RESEARCH PAPER

Haematocrit and Platelet Count in Relation to Parenchymal Hounsfield Unit on Non-Contrast Cranial Ct in Acute Ischaemic Stroke: A Case-Control Study with Implications for Cerebral Drug Delivery and Antithrombotic Therapy

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ABSTRACT

Hounsfield unit (HU) measurement on non-contrast cranial computed tomography (CT) is widely used in acute ischaemic stroke (AIS), but whether peripheral haematological parameters shape parenchymal HU has not been examined in Southeast Asian populations. The question has a pharmacological edge that is easy to miss. Haematocrit sets whole-blood viscosity and therefore the resistance to residual flow through the ischaemic bed, which is the same bed that any systemically administered thrombolytic, neuroprotective, or nanocarrier-borne agent has to reach; platelets, meanwhile, are the target of antiplatelet therapy and a physical obstruction within it. We tested whether haematocrit and platelet count separate patients with severe from milder cranial hypoattenuation. This was a single-centre, retrospective case-control study at a tertiary centre in Makassar, Indonesia, covering January 2023 to December 2024. From 1,256 AIS admissions, 150 patients with complete clinical, haematological and CT data were dichotomised at the cohort-median HU of 20: cases (HU ≤ 20, n = 95) and controls (HU > 20, n = 55). Univariate and multivariable logistic regression estimated odds ratios (OR), adjusting for the National Institutes of Health Stroke Scale (NIHSS), infarct volume, age, sex and onset-to-admission interval. Haematocrit above 39% was protective against severe hypoattenuation (OR 0.494, 95% CI 0.252-0.969; P = 0.040), and haematocrit correlated positively with HU (Spearman ρ = +0.171, P = 0.036). Platelet count showed no association on any scale. The haematocrit signal lost significance after multivariable adjustment (adjusted OR 1.026, 95% CI 0.954-1.103; P = 0.49), reflecting strong inter-correlations of haematocrit with NIHSS (ρ = +0.601) and infarct volume (ρ = +0.659). Haematocrit, but not platelet count, modestly tracks severe parenchymal hypoattenuation in AIS, with the signal largely absorbed by clinical severity. Pairing admission haematocrit with HU is simple and inexpensive, and because haematocrit governs the rheological environment through which drugs must travel to reach ischaemic tissue, it deserves consideration as a stratification variable in cerebral drug delivery research and in trials of acute antithrombotic therapy.

Keywords: Acute ischaemic stroke, Haematocrit, Platelet count, Hounsfield unit, Cerebral drug delivery, Antithrombotic therapy, Blood viscosity.

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INTRODUCTION

Stroke continues to rank among the leading causes of death and long-term disability worldwide, and the picture

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in Asia has shifted in ways that demand closer attention. The Global Burden of Disease Study 2021 documented marked increases in stroke incidence, mortality and disability across Southeast Asia and other lower socio-demographic index regions, reversing the slow decline observed in higher-income countries.[1] Indonesia is part of that trajectory. National surveys place stroke prevalence at roughly 10 to 11 per 1,000 population, with the highest rates among older adults and in provinces outside Java, and specialist stroke services remain unevenly distributed, most tertiary capacity being concentrated in a handful of referral hospitals.[2] South Sulawesi, where the present study was performed, sits within the regional catchment of Dr. Wahidin Sudirohusodo Hospital in Makassar, a tertiary neurovascular centre serving the eastern half of the country and admitting several hundred new acute ischaemic stroke (AIS) cases each year.[2]

Non-contrast cranial computed tomography (NCCT) remains the imaging modality of first choice in the acute setting, largely because of its speed, accessibility and cost-effectiveness. Even within the hyperacute window, NCCT can reveal subtle parenchymal hypoattenuation, loss of grey–white differentiation and the hyperdense vessel sign, all of which carry diagnostic and prognostic weight.[3] To bring more structure to these visual findings, Barber and colleagues introduced the Alberta Stroke Program Early CT Score (ASPECTS), a 10-point topographic scoring system that has since become a standard tool in stroke triage worldwide.[4,5] More recently, several groups have moved beyond categorical scoring and argued that direct quantitative measurement of Hounsfield unit (HU) values within the ischaemic territory captures information the ASPECTS scheme cannot fully convey.[6]

The same logic has been extended to the occluding clot. Puig and colleagues showed that HU values measured within the affected vessel correlate with thrombus composition and respond differently to intravenous thrombolysis, with red-cell-rich clots showing higher HU and greater lysability than platelet-rich, fibrin-dominant clots.[7] Working with thin-slice NCCT, other groups demonstrated a modest but consistent correlation between patient haematocrit and the HU of the contralateral patent artery, in keeping with the principle that red cells dominate intravascular radiodensity.[8,9] These observations open a clinically attractive possibility: that peripheral haematological parameters might explain a non-trivial fraction of HU variability on CT. Walton and colleagues, in an experimental model, showed that elevated haematocrit also enhances platelet accumulation at sites of vascular injury, providing a biological bridge between the two cell types and the radiodensity they generate.[10]

There is a pharmacological reason to care about this, and it is not obvious from the imaging literature alone. Haematocrit is the principal determinant of whole-blood viscosity, and viscosity governs the resistance to flow through collateral and microvascular channels. Elevated blood viscosity has been linked to delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage, which is a different disease but the same physical problem of flow through a compromised bed.[11] Residual flow is precisely what decides whether a systemically administered agent reaches the tissue it was meant to rescue. Much of the recent drug delivery work in stroke has been built around this obstacle, using nanocarriers and biomimetic platforms designed to cross a compromised blood-brain barrier and release their payload where perfusion has failed.[12,13] Some of the more elegant designs borrow platelet membranes as targeting coats for thrombus-directed nanoparticles, which shows how central both cell types have become to delivery design.[14] If haematocrit and platelet count leave a measurable trace on routine CT attenuation, that trace would be a cheap and universally available window onto the environment into which these drugs must be delivered.

Within our own catchment area, a recent case-control study from our research group examined this exact triad of variables (platelet count, haematocrit and HU) in patients with cerebral venous sinus thrombosis (CVST). Both HU and the HU-to-haematocrit (HU/Hct) ratio were significantly higher in CVST cases than in controls, although platelet count and haematocrit individually did not separate the two groups.[15] Other investigators have reported similar findings for the HU/Hct ratio in CVST diagnosis.[16,17] In parallel, we have characterised the contribution of intracranial atherosclerosis to AIS in this region, identifying hypertension and dyslipidaemia as the leading modifiable risk factors in our hospital-based cohort.[18] The two strands of work, on the venous side and on the arterial side of cerebrovascular disease, motivate the natural follow-up question of whether a comparable haemato-radiological relationship can be detected on the arterial-ischaemic side, where HU within the affected parenchyma is generally lower than baseline brain density rather than higher than baseline vessel density.

Published data on the relationship between peripheral haematological parameters and quantitative HU in AIS patients remain limited, particularly from Southeast Asian populations whose demographic and risk-factor profile differs from that of higher-income regions. This evidence gap is what the present study addresses. Using a curated single-centre cohort of 150 AIS patients with complete clinical, haematological and CT data, we framed a case-control analysis in which severe parenchymal hypoattenuation was contrasted with milder hypoattenuation, and we asked whether platelet count and haematocrit, alone or in combination, separated the two groups. The primary aim was to estimate the strength and direction of any haematological-radiological association in this setting. The secondary aim was to position the finding within the broader haemato-radiological framework that our group has been developing, and to consider what it might mean for the delivery of drugs to ischaemic brain.

MATERIALS AND METHODS

Study design and setting

This was a single-centre, hospital-based retrospective case-control study conducted at the acute ischaemic stroke service of Dr. Wahidin Sudirohusodo General Hospital, a tertiary teaching hospital affiliated with the Faculty of Medicine, Hasanuddin University, in Makassar, South Sulawesi, Indonesia. The institution serves as the regional referral centre for stroke and neurovascular care for eastern Indonesia and has a dedicated stroke care unit and integrated brain centre with 24-hour CT imaging capability. The study used a curated subset of the institutional stroke registry covering all consecutive admissions for acute ischaemic stroke between January 2023 and December 2024. Design and reporting followed the principles outlined in the STROBE statement for observational research, and the analytical framework was adapted from a recent case-control investigation by our group that applied the same triad of variables (platelet count, haematocrit and Hounsfield unit) to a different cerebrovascular condition at the same institution.[15]

Source population and eligibility

The source registry held 1,256 admission records of acute ischaemic stroke during the 24-month period. From this pool, we selected patients for whom complete, curated data on the seven variables central to the analytical question were available: cranial Hounsfield unit measurement on non-contrast CT, peripheral platelet count, haematocrit, time from symptom onset to hospital admission, National Institutes of Health Stroke Scale (NIHSS) at admission, volume of cerebral infarct on CT, and basic demographics (age, sex). Patients younger than 18 years, those with pure intracranial haemorrhage, and those with incomplete imaging or laboratory data were excluded. After application of these criteria, 150 patients remained as the analytical cohort. No upper age limit was imposed, since stroke in Indonesia, as elsewhere in Southeast Asia, has a high prevalence in older adults and the demographic spectrum of our patients reflects this.[1,2] Patients with diabetes mellitus were not excluded, in order to keep the analytical sample inclusive of the routine clinical population at our centre.

Variable definitions and data collection

All variables were extracted from the secondary medical record system, in line with the data-handling approach already used by our group in the parallel cerebral venous sinus thrombosis case-control study.[15] Data collection was carried out independently by two trained extractors and cross-checked by a third investigator for internal consistency. Discrepancies were resolved by reference to the original electronic record. Variables were grouped into three sets: imaging, haematological and clinical.

Cranial CT and Hounsfield unit measurement. All cases underwent non-contrast cranial CT on hospital admission as part of standard stroke triage. Images were acquired on a 128-slice multidetector scanner with 5 mm axial reconstruction. Hounsfield unit values were measured by neurology and radiology staff using region-of-interest (ROI) tools on the institutional PACS workstation. An ROI of approximately 30 mm² was placed at the centre of the largest hypoattenuated parenchymal area, avoiding visible vessel structures, cortical sulci and bone artefact. A second contralateral ROI was placed at the mirror-image healthy region for visual reference, and the ipsilateral value within the ischaemic territory was recorded as the patient's HU. The general procedure for HU-based assessment of early ischaemic changes on CT has been described in detail within the ASPECTS framework,[4,5] which uses parenchymal hypoattenuation as the key visual marker. We did not assign a numerical ASPECTS score in this study, since our analytical interest was in the quantitative HU rather than in a topographic score, although the ROI procedure was conceptually aligned with the same principle of parenchymal density assessment.[6] The dependence of HU on haematocrit through the radiodensity of intravascular blood has been described both for ischaemic stroke and for cerebral venous thrombosis,[7-10,15] which is the methodological rationale for pairing the two variables in this analysis. Volume of infarct was computed using the ABC/2 approximation on the same axial slices, with A and B as the longest perpendicular diameters of the hypoattenuated region on the slice with the largest extent, and C as the product of the number of slices in which the lesion was visible and slice thickness.

Haematological parameters. Platelet count ($\times 10^3/\mu L$) and haematocrit (%) were obtained from the first complete blood count drawn at admission to the emergency department, processed by an automated haematology analyser at the central clinical pathology laboratory of the hospital. Same-day values were used to avoid any post-admission haemodilution or transfusion effects from confounding the measurement.

Clinical variables. NIHSS at admission was scored by attending neurologists at presentation. Time from symptom onset to admission was extracted from the triage record in days. Age and sex were taken from the patient identification record.

Case and control definition

Because there is no universally accepted clinical cut-off to dichotomise cranial parenchymal Hounsfield unit within the narrow range observed in our cohort (11-32), we adopted a cohort-derived threshold based on the median value (HU = 20). Patients with HU at or below the median were classified as cases, reflecting more severe parenchymal hypoattenuation in the ischaemic territory. Patients with HU above the median were classified as controls. This produced 95 cases and 55 controls. The flow of the cohort, from the full registry to the final case-control split, is depicted in Figure 1. A single-cohort split was preferred over the recruitment of external non-stroke controls because the focus of the present study is the within-disease relationship between haematological parameters and HU, rather than a contrast between AIS and a non-stroke comparator. This design choice is consistent with the analytical strategy commonly adopted in CT-density studies of cerebrovascular disease.[7,15,16]

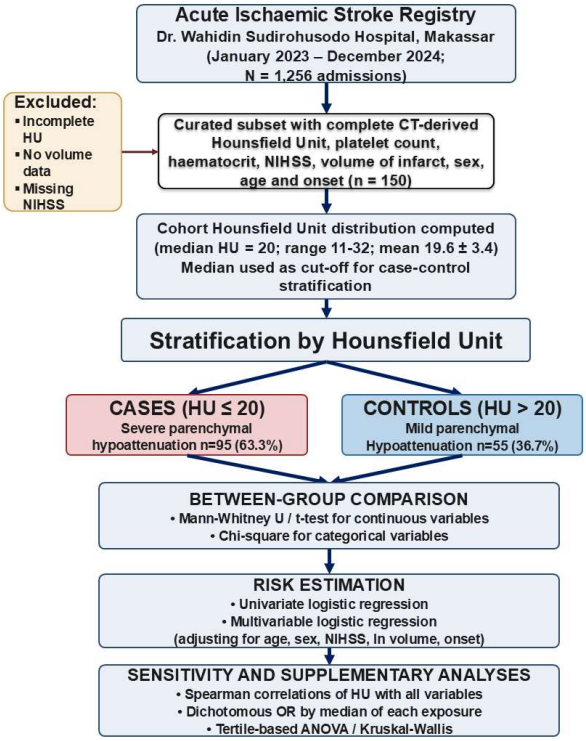

Figure 1. Flow of the cohort from the source registry to the final case-control stratification by cranial Hounsfield unit. The median HU value of the curated cohort (HU = 20) was used as the cut-off for case-control assignment. HU, Hounsfield unit; NIHSS, National Institutes of Health Stroke Scale.

Statistical analysis

All analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA), and figures were prepared with GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were summarised as mean ± standard deviation when approximately normally distributed and as median with interquartile range (IQR) when skewed. Normality was assessed by the Shapiro-Wilk test together with visual inspection. Between-group comparisons used the independent-samples t-test for variables with normal distribution and the Mann-Whitney U test otherwise. Categorical variables were summarised as counts and percentages and compared by the chi-square test. Two-sided P values below 0.05 were taken as statistically significant. We estimated odds ratios (OR) for case status using univariate logistic regression, treating each candidate predictor on its native continuous scale and again after dichotomisation at the cohort median. Multivariable logistic regression was then fitted with age, sex, platelet count, haematocrit, NIHSS, log-transformed volume of infarct and onset-to-admission interval entered simultaneously. Sensitivity analyses included Spearman rank correlation of HU with each predictor on the continuous scale, and tertile-based analysis of variance and Kruskal-Wallis comparisons for platelet count and haematocrit. No formal sample-size calculation was performed before the analysis, since the cohort size was fixed by the curated dataset; we instead computed and reported the precision of effect estimates by 95% confidence intervals (CI). With 95 cases and 55 controls, the study had approximately 80% power to detect an odds ratio of 0.45 or smaller, or 2.20 or larger, for a binary exposure with 40-60% prevalence, at an alpha level of 0.05.

Ethical approval

The protocol was approved by the institutional review board and the study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical clearance was obtained from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University (518/UN4.6.4.5.31/PP36/2026; protocol number UH26030458) on 15 April 2026. All data were anonymised prior to analysis.

RESULTS

Study cohort and case-control definition

Out of 1,256 admissions, 150 patients met all eligibility criteria and formed the analytical cohort. The distribution of cranial HU was tight, with values ranging from 11 to 32 (mean 19.6 ± 3.4, median 20). Applying the median as the cut-off produced 95 cases (HU ≤ 20, 63.3%) representing more severe parenchymal hypoattenuation, and 55 controls (HU > 20, 36.7%) representing milder hypoattenuation. Figure 2A shows the distribution of HU with the case-

control split, and Figure 2B shows the corresponding distribution of platelet count and haematocrit across the two groups. The histogram shows a roughly symmetrical, unimodal HU distribution with a gentle left tail, suggesting that the median split felt close to the centre of mass of the cohort and was therefore an internally balanced cut-off.

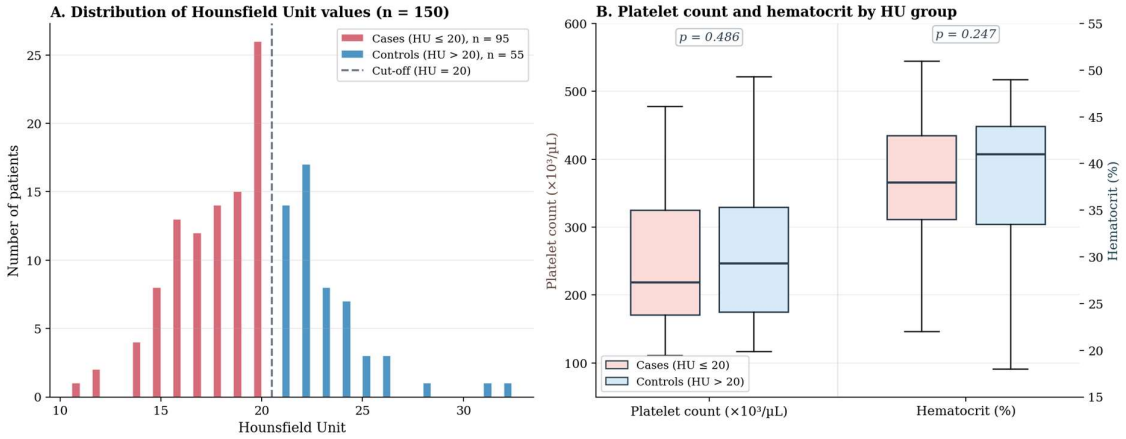

Figure 2. (A) Frequency distribution of Hounsfield unit values in the analytical cohort (n = 150), coloured by case-control assignment. The dashed vertical line indicates the median-derived cut-off at HU = 20. (B) Box plots of platelet count and haematocrit by HU group, with median, interquartile range and whiskers extending to non-outlier extremes. Reported P values are from the Mann-Whitney U test.

Baseline demographic and clinical characteristics

Median age was 59 years among cases (IQR 52-64) and 56 years among controls (IQR 50.5-64) (P = 0.24) (Table 1). Men comprised 58.9% of cases and 69.1% of controls (P = 0.29). Time from symptom onset to admission was virtually identical between the two groups, with a median of 2 days in each (IQR 1-3 days; P = 0.99). Within the 150-patient cohort, 72 (48.0%) were admitted within 24 hours of onset, 45 (30.0%) within 2-3 days, and 33 (22.0%) after more than 3 days. None of these distributions differed across the HU strata.

Table 1. Baseline demographic and clinical characteristics by Hounsfield unit group.

Variable	Cases – HU ≤ 20 (n = 95)	Controls – HU > 20 (n = 55)	*P* value
Age, years, median (IQR)	59 (52–64)	56 (50.5–64)	0.24
Male sex, n (%)	56 (58.9)	38 (69.1)	0.29
Onset to admission, days, median (IQR)	2 (1–3)	2 (1–3)	0.99
Onset category, n (%)			
Within 24 h	46 (48.4)	26 (47.3)	0.91
2–3 days	28 (29.5)	17 (30.9)	
>3 days	21 (22.1)	12 (21.8)	

HU, Hounsfield unit; IQR, interquartile range. Continuous variables compared by Mann–Whitney U test; categorical variables by chi-square test.

Primary exposures: platelet count and haematocrit

Median platelet count was 219 ×10³/μL (IQR 171-325.5) in cases and 247 ×10³/μL (IQR 175.5-329.5) in controls; the difference was not statistically significant (P = 0.49) (Table 2). Haematocrit was lower in cases (median 38%, IQR 34-43) than in controls (median 41%, IQR 33.5-44), although the rank-based test did not cross the conventional threshold (P = 0.25). When haematocrit was dichotomised at the cohort median of 39%, a clearer signal emerged: patients with haematocrit above 39% had less than half the odds of being in the case (severe hypoattenuation) group, with an OR of 0.494 (95% CI 0.252-0.969; P = 0.040). The same dichotomous OR for platelet count was non-significant (OR 0.750, 95% CI 0.385-1.460; P = 0.40). Scatter plots of HU against the two exposures, with the regression line and Spearman coefficient overlaid, are shown in Figure 3.

Table 2. Platelet count and haematocrit by Hounsfield unit group.

Variable	Cases-HU ≤ 20 (n = 95)	Controls-HU > 20 (n = 55)	*P* value
Platelet count, ×10³/μL, median (IQR)	219 (171.0–325.5)	247 (175.5–329.5)	0.49
Platelet count, ×10³/μL, mean ± SD	248.4 ± 87.5	264.9 ± 99.3	0.31
Platelet >230.5 ×10³/μL, n (%)	46 (48.4)	31 (56.4)	0.40
Haematocrit, %, median (IQR)	38 (34.0–43.0)	41 (33.5–44.0)	0.25
Haematocrit, %, mean ± SD	38.3 ± 6.2	39.1 ± 7.0	0.49
Haematocrit >39%, n (%)	38 (40.0)	31 (56.4)	0.040

HU, Hounsfield unit; IQR, interquartile range; SD, standard deviation.

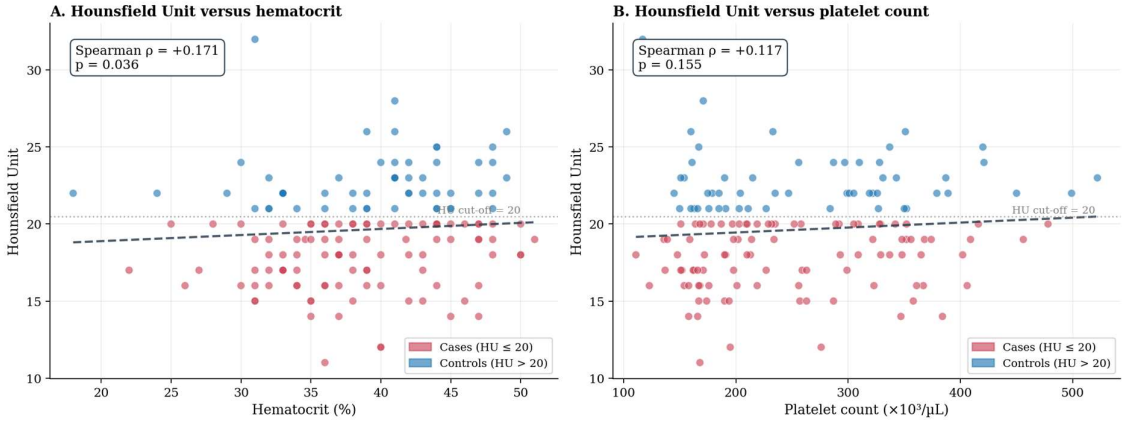

Figure 3. Scatter plots of Hounsfield unit against haematocrit (A) and platelet count (B) for the full case-control cohort (n = 150). Each dot represents a patient, with case status colour-coded. The dashed line is the ordinary least-squares regression fit. Spearman rank correlation coefficients with P values are overlaid.

Stroke severity and imaging burden

Clinical and radiological severity were broadly similar across the two HU strata (Table 3). Median NIHSS was 7 (IQR 4-13) in cases and 10 (IQR 4-16) in controls (*P* = 0.28). When categorised, mild stroke (NIHSS 1-4) accounted for 27.4% of cases and 27.3% of controls; moderate stroke (NIHSS 5-15) for 50.5% versus 41.8%; and severe stroke (NIHSS ≥ 16) for 22.1% versus 30.9% (*P* = 0.44). Median volume of infarct was numerically smaller in cases (3.10 cm³, IQR 1.54-21.03) than in controls (8.74 cm³, IQR 1.75-43.90; *P* = 0.17). On the continuous scale, volume had a small but borderline-significant inverse association with case status (OR 0.990 per 1 cm³, 95% CI 0.980-1.000; *P* = 0.048).

Table 3. Stroke severity and imaging parameters by Hounsfield unit group.

Variable	Cases-HU ≤ 20 (n = 95)	Controls-HU > 20 (n = 55)	*P* value
NIHSS, median (IQR)	7 (4–13)	10 (4–16)	0.28
NIHSS category, n (%)			
Mild (1–4)	26 (27.4)	15 (27.3)	0.44
Moderate (5–15)	48 (50.5)	23 (41.8)	
Severe (≥16)	21 (22.1)	17 (30.9)	
Volume of infarct, cm³, median (IQR)	3.10 (1.54–21.03)	8.74 (1.75–43.90)	0.17
Volume category, n (%)			
<5 cm³	54 (56.8)	26 (47.3)	0.25
5–30 cm³	20 (21.1)	10 (18.2)	
>30 cm³	21 (22.1)	19 (34.5)	

HU, Hounsfield unit; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

Univariate risk estimates

Univariate logistic regression, with case status (HU ≤ 20) as the outcome and each candidate predictor entered separately, is summarised in Figure 4 and detailed in Table 4. Haematocrit above 39% was significantly protective against severe hypoattenuation (OR 0.494, 95% CI 0.252-0.969; P = 0.040), and the continuous-scale estimate for volume of infarct was borderline negative (OR 0.990 per cm³, 95% CI 0.980-1.000; P = 0.048). Platelet count, whether modelled continuously or by dichotomy at the median, did not show any association. The forest plot makes plain that of the predictors examined, only haematocrit above the cohort median crossed the conventional threshold of significance in a clinically interpretable direction.

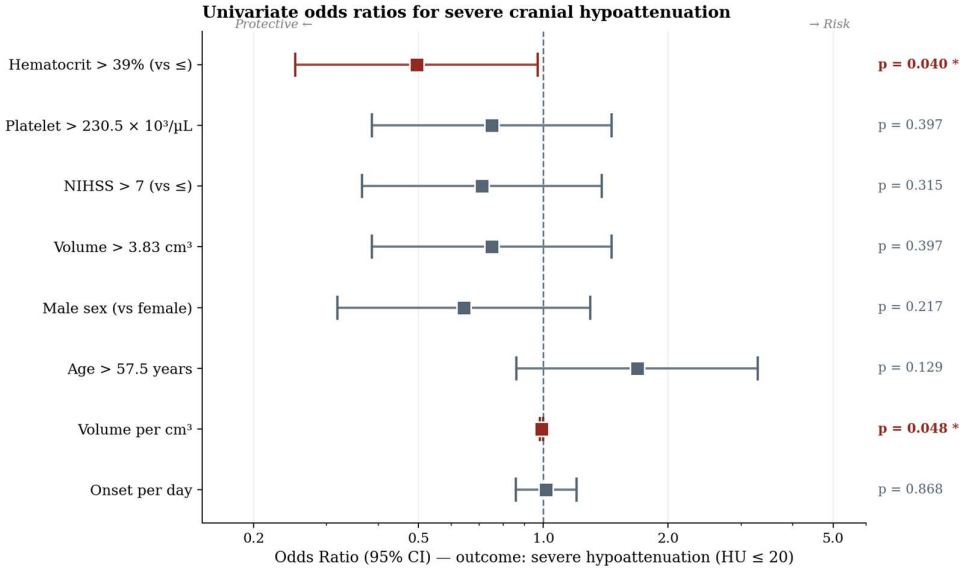

Figure 4. Forest plot of univariate odds ratios for severe cranial hypoattenuation (HU ≤ 20). Each square marks the point estimate of the odds ratio and the horizontal bar give the 95% confidence interval. Estimates with $P < 0.05$ are coloured in red. The dashed vertical line at OR = 1 corresponds to no association.

Table 4. Univariate logistic regression for severe hypoattenuation (HU ≤ 20).

Predictor	Crude OR	95% CI	P value
Age (per year)	1.017	0.985–1.050	0.29
Male sex (vs female)	0.642	0.318–1.297	0.22
Platelet count (per 50 ×10³/μL)	0.908	0.758–1.087	0.29
Platelet >230.5 ×10³/μL	0.750	0.385–1.460	0.40
Haematocrit (per 5% point)	0.910	0.702–1.178	0.47
Haematocrit >39%	0.494	0.252–0.969	0.040
NIHSS (per point)	0.964	0.920–1.010	0.13
Volume of infarct (per cm³)	0.990	0.980–1.000	0.048
Onset (per day)	1.014	0.857–1.201	0.87

CI, confidence interval; HU, Hounsfield unit; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Multivariable logistic regression

Multivariable logistic regression with all the above predictors entered simultaneously is summarised in Table 5. After mutual adjustment, none of the covariates remained statistically significant. The adjusted odds ratio for haematocrit (per 1% point) was 1.026 (95% CI 0.954-1.103; P = 0.49), and for platelet count (per 1 ×10³/μL) was 1.001 (95% CI 0.994-1.008; P = 0.74). The most plausible explanation for the attenuation of the univariate haematocrit signal is the strong positive inter-correlation in our cohort between haematocrit and the severity indicators NIHSS (Spearman ρ = +0.601, $P < 0.001$) and volume of infarct (ρ = +0.659, $P < 0.001$); this is visualised in Figure 5. When these severity indicators were placed in the same model, the marginal contribution of haematocrit became small, consistent with the principle that haematocrit reflects information that is largely shared with clinical severity rather than carrying an independent component.

Table 5. Multivariable logistic regression for severe hypoattenuation (HU ≤ 20).

Predictor	Adjusted OR	95% CI	P value
Age (per year)	1.016	0.983–1.050	0.34
Male sex (vs female)	0.652	0.308–1.378	0.26
Platelet count (per 1 ×10³/μL)	1.001	0.994–1.008	0.74
Haematocrit (per 1% point)	1.026	0.954–1.103	0.49
NIHSS (per point)	0.974	0.884–1.072	0.59
ln(Volume of infarct)	0.832	0.478–1.448	0.52
Onset (per day)	1.040	0.867–1.248	0.67

CI, confidence interval; HU, Hounsfield unit; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio. Outcome: case status (HU ≤ 20). Complete-case n = 150.

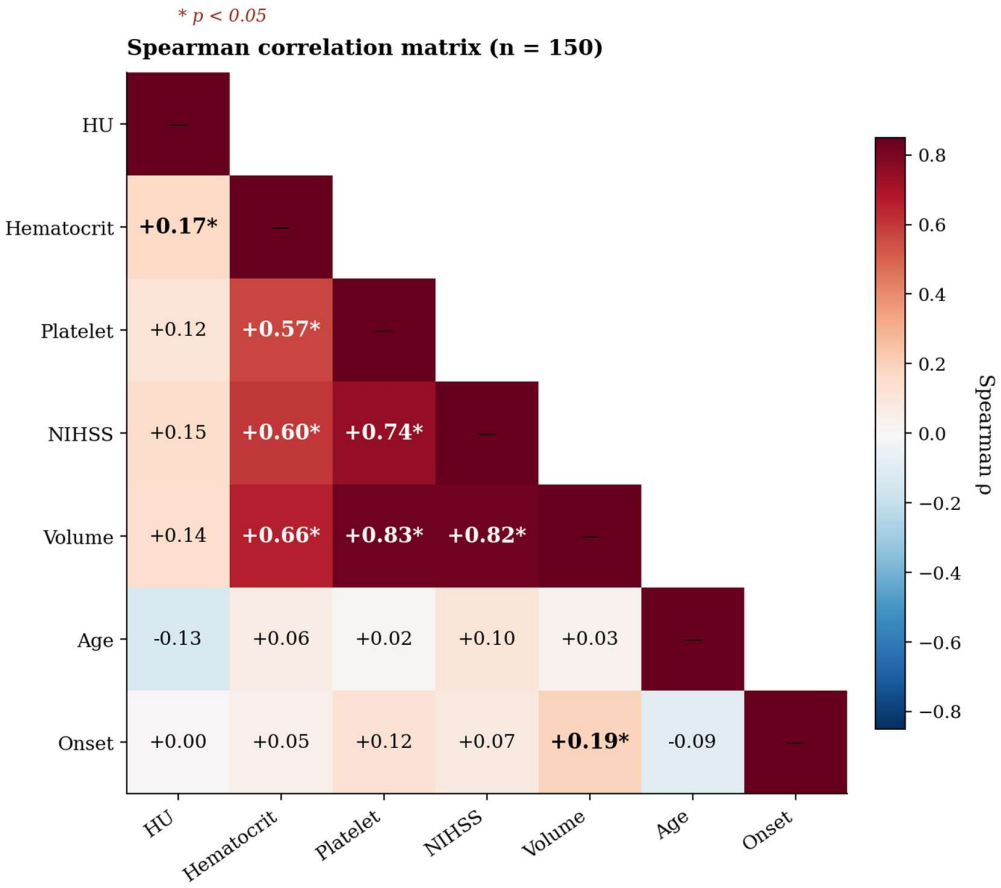

Figure 5. Spearman correlation matrix of the seven variables in the analytical cohort (n = 150). Coefficients are shown in the lower triangle; cells are coloured by direction and magnitude. Asterisks denote $P < 0.05$. Note the strong cluster of inter-correlations among haematocrit, platelet count, NIHSS and volume of infarct, and the relatively isolated position of Hounsfield unit, which has only a weak independent positive association with haematocrit.

Supplementary correlation analysis

As a sensitivity check, the relationship between HU and the candidate predictors was examined on the continuous scale using Spearman rank correlation in the full cohort. Haematocrit showed a statistically significant positive correlation with HU (ρ = +0.171, $P = 0.036$), confirming that patients with higher haematocrit tended to have higher HU values, that is, less hypoattenuation in the ischaemic

region. Platelet count was weakly and non-significantly correlated with HU (ρ = +0.117, P = 0.16). NIHSS (ρ = +0.147, P = 0.072) and volume of infarct (ρ = +0.143, P = 0.080) showed borderline positive correlations, while age trended negative (ρ = -0.127, P = 0.12) and onset was effectively zero (ρ = +0.003, P = 0.97). The continuous-scale results agree with the dichotomous case-control findings in identifying haematocrit as the only haematological marker with a detectable, though modest, signal in this cohort, in keeping with the well-known dependence of cerebral CT attenuation on intravascular blood density.[8,15]

DISCUSSION

This case-control analysis, carried out within a single curated cohort of 150 patients with acute ischaemic stroke, set out to examine whether peripheral platelet count and haematocrit differ between patients with severe and milder cranial parenchymal hypoattenuation. Three findings emerged. Haematocrit was the only haematological marker associated with severe hypoattenuation (HU $\leq$ 20), with patients having haematocrit above 39% showing roughly half the odds of falling into the severe-hypoattenuation group. Platelet count did not show any association in any of the analytical lenses we used, whether continuous, dichotomous at the median, or in tertiles. And the haematocrit signal lost statistical significance once clinical severity indicators were entered alongside it in the multivariable model, suggesting that haematocrit carries information largely co-varying with disease severity rather than independent of it.

Biological coherence of the haematocrit signal

The direction of the haematocrit-HU association we observed is biologically coherent. Haematocrit, by definition, is the volume fraction of red blood cells in whole blood, and red cells contribute the bulk of the intravascular radiodensity that CT picks up.[6,8,9] In an ischaemic territory where perfusion is impaired and parenchymal density is already drifting downward, a low circulating haematocrit will further reduce the contribution of intravascular blood to the local CT signal, allowing more pronounced hypoattenuation to develop. This same physical principle drives the use of the HU-to-haematocrit ratio in cerebral venous sinus thrombosis, where the goal is to correct an elevated HU reading for the patient's own blood density.[15-17] In the venous setting the ratio improves diagnostic specificity; in the arterial-ischaemic setting that we examined here the same dependence operates in the opposite direction, with low haematocrit pushing HU down rather than pulling it up.

Why platelet count showed nothing

Why platelet count showed no association deserves comment. In studies of thrombus composition, platelet-rich (white) thrombi tend to have lower HU than red-cell-rich thrombi, and this difference has clinical implications for thrombolysis response.[7,8] Those findings, however, refer to HU measured within the clot itself, not to parenchymal HU measured downstream from the occlusion, which is what we examined here. Platelets contribute relatively little to whole-blood radiodensity in the peripheral circulation, so it is plausible, on physical grounds, that peripheral platelet count would not move parenchymal HU values in a measurable way. The present results are consistent with this expectation and align with the negative platelet finding from our group's CVST case-control work.[15] Walton and colleagues' demonstration that elevated haematocrit enhances platelet accumulation at sites of vascular injury suggests that platelet biology may matter most at the level of thrombus formation rather than at the level of parenchymal attenuation.[10]

Interpreting the multivariable attenuation

The attenuation of the haematocrit signal in the multivariable model has an interpretation grounded in the inter-correlation structure of our data. Within cases, haematocrit was strongly correlated with NIHSS (Spearman ρ = +0.601) and with volume of infarct (ρ = +0.659), and these correlations were essentially absent in the control series. The simplest reading is that haematocrit, in this cohort, behaves as a marker co-varying with severity rather than as one that adds independent information beyond what NIHSS and volume already encode. Cui and colleagues, in a 14,832-patient analysis of the China National Stroke Registry-III, reported a J-shaped association between baseline haematocrit and three-month functional outcome, with both anaemia and high haematocrit linked to worse outcomes.[19] In their analysis, as in ours, the haematological signal carried part, but not all, of the variance attributable to disease severity. The clinical implication is that haematocrit is informative as a single, easily measured marker, but the marginal value of adding it to a model that already contains NIHSS and infarct volume is modest.

Comparison with the venous compartment

The comparison with our group's earlier work on cerebral venous sinus thrombosis is instructive. In that study, haematocrit alone did not separate cases from controls, but HU and the HU/Hct ratio were both significantly elevated in CVST patients, with the ratio achieving 91.2% sensitivity and 94.1% specificity at a cut-off of 1.41.[15] The case-control design and the variable triad were the same; the radiological direction was opposite, with thrombus hyperdensity rather than parenchymal hypoattenuation as the defining feature. Taken together, the two studies sketch a unified haemato-radiological framework in which haematocrit modulates the patient's baseline blood radiodensity, and this baseline then interacts with the local cerebrovascular pathology, either as hyperdensity (CVST) or as hypoattenuation (AIS), to produce the HU reading on which clinicians ultimately act. The framework is also consistent with what we have observed for the arterial side in our regional cohort of intracranial atherosclerosis, where the dominant risk factors were hypertension and dyslipidaemia rather than haematological abnormalities,[18] suggesting that haematological parameters modulate, rather than drive, the radiological signal of AIS.

Relevance to cerebral drug delivery and antithrombotic therapy

The pharmacological reading of these data is the one we find most interesting, and it turns on viscosity rather than on radiodensity. Haematocrit is the dominant determinant of whole-blood viscosity, and viscosity sets the resistance to flow through collateral and microvascular channels. The link between elevated viscosity and delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage makes the same point in a different disease: when the bed is compromised, rheology matters.[11] For drug delivery this is not an abstraction. A thrombolytic, a neuroprotective agent, or a nanocarrier given systemically has to be carried to the penumbra by residual flow, and residual flow through a partially obstructed bed depends on the viscosity of the blood doing the carrying. Our finding that haematocrit tracks parenchymal attenuation, weakly but in the expected direction, means that a routine complete blood count carries some information about the rheological environment a drug will encounter. The current generation of delivery platforms is built precisely for this environment, whether by crossing a compromised blood–brain barrier, by scavenging reactive oxygen species while an antiplatelet payload reopens the microcirculation, or by borrowing platelet membrane to gain thrombus affinity.[12,13,14,20] Protein-based nanocarriers are being pushed in the same direction, with the explicit goal of widening the therapeutic window.[21]

Two practical points follow, and both are modest. The first concerns stratification. Preclinical and early-phase delivery studies rarely record the recipient's haematocrit, yet haematocrit is not neutral with respect to the flow that carries a carrier to its target, and our data suggest it is not neutral with respect to the tissue state either. It costs nothing to record, and it could reasonably be entered as a covariate in trials of targeted delivery systems. The second concerns monitoring. Quantitative HU comes from a scan performed anyway, without extra cost, contrast or radiation, so pairing it with admission haematocrit is essentially free. Where thrombectomy and advanced perfusion imaging are not available and decisions about single, dual or triple antithrombotic regimens are made on basic imaging and a complete blood count, that pairing may help frame the picture.[22] We should be plain about what our data do not show. Haematocrit lost significance on adjustment, platelet count showed nothing at all, and we measured neither drug exposure nor perfusion. Nothing here demonstrates that haematocrit predicts drug delivery. It is a direction worth testing, not a result.

Clinical implications

The clinical implications of this work are pragmatic. Haematocrit is a routine measurement available in every emergency department, including those in resource-limited settings. Pairing it with HU at admission is essentially free in terms of additional data acquisition, and the present results suggest that this pairing carries useful information for stratifying severity, particularly in younger or sicker patients where rapid triage to thrombolysis or thrombectomy is needed. In our group's recent case report of triple antiplatelet therapy in a young patient with hemiplegic cerebral infarction, the radiological and clinical picture was similarly nuanced, with HU and clinical severity acting as complementary axes for decision-making.[22] In Indonesian and broader Southeast Asian settings, where anaemia prevalence in older adults is appreciable and where many stroke admissions are delayed by transport and triage logistics, routine integration of HU and haematocrit in the initial stroke evaluation may help flag the subset of patients in whom HU alone would either underestimate or overestimate the severity of cerebral injury.[1,2]

Limitations

This study has several limitations that should be acknowledged. The design is retrospective and single-centre, which constrains the generalisability of the absolute effect estimates even though the internal comparison between strata is robust. Hounsfield unit was measured with a single representative ROI rather than averaged across multiple slices, and no formal ASPECTS score was assigned, although the ROI procedure was conceptually aligned with the same principles of parenchymal density assessment.[4-6] The analysis did not separate ischaemic stroke subtypes by TOAST classification, and we did not stratify by diabetic status, both of which could be useful in future replications. Antithrombotic exposure before admission was not captured, which is a real weakness given the pharmacological framing above and one that cannot be reconstructed from existing records. Functional outcomes beyond the index admission were not available, so the prognostic value of the HU and haematocrit signal could not be tested directly; existing literature on haematocrit and stroke outcome strongly suggests such a follow-up would be worthwhile.[19,23] Finally, the cohort-derived median was used as the HU cut-off for case-control assignment because no universal clinical threshold exists in this range; this is a reasonable but data-dependent choice that should be re-tested in independent cohorts.

Future directions

Replication in a multicentre setting, with serial CT imaging to track HU evolution over the acute phase, and with the inclusion of the HU/Hct ratio as a secondary outcome, would help to consolidate the framework. Studies that measure haematocrit alongside perfusion imaging and, where possible, drug exposure would be needed to test whether the rheological argument sketched above has any real purchase.

CONCLUSION

In this single-centre case-control analysis of acute ischaemic stroke in eastern Indonesia, haematocrit, but not platelet count, was modestly associated with severe parenchymal hypoattenuation on non-contrast cranial CT. Patients with haematocrit above 39% had approximately half the odds of severe hypoattenuation compared with those at or below the median. The signal was largely absorbed by clinical severity in multivariable adjustment, which indicates that haematocrit carries information overlapping with NIHSS and infarct volume rather than

being independent of them. Together with our group's earlier work on the same triad of variables in cerebral venous sinus thrombosis, the present results support an emerging haemato-radiological framework in which haematocrit modulates baseline blood radiodensity and interacts with local cerebrovascular pathology to shape HU readings. Because haematocrit also governs whole-blood viscosity, and therefore the residual flow that carries any systemically administered agent into ischaemic tissue, pairing haematocrit with HU at admission is worth carrying forward as an inexpensive stratification variable in cerebral drug delivery research. The pairing is simple and easily implementable in resource-limited stroke services, and may contribute to more nuanced acute stratification of patients with ischaemic cerebrovascular disease.

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AUTHORS' CONTRIBUTIONS
IPP contributed to study conception, data acquisition, statistical analysis, and drafting of the manuscript. MYA supervised the project, contributed to study design and data interpretation, and critically revised the manuscript. HB contributed to methodology and critical revision. MA contributed to data interpretation and critical revision. ML contributed to data analysis and critical revision. All authors reviewed and approved the final version.

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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
AIS: acute ischaemic stroke

ASPECTS: Alberta Stroke Program Early CT Score

CI: confidence interval

CT: computed tomography

CVST: cerebral venous sinus thrombosis

Hct: haematocrit

HU: Hounsfield unit

IQR: interquartile range

NCCT: non-contrast cranial computed tomography

NIHSS: National Institutes of Health Stroke Scale

OR: odds ratio

ROI: region of interest

SD: standard deviation

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