RESEARCH PAPER

Admission Serum Electrolyte Disturbances and In-Hospital Mortality in Spontaneous Intracerebral Haemorrhage: A Case-Control Study with Implications for Hyperosmolar Drug Therapy and Electrolyte Monitoring

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ABSTRACT

Electrolyte disturbances are common at admission for intracerebral haemorrhage (ICH), are measured routinely, and cost almost nothing to obtain. They are also the variable against which hyperosmolar drug therapy is dosed and monitored, since both mannitol and hypertonic saline are titrated with an eye on serum sodium and chloride. Most published work has focused on hyponatraemia, and much less is known about disturbance in the opposite direction, or about potassium and chloride. Using a case-control design, we asked whether admission disturbances of sodium, potassium and chloride, in either direction, are associated with in-hospital death. This was a case-control study nested in a single-centre ICH registry. Cases were patients who died in hospital (discharge modified Rankin Scale 6); controls were those who survived to discharge (modified Rankin Scale 0 to 5). Admission sodium, potassium and chloride were classified as low, normal or high by standard thresholds. Crude odds ratios were obtained from 2x2 tables, and adjusted odds ratios from logistic regression including age, sex, Glasgow Coma Scale and haematoma volume. There were 118 cases and 281 controls. Hyponatraemia was equally frequent in the two groups and was not associated with death (adjusted OR 1.08, 95% CI 0.57 to 2.04). Three disturbances were each independently associated with death: hypernatraemia (adjusted OR 3.51, 95% CI 1.42 to 8.66), hyperchloraemia (2.14, 1.23 to 3.72) and hypokalaemia (2.14, 1.18 to 3.87). A lower Glasgow Coma Scale and a larger haematoma volume were the expected strong correlates of death. In this cohort it was the hypertonic-direction disturbances, hypernatraemia and hyperchloraemia, together with hypokalaemia, rather than hyponatraemia, that marked higher in-hospital mortality. The associations are exploratory. Hypernatraemia and hyperchloraemia may partly reflect dehydration or hyperosmolar therapy given before or at referral in the sickest patients, and we could not measure either. Prospective confirmation with recorded drug exposure and serial sampling is needed.

Keywords: Intracerebral haemorrhage, Hypernatraemia, Hyperchloraemia, Hypokalaemia, Hyperosmolar therapy, Mannitol, Hypertonic saline, Mortality.

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INTRODUCTION

Intracerebral haemorrhage is the most lethal of the common stroke types, and much of its early mortality is driven by the size of the bleed and the depth of impaired consciousness at presentation.[1,2] Alongside these established predictors, a set of cheap and universally available admission values, the serum electrolytes, is measured in almost every patient and may carry prognostic information of its own.[3,4]

Attention has fallen mainly on hyponatraemia, which is common after ICH and has been linked in several series to longer stays and higher mortality.[5-7] Far less has been written about disturbance in the opposite direction, or about potassium and chloride. Yet a high sodium or chloride at admission may mark dehydration, an early osmotic response, or the use of hyperosmolar therapy in the sickest patients, and potassium disturbance is frequent in acute brain injury. Whether these less-studied disturbances add anything to the familiar predictors of death has not been well examined.

There is a pharmacological reason to look at the whole panel rather than sodium alone, and it is easy to overlook. Perihaematomal oedema is one of the main drivers of secondary injury after ICH, and osmotherapy remains the pharmacological mainstay for the resulting rise in intracranial pressure.[8-10] The two agents in routine use, mannitol and hypertonic saline, are not dosed to a fixed schedule. They are titrated, and the parameter they are titrated against is the serum electrolyte panel. Guidance on hypertonic saline devotes considerable space to formulation, concentration, route, and the monitoring of serum sodium and chloride that keeps the drug safe to give.[11] Comparative work on 23.4% sodium chloride against mannitol treats the resulting sodium load as the thing to watch,[12] and when regimens are overlapped in refractory intracranial hypertension, peak sodium and chloride values in the high 140s and mid 110s are reported as safety outcomes rather than as incidental findings.[13] Chloride load has itself been linked to harm in critically ill populations, including an association with acute kidney injury in paediatric intensive care.[14] In other words, the admission electrolyte panel sits at the interface between a drug class and its monitoring, and a high sodium or chloride in an ICH patient is as likely to be a pharmacological signature as a physiological one.

We therefore took a deliberately simple prognostic question and a design suited to it. In a case-control analysis nested within a single-centre ICH registry, we compared the odds of each admission electrolyte disturbance, low and high sodium, potassium and chloride, between patients who died in hospital and those who survived, before and after adjustment for age, sex, conscious level and haematoma volume. Our aim was descriptive and hypothesis-generating: to see which routine electrolyte disturbances, if any, flag a higher risk of in-hospital death, and to consider what that would mean for a drug class who's dosing already depends on these same numbers.

MATERIALS AND METHODS

Design and setting

We performed a case-control study nested in a registry of consecutive adults admitted with spontaneous ICH to Dr Wahidin Sudirohusodo General Hospital, the regional referral centre in Makassar, and its network hospitals. The same registry has been used, under separate analyses addressing different questions, to study imaging determinants of perilesional attenuation; the present work concerns clinical outcome and does not overlap in exposure or endpoint. The registry sits within a wider programme in which our group has paired routine admission laboratory values with quantitative neuroimaging in stroke.[15,16] Reporting follows the STROBE statement.[17]

Cases, controls and participants

Eligible patients were adults aged 18 years or older with a first spontaneous ICH confirmed on non-contrast CT, admitted within seven days of onset, with a complete admission electrolyte panel and a recorded discharge outcome. Haemorrhage from trauma, tumour or a vascular malformation was excluded. Cases were patients who died in hospital, defined as a discharge modified Rankin Scale of 6. Controls were patients who survived to discharge (modified Rankin Scale 0 to 5). Figure 1 shows the design.

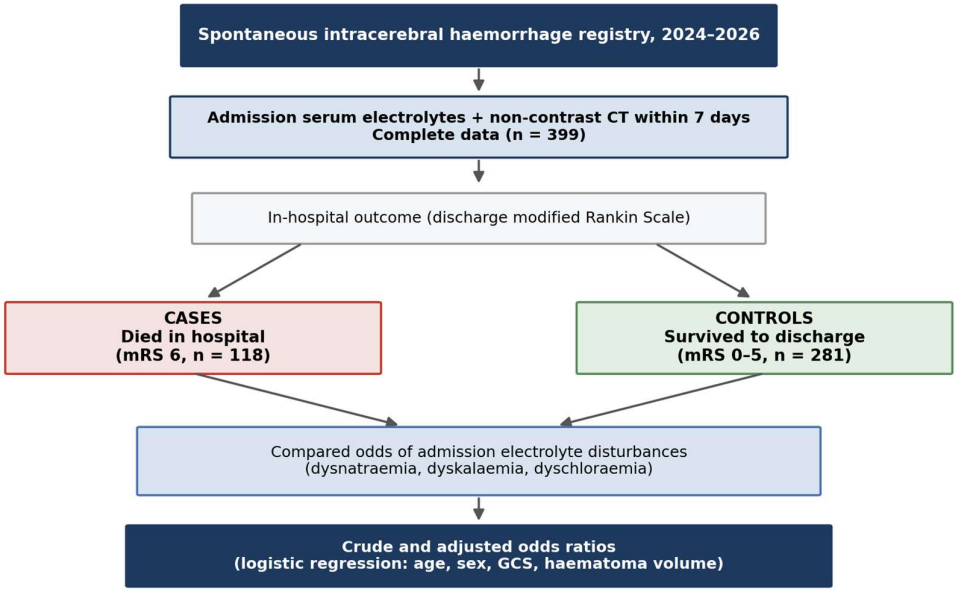

Figure 1. Case-control design. GCS, Glasgow Coma Scale; mRS, modified Rankin Scale.

Exposures

Serum sodium, potassium and chloride were taken from the first sample drawn at admission. Disturbances were defined by standard laboratory thresholds: hyponatraemia (sodium <135 mmol/L) and hypernatraemia (>145 mmol/L); hypokalaemia (potassium <3.5 mmol/L) and hyperkalaemia (>5.0 mmol/L); hypochloraemia (chloride <98 mmol/L) and hyperchloraemia (>106 mmol/L). Any dysnatraemia combined the low and high sodium groups. Because onset was recorded only to the nearest day, the exact interval from ictus to sampling could not be reconstructed; we treat this as a limitation. We also had no record of hyperosmolar therapy given before arrival. Many patients reach us on referral from network hospitals, where mannitol is in common use, so an admission sample is not always a treatment-naive sample. This matters for how the sodium and chloride findings should be read, and we return to it in the Discussion.

Covariates

Admission covariates were age, sex, the Glasgow Coma Scale as a measure of conscious level,[18] and haematoma volume measured on the admission CT. These are the established determinants of early death in ICH[3,4] and were chosen a priori as the adjustment set.

Statistical analysis

Cases and controls were compared with the Mann-Whitney test for continuous variables and the chi-squared test for proportions. For each electrolyte disturbance we estimated a crude odds ratio from the 2x2 table, with the Haldane correction where a cell was small, and Fisher's exact test for the p value. Adjusted odds ratios came from separate logistic regression models, each containing one disturbance together with age, sex, Glasgow Coma Scale and haematoma volume. A two-sided p below 0.05 was significant. Analyses used IBM SPSS Statistics v26.0 (IBM Corp., Armonk, NY, USA), with figures prepared in GraphPad Prism v9.0 (GraphPad Software, San Diego, CA, USA).

Ethics

The study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (approval no. 291A/UN4.6.4.5.31/PP36/2026 and protocol no. UH26010158), which waived individual consent given the retrospective use of de-identified data.

RESULTS

Of the registry patients with a complete admission electrolyte panel and a recorded outcome, 118 died in hospital (cases) and 281 survived to discharge (controls). Table 1 compares the two groups. Cases were a little older, and had a markedly lower Glasgow Coma Scale and a larger haematoma volume, as expected. Admission sodium and chloride were modestly higher in cases, while potassium did not differ; systolic blood pressure was slightly higher in cases but not significantly so.

Table 1. Admission characteristics of cases and controls.

Variable	Cases: died (n = 118)	Controls: survived (n = 281)	*p*
Age, years	58 (48 to 68)	54 (45 to 63)	0.005
Male sex, n (%)	73 (61.9)	153 (54.4)	0.21
Glasgow Coma Scale	9 (7 to 11)	15 (12 to 15)	<0.001

Variable	Cases: died (n = 118)	Controls: survived (n = 281)	*p*
Haematoma volume, mL	16.9 (6.0 to 35.9)	9.5 (3.3 to 20.7)	<0.001
Systolic BP, mmHg	160 (140 to 181)	151 (131 to 175)	0.079
Serum sodium, mmol/L	139 (136 to 142)	137 (135 to 140)	0.004
Serum potassium, mmol/L	3.7 (3.3 to 4.3)	3.8 (3.5 to 4.2)	0.19
Serum chloride, mmol/L	105 (102 to 109)	104 (101 to 106)	0.017

Values are median (IQR) unless stated. BP, blood pressure. p from Mann-Whitney or chi-squared test.

Electrolyte disturbances and death

The pattern of disturbance differed sharply by direction (Table 2, Figure 2). Hyponatraemia was present in almost exactly one in five patients in both groups, and carried no association with death (crude OR 1.00). Hypernatraemia, by contrast, was three times more common in cases than controls (15.3% versus 4.6%), and hyperchloraemia was far more common in cases (42.4% versus 24.6%). Hypokalaemia was also more frequent in those who died. Hypochloraemia and hyperkalaemia were uncommon and showed no clear signal.

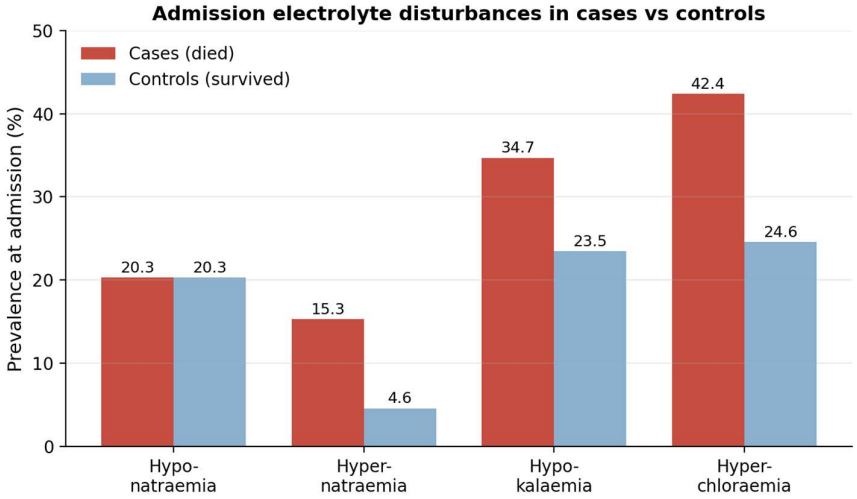

Figure 2. Prevalence of admission electrolyte disturbances in cases (died) and controls (survived).

Table 2. Prevalence and crude odds ratios of admission electrolyte disturbances.

Disturbance	Cases, n (%)	Controls, n (%)	Crude OR (95% CI); *p*
Hyponatraemia (<135)	24 (20.3)	57 (20.3)	1.00 (0.59 to 1.71); 1.00
Hypernatraemia (>145)	18 (15.3)	13 (4.6)	3.71 (1.75 to 7.85); <0.001
Any dysnatraemia	42 (35.6)	70 (24.9)	1.67 (1.05 to 2.65); 0.038
Hypokalaemia (<3.5)	41 (34.7)	66 (23.5)	1.73 (1.09 to 2.77); 0.026
Hyperkalaemia (>5.0)	7 (5.9)	6 (2.1)	2.89 (0.95 to 8.79); 0.065
Hypochloraemia (<98)	9 (7.6)	25 (8.9)	0.85 (0.38 to 1.87); 0.85
Hyperchloraemia (>106)	50 (42.4)	69 (24.6)	2.26 (1.43 to 3.56); <0.001

OR, odds ratio; CI, confidence interval. Crude OR from 2x2 tables (Haldane correction where needed); p from Fisher's exact test. Thresholds are in mmol/L.

Independent associations

After adjustment for age, sex, Glasgow Coma Scale and haematoma volume, three disturbances remained independently associated with in-hospital death (Table 3, Figure 3). Hypernatraemia carried the largest effect (adjusted OR 3.51, 95% CI 1.42 to 8.66), followed by hyperchloraemia (2.14, 1.23 to 3.72) and hypokalaemia (2.14, 1.18 to 3.87). Any dysnatraemia was borderline (1.72, 0.98 to 3.00). Hyponatraemia, hyperkalaemia and hypochloraemia showed no independent association. The direction of the sodium and chloride findings is the notable

point: it was the hypertonic end of the range, not the low end, that marked risk.

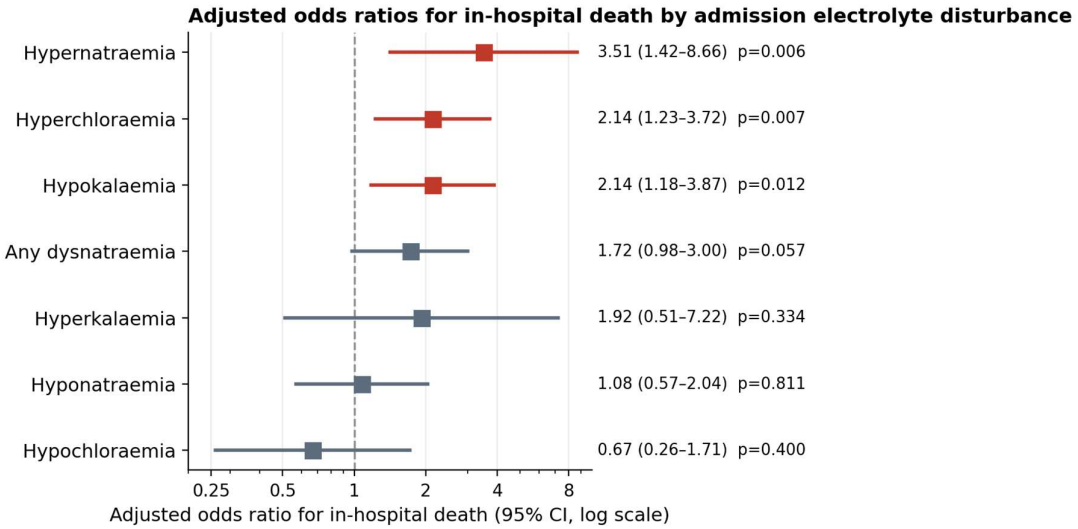

Figure 3. Adjusted odds ratios (95% CI, log scale) for in-hospital death by admission electrolyte disturbance, from logistic models adjusted for age, sex, Glasgow Coma Scale and haematoma volume. Red denotes an interval excluding 1.

Table 3. Adjusted odds ratios for in-hospital death.

Disturbance	Adjusted OR (95% CI)	*p*
Hypernatraemia	3.51 (1.42 to 8.66)	0.006
Hyperchloraemia	2.14 (1.23 to 3.72)	0.007
Hypokalaemia	2.14 (1.18 to 3.87)	0.012
Any dysnatraemia	1.72 (0.98 to 3.00)	0.057
Hyperkalaemia	1.92 (0.51 to 7.22)	0.334
Hyponatraemia	1.08 (0.57 to 2.04)	0.811
Hypochloraemia	0.67 (0.26 to 1.71)	0.400

Each row is a separate logistic model adjusted for age, sex, Glasgow Coma Scale and haematoma volume. OR, odds ratio; CI, confidence interval.

DISCUSSION

In this case-control study, the admission electrolyte disturbances that flagged in-hospital death were not the ones usually emphasised. Hyponatraemia, the most studied electrolyte problem in ICH, was common but carried no association with death here. What marked risk instead were disturbances at the opposite, hypertonic end, hypernatraemia and hyperchloraemia, together with hypokalaemia, each independent of age, sex, conscious level and haematoma volume. The finding is essentially about direction: a high admission sodium or chloride, rather than a low one, went with a higher chance of dying.

Relation to the hyponatraemia literature

This sits a little against the well-known hyponatraemia literature, in which low sodium has been tied to worse outcome after ICH.[5-7] We do not read our result as contradicting that work so much as reframing it for this endpoint and cohort. Hyponatraemia in ICH is often mild and develops or is corrected over the admission, so a single admission value may not capture its prognostic weight, and any effect it does have may be absorbed by the strong influence of conscious level and haematoma volume, which we adjusted for. The hyponatraemia in our patients was, by prevalence, no different between those who lived and those who died.

Interpreting the hypertonic findings

The hypertonic findings need careful and honest interpretation, because association here is not the same as cause. A high sodium or chloride at admission in ICH is frequently not a primary event. It may reflect dehydration in a patient who has been unwell and unable to drink, an early stress response, or the deliberate use of hyperosmolar therapy in the most severely injured patients.[8-10] Any of these would tie a high sodium or chloride to severity, and thus to death, without the electrolyte itself being harmful. The timing point deserves emphasis rather than a footnote. Our centre takes referrals from network hospitals across the region, and mannitol is widely given before transfer. An admission sample drawn after a referring hospital has already started osmotherapy is not a baseline measurement

of the patient; it is partly a measurement of the treatment. We had no data on fluid balance or on osmotic therapy given before or at arrival, and we cannot separate these strands. What can be said is that the associations survived adjustment for the two dominant prognosticators, conscious level and clot volume, so they are not simply a restatement of those. Hyperchloraemia in particular has been linked to harm in other critically ill populations,[14] and its appearance here as an independent marker is worth flagging for prospective study rather than dismissing.

Hypokalaemia

Hypokalaemia is easier to place. It is common in acute brain injury, where catecholamine surge and stress drive potassium into cells, and it may mark the intensity of the acute response as much as any direct effect; it also carries its own arrhythmic risk. Its independent association with death fits that picture and, like the sodium and chloride findings, argues for reading the whole admission electrolyte profile rather than sodium alone.

Relevance to hyperosmolar drug therapy and monitoring

The pharmacological reading of these data is the one we find most useful, and it cuts both ways. If a high admission sodium or chloride is partly the signature of osmotherapy already given, then our result is in part a statement about the patients who get that therapy, which is to say the sickest ones, and the electrolyte is a marker of treatment intensity rather than a hazard in itself. If instead the disturbance is primary, from dehydration or an early osmotic response, then it is a physiological warning sign that happens to be free to obtain. Our data cannot tell these apart, and we want to be plain about that. What our data do establish is that the association is not simply a proxy for conscious level or clot volume, since it survives adjustment for both.

This matters for how the drug class is handled. Mannitol and hypertonic saline are among the few agents in ICH whose safe use depends on repeated measurement of the very parameters we studied, and the published guidance on hypertonic saline is largely a document about formulation, dosing, route and monitoring.[11] Comparative studies of 23.4% sodium chloride against mannitol are read through the sodium they produce,[12] and reports of overlapping regimens list peak sodium and chloride among the safety outcomes.[13] A patient who arrives already hypernatraemic or hyperchloraemic therefore starts from a narrower therapeutic margin than one who does not, whatever the reason for the disturbance. Two practical points follow, and both are modest. Recording pre-referral osmotherapy at the point of admission would cost nothing and would let a future analysis separate drug effect from physiology, which our design could not. And admission sodium and chloride, already drawn in every patient, deserve to be read as the starting position for any osmotic agent that is about to be given, rather than as a routine number to be glanced at. Neither point is a finding of this study. Both are directions it suggests.

Clinical message

For the practising clinician the message is modest but useful. The admission electrolyte panel is drawn for every patient at no extra cost, and this analysis suggests its prognostic content is not confined to hyponatraemia. A high sodium or chloride, or a low potassium, at presentation should at least prompt attention to the patient's fluid state, to what has already been given, and to severity, rather than being passed over. Because the whole panel is already available, this adds nothing to the cost of care, which makes it attractive where resources are limited.

Strengths and limitations

The study is a reasonable size, examined all three routine electrolytes in both directions, and adjusted for the established determinants of early death. Its limits are real and shape how far the findings can be taken. It is retrospective and from a single referral centre, so selection towards more severe disease is likely and the mortality was high. Electrolytes were measured once, at admission, so we describe a single point rather than a trajectory. Most importantly, we lacked data on fluid balance and on hyperosmolar therapy, including therapy given at referring hospitals before transfer, and these are plausible common causes of both a high admission sodium or chloride and of death. The outcome was in-hospital mortality alone, without longer-term or functional follow-up. For these reasons the associations are exploratory. The registry has been used for other, non-overlapping analyses, which we disclose in the interest of transparency.

Future directions

A prospective study that records fluid balance and osmotic therapy, including any given before arrival, and that tracks electrolytes serially rather than once, would show whether the hypertonic disturbances are markers of severity and treatment or carry independent risk, and whether correcting them changes anything. Until then, admission hypernatraemia, hyperchloraemia and hypokalaemia are best read as warning signs worth noting on the first blood panel, not as established causes of death.

CONCLUSION

In spontaneous ICH, it was admission hypernatraemia, hyperchloraemia and hypokalaemia, not hyponatraemia, that were independently associated with in-hospital death, over and above conscious level and haematoma volume. The signal lay at the hypertonic end of the range and across the whole routine electrolyte panel, not in sodium alone. Because sodium and chloride are also the parameters against which mannitol and hypertonic saline are dosed and monitored, an admission panel at the hypertonic end marks a narrower starting margin for the one drug class routinely used against perihaematomal oedema. These associations are exploratory and may partly reflect osmotic therapy or dehydration in the sickest patients, some of it given before referral. Prospective, serially sampled confirmation with recorded drug exposure is needed before any causal or therapeutic claim can be made.

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AUTHORS' CONTRIBUTIONS
DFK contributed to study conception, data acquisition, statistical analysis, and drafting of the manuscript. MYA, and AWS supervised the project, contributed to study design and data interpretation, and critically revised the manuscript. AAZ contributed to methodology and critical revision. CK contributed to data interpretation and critical revision. SWG contributed to data analysis and critical revision. All authors reviewed and approved the final version.

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CONFLICT OF INTEREST
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT
Data are available from the corresponding author on reasonable request.

CONSENT FOR PUBLICATION
All authors have given their consent for publication.

DECLARATION ON THE USE OF ARTIFICIAL INTELLIGENCE
AI-assisted tools were used for language editing only. The authors reviewed and edited all content and take full responsibility for the accuracy and integrity of the published work.

ABBREVIATIONS
CI: confidence interval

CT: computed tomography

GCS: Glasgow Coma Scale

ICH: intracerebral haemorrhage

ICP: intracranial pressure

IQR: interquartile range

mRS: modified Rankin Scale

OR: odds ratio

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

REFERENCES
1. **Feigin VL, Brainin M, Norrving B, et al.** World Stroke Organization: Global Stroke Fact Sheet 2025. International Journal of Stroke. 2025;20(2):132-144. DOI: 10.1177/17474930241308142
2. **Magid-Bernstein J, Girard R, Polster S, et al.** Cerebral hemorrhage: pathophysiology, treatment, and future directions. Circulation Research. 2022;130(8):1204-1229. DOI: 10.1161/CIRCRESAHA.121.319949
3. **Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G.** Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993;24(7):987-993. DOI: 10.1161/01.STR.24.7.987
4. **Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC.** The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32(4):891-897. DOI: 10.1161/01.STR.32.4.891
5. **Kuramatsu JB, Bobinger T, Volbers B, et al.** Hyponatremia is an independent predictor of in-hospital mortality in spontaneous intracerebral hemorrhage. Stroke. 2014;45(5):1285-1291. DOI: 10.1161/STROKEAHA.113.004136
6. **Carcel C, Sato S, Zheng D, et al.** Prognostic significance of hyponatremia in acute intracerebral hemorrhage. Critical Care Medicine. 2016;44(7):1388-1394. DOI: 10.1097/CCM.0000000000001628
7. **Shah A, Sabir S, Artani M, et al.** Significance of hyponatremia as an independent factor in predicting short-term mortality in patients with hemorrhagic stroke. Cureus. 2019;11(4):e4549. DOI: 10.7759/cureus.4549
8. **Chen Y, Chen S, Chang J, Wei J, Feng M, Wang R.** Perihematomal edema after intracerebral haemorrhage: an update on pathogenesis, risk factors, and therapeutic advances. Frontiers in Immunology. 2021;12:740632. DOI: 10.3389/fimmu.2021.740632
9. **Krishnan K, Campos PB, Nguyen TN, et al.** Cerebral edema in intracerebral haemorrhage: pathogenesis, natural history, and potential treatments. Frontiers in Stroke. 2023;2:1256664. DOI: 10.3389/fstro.2023.1256664
10. **Wan Y, Holste KG, Hua Y, Keep RF, Xi G.** Brain edema formation and therapy after intracerebral haemorrhage. Neurobiology of Disease. 2023;176:105948. DOI: 10.1016/j.nbd.2022.105948
11. **Holden DN, Mucksavage JJ, Cokley JA, et al.** Hypertonic saline use in neurocritical care for treating cerebral edema: a review of optimal formulation, dosing, safety, administration and storage. American Journal of Health-System Pharmacy. 2023;80(6):331-342. DOI: 10.1093/ajhp/zxac368
12. **Tatro HA, McMillen JC, Hamilton LA, Rowe AS.** 23.4% sodium chloride versus mannitol for the reduction of intracranial pressure in patients with traumatic brain injury: a single-center retrospective cohort study. The Annals of Pharmacotherapy.

2021;55(8):988-994. DOI: 10.1177/1060028020982379

13. **Johnson MJ, Brown CS, Rabinstein AA, Hawkes MA, Cole KC, Vollmer NJ.** Overlapping hyperosmolar therapy in patients with elevated and refractory intracranial pressure. Clinical Neuropharmacology. 2026; online ahead of print. DOI: 10.1097/WNF.0000000000000687
14. **Ginter D, Gilfoyle E, Wade A, Lethebe BC, Gilad E.** Hyperchloremia and association with acute kidney injury in critically ill children. Pediatric Nephrology. 2023;38(7):2233-2242. DOI: 10.1007/s00467-022-05823-8
15. **Putra AWL, Amran MY, Lotisna M, Idris I, Akbar M, Sompa AW.** Atherogenic index of plasma as a predictor of Hounsfield unit attenuation, infarct lesion number, and stroke severity in acute ischemic stroke. Acta Biomedica. 2025;96(4):17321. DOI: 10.23750/abm.v96i4.17321
16. **Worang JA, Amran MY, Norwanto DA, Ikbal M, Akbar M, Soraya GV, et al.** Serum vascular endothelial growth factor (VEGF) levels and neuroimaging markers in acute ischemic stroke: a cross-sectional analysis of Hounsfield units, infarct volume, and clinical severity. Acta Biomedica. 2025; online first. DOI: 10.23750/abm.v96iS4.17979
17. **von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative.** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The Lancet. 2007;370(9596):1453-1457. DOI: 10.1016/S0140-6736(07)61602-X
18. **Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G.** The Glasgow Coma Scale at 40 years: standing the test of time. The Lancet Neurology. 2014;13(8):844-854. DOI: 10.1016/S1474-4422(14)70120-6