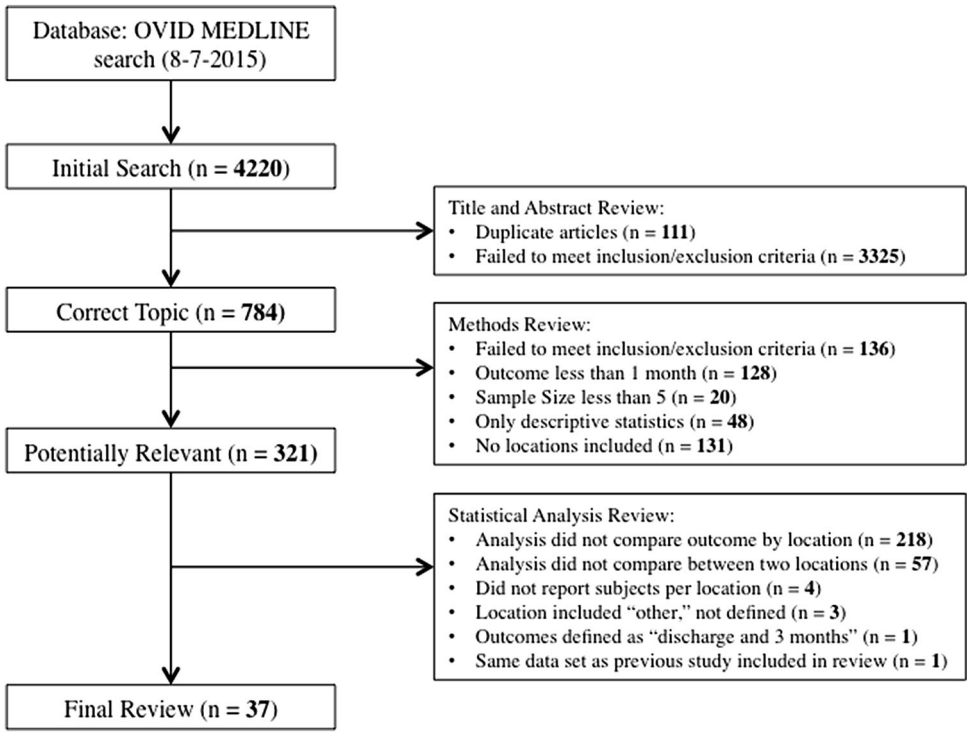

Fig. 1 Flowchart outlining study selection

one cross-sectional study [34]. Comparisons within the lobe (i.e., frontal, parietal, temporal, occipital) suggested differences between different lobar regions utilizing the GOS [13] ($p = 0.01$); no follow-up statistics were provided. Six studies did not show any significant results in regard to lobar ICH [19, 23, 25, 28, 29, 35, 36].

Outcomes: Basal Ganglia, Thalamic, Putaminal ICH

Select studies examined the role of deep ICH specifically, compared to lobar and infratentorial locations combined. In these analyses, deep ICH was associated with worse outcomes on the mRS at 1 month [37] and 3 months [23] ($p < 0.02$ for both studies).

The influence of thalamic ICH on outcome was studied specifically in five studies. While two studies [28, 47] did not show statistical significance [14, 30], one study [38] suggested poor outcomes on the mRS at 6 months for thalamic ICH (OR 15.637, $p = 0.026$). Patients with these bleeds also showed worse gains in mobility compared to other deep ICH [39] ($p < 0.05$). Comparisons between nuclei of the thalamus suggested better outcomes specifically for lateral thalamic nuclei compared to all other thalamic nuclei [12] ($p < 0.025$).

Putaminal ICH was specifically analyzed in three studies [17, 28, 56]; however, none of these studies achieved statistical significance. One of these studies [39] did exhibit a trend toward worse gains in mobility for putaminal ICH compared to other deep ICH ($p = 0.058$). Finally, comparisons between putaminal and thalamic ICH did not achieve statistical significance [10, 40].

Outcomes: Infratentorial ICH

Comparisons between supratentorial and infratentorial locations suggested poor mRS outcomes for infratentorial ICH at 3 months [23] and 1 year [1] ($p < 0.03$ for both studies). However, one study [27] reported better outcomes for cerebellar ICH compared to all other locations at 1 year using the GOS (OR 0.13, $p = 0.04$).

Outcomes: Laterality

The influence of laterality of hemorrhage was studied in 11 studies, with eight studies [14, 26, 28, 31, 32, 35, 41, 42] reporting nonsignificant results. One study [30] reported better mRS outcomes for left-sided ICH ($p = 0.034$), while another [15] suggested worse GOS outcomes for this side ($p = 0.013$). Right-sided ICH showed poorer ability to discriminate objects compared to left-sided ICH in one cross-sectional study [18] ($p = 0.009$).

Meta-Analysis: Lobar Versus Non-lobar Hemorrhages

Odds ratios were constructed using available data from 21 studies and presented in Fig. 2. The ratios reflect the odds

Table 1 Types of location analysis schemes utilized by the 37 studies within the review

Ref #	Location comparison in analysis	Laterality analysis	Location restrictions
[6]	Lobar vs. non-lobar	No	None
[16]	Lobar vs. non-lobar	No	None
[29]	Lobar vs. non-lobar	No	None
[36]	Lobar vs. non-lobar	No	None
[33]	Lobar vs. non-lobar	No	None
[34]	Lobar vs. non-lobar	No	None
[30]	Lobar vs. non-lobar; thalamus vs. non-thalamus	Yes	Supratentorial
[23]	Lobar vs. non-lobar; deep vs. non-deep; supratentorial vs. infratentorial	No	None
[19]	Lobar vs. deep	No	Supratentorial
[20]	Lobar vs. deep	No	Supratentorial
[25]	Lobar vs. deep	No	None
[26]	Lobar vs. deep	Yes	Supratentorial
[28]	Lobar vs. deep	Yes	Supratentorial
[35]	Lobar vs. deep	Yes	Supratentorial
[31]	Lobar vs. deep	Yes	Supratentorial
[32]	Lobar vs. deep	Yes	Supratentorial
[24]	Subcortical vs. non-subcortical	No	None
[27]	Subcortical vs. non-subcortical; cerebellar vs. non-cerebellar	No	None
[1]	Supratentorial vs. infratentorial	No	None
[37]	Ganglio-thalamus (GT) vs. non-GT	No	None
[38]	Thalamus vs. non-thalamus	No	None
[39]	Thalamus vs. deep; putamen vs. deep	No	Deep
[10]	Thalamus vs. putamen	No	Thalamus/Putamen
[40]	Thalamus vs. putamen	No	Thalamus/Putamen
[12]	Lateral nuclei vs. non-lateral nuclei	No	Thalamus
[14]	Putamen vs. lobar; thalamus vs. lobar	Yes	Supratentorial
[8]	Putamen vs. non-putamen	No	Supratentorial
[9]	Across all locations[a]	No	None
[13]	Across all locations[a]	No	Lobar
[21]	Across all locations[a]	No	None
[22]	Across all locations[a]	No	Supratentorial
[41]	Across all locations[a]	Yes	None
[46]	Across all locations[a]	No	None
[47]	Across all locations[a]	No	None
[18]	N/A[b]	Yes	Supratentorial
[15]	N/A[b]	Yes	Supratentorial
[42]	N/A[b]	Yes	Basal Ganglia

[a] ANOVA conducted to compare differences among all locations in study, rather than dicotomous comparisons

[b] Only laterality examined

of poor outcome, defined by the individual studies, for lobar ICH compared to deep/non-lobar ICH. Eight studies [24, 30, 31, 37–39, 41, 43] in the meta-analysis achieved statistical significance matching the initial conclusions of the original papers [20, 26, 27, 30–33, 37]. The weighted odds ratio was significant for studies utilizing mRS >3 or GOS <4 for poor outcomes (Fig. 2b).

Discussion

This is the first systematic review to investigate differences in functional outcome of ICH patients by various location classification schemes. Our literature search identified 37 studies, 21 of which were included in a meta-analysis (Table 1; Fig. 2). Most studies concluded better lobar ICH

Table 2 Outcome measures of 37 studies in review

Ref #	Sample size (n)	Follow-up time	Outcome measures	Cutoff of "Good Outcome"
[6]	629	3 months	GOS[a]	GOS >2
[16]	584	3 months	EQ-5D	Used as a scale
[29]	128	12 months	mRS	mRS < 3
[36]	546	3 months	HDRS[b]	See legend[b]
[33]	460	12 months	mRS	mRS < 3
[34]	83	Median 3.8 years	MoCA[c]	See legend[c]
[30]	585	3 months	mRS	mRS < 4
[23]	252	3 months	mRS	mRS < 3
[19]	48	3 months	mRS	mRS < 3
[20]	138	3 months	mRS	mRS < 3
[25]	323	3 months	mRS	mRS < 3
[26]	185	6 months	mRS	mRS < 3
[28]	60	6 months	mRS	mRS < 5
[35]	47	3 months	GOS[a]	GOS > 3
[31]	60	3 months	mRS	mRS < 5
[32]	203	6 months	mRS	mRS < 4
[24]	807	3 months	GOS[a]	GOS > 4
[27]	156	12 months	GOS[a]	GOS > 3
[1]	3,255	12 months	mRS	mRS < 3
[37]	108	1 month	ADLs[d]	ADL < 3
[38]	47	6 months	mRS	mRS < 3
[39]	94	Mean 106 days	FIM	Used as a scale
[10]	30	1 month	MMT[e]	See legend[e]
[40]	23	3 months	NIHSS	NIHSS < 4
[12]	29	6 months	Ability in Daily Life[d]	ADL < 4
[14]	166	6 months	GOS[a]	GOS > 3
[8]	211	3 months	mRS	mRS < 4
[9]	32	Mean 42 days	mRS	Used as a scale
[13]	37	Mean 32.5 days	GOS[a]	GOS > 3
[21]	60	Mean 40 months	Clinical Exam[f]	See legend[f]
[22]	32	Median 221.5 days	mRS	mRS < 3
[41]	141	1 month	mRS	mRS < 3
[46]	211	3 months	mRS	mRS < 4
[47]	32	6 months	ADLs[d]	Used as a scale
[18]	22	Mean 51.7 days	RPAB	Used as a scale
[15]	73	3 months	GOS[a]	GOS > 3
[42]	25	3 months	NIHSS	NIHSS < 4

ADLs activities of daily living, EQ-5D euroQol, *FIM* functional independence measure, *GOS* glasgow outcome score, *HDRS* hamilton depression rating scale, *MMT* manual muscle testing, *MoCA* montreal cognitive assessment, *mRS* modified rankin scale, *NIHSS* National Institutes of Health Stroke Scale, *RPAB* rivermead perceptual assessment battery

[a] Numerical designations were standardized between studies

[b] "Depression" defined as HDRS > 10

[c] "Poor outcome" defined as positive screen on MoCA, score <24

[d] Scales are variations of mRS

[e] "Good outcome" defined as increase between time points

[f] "Poor outcome" defined as significant impairment in one cognitive domain without impairment in ADLs

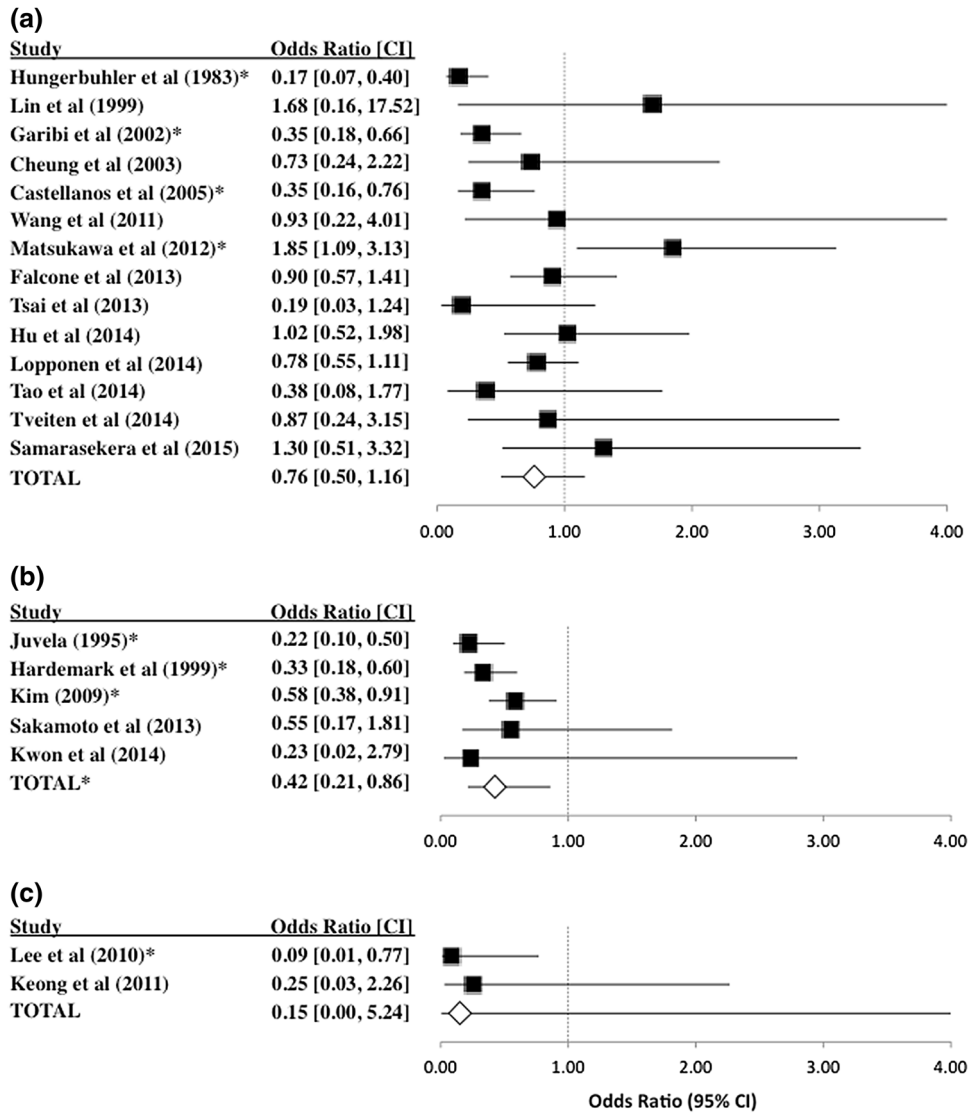

Fig. 2 Meta-analysis of studies describing the odds ratio of poor outcomes for lobar compared to deep/non-lobar ICH. **a** Poor outcome mRS (3, 4, 5, 6) or GOS (4, 3, 2, 1); **b** Poor outcome mRS (4, 5, 6) or GOS (3, 2, 1); **c** Poor outcome mRS (5, 6). *Significant results ($p < 0.05$)

outcomes vs. non-lobar ICH, supported by our own meta-analysis utilizing a cutoff of mRS <4 or GOS >3 ($p < 0.005$). The one study [33] that presented contrary evidence of poorer lobar ICH prognosis reported wider confidence intervals compared to the other studies of its size, reflecting greater variability in their underlying population. The retrospective nature of the study's design and noted variability may explain the differing conclusion from the rest of the review.

We also reviewed the potential impact of laterality on ICH outcome. Most of the studies [14, 26, 28, 31, 32, 35, 41, 42] that examined mRS/GOS outcome by laterality failed to show a significant difference, and those that did reported contradictory results [15, 30]. Neither the mRS nor the GOS explicitly consider traditionally lateralized functions (e.g., aphasia, neglect, etc.) when determining scores. While these functions affect recovery and independence, the stronger emphasis on motor-based functioning [10, 23], especially for higher-degree disability (i.e., mRS 3, 4, 5, 6 or GOS 1, 2, 3), could explain the lack of significant results. Only the study utilizing cognitive measures [18] suggested a role for lateralization in prognostication. Thus, differentiating laterality in an analysis may only be prudent in future, non-motor-based studies.

As Table 1 demonstrates, location comparisons vary remarkably between studies especially regarding differentiation of deeper structures. Despite its prevalence, the comparison of lobar to deep/non-lobar ICH has limited clinical value. Unlike a topographic comparison (i.e., internal capsule, thalamus, etc.), which aligns function with location, an anatomical comparison (i.e., lobar, deep, etc.) fails to differentiate between neurological functions. This aggregation of regions can misattribute the influence of an individual region, a concept suggested by studies in the

review that analyzed thalamic ICH separately from deep ICH [38, 39]. Given that thalamic ICH accounts for an estimated 8.3–15 % of all ICH [43], it is pragmatic that this region warrants specific consideration. Similarly, the difference in outcomes between different lobar regions [13] prompts consideration of differentiating lobar ICH into its respective lobes for analysis as well.

While an individual study may be underpowered to look at differences between these small divisions, meta-analyses have the potential to leverage this limitation. However, this approach can only be undertaken if studies are consistent with their location schema and methods. Methods to increase consistency in location identification include: (1) validation by a qualified neuroimaging reader, (2) multiple abstractors to replicate results, and (3) adjudication of conflicting abstraction by a qualified neuroimaging reader. Additionally, new advancements in imaging techniques are addressing current limitations in performing more refined location analyses. Research within ischemic stroke now utilizes programs to correlate functional measures to a voxel-to-voxel base [5]. While this technique has yet to be applied to ICH patients, recent studies are attempting other quantitative approaches to validate localization of hemorrhage against neuroanatomical atlases [44].

Our current understanding of the interplay between ICH location and cognitive, mood, and QoL outcomes are limited, evidenced by the lack of studies identified by this review. The results are currently confined to lobar ICH and suggest a mixed picture of poorer cognitive outcomes [34] yet better QoL [16]. There has been no systematic attempt to examine cognition prospectively and assess rate of recovery by location. Additionally, no location studies have utilized a QoL measure specific to neurological disease [22, 24] in this patient population. All these clinical questions highlight potential avenues for future research.

The review has certain limitations that must be kept in mind when interpreting the results. In particular, studies were not excluded based on quality or intervention. Due to the limited amount of suitable studies and different methodological approaches, we chose to highlight different methods utilized to examine this topic. Although this affects the generalizability of the results, this was a necessary step to accomplish a thorough descriptive review of different outcome measures. An additional limitation is the exclusion of studies that failed to report statistics regarding our analysis of interest. This is a necessary limitation when comparing studies and assessing reproducibility. Finally, the majority of studies were conducted in Asia, consequently limiting generalizability to Western countries [45].

This review highlights the need for ICH outcome research to include location to a higher degree of resolution than is currently being analyzed. While the practicality of a voxel-to-voxel analysis may not be available for ICH research yet, location analyses with more specific topographic comparisons are beneficial to future research and clinical practice. Future studies should emphasize cognition, mood, and QoL of ICH patients, which are currently lacking. Additionally, standardization in imaging abstraction will allow for better comparisons between studies as well as evaluation of other imaging-based characteristics (i.e., midline shift, hemorrhage volume). In the future, our understanding of ICH location can better guide meaningful endpoints for clinical trials and help improve prognostication of outcome.

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