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Volume contracted state, mortality and functional outcomes in patients with acute ischaemic stroke due to large vessel occlusion

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ABSTRACT

Background Acute ischaemic stroke (AIS) is a leading cause of mortality and disability globally, with volume contracted state (VCS), as indicated by an elevated blood urea nitrogen to creatinine (BUN/Cr) ratio, potentially influencing outcomes. This study investigates the association between VCS and clinical outcomes in patients with AIS due to large vessel occlusion (LVO).

Methods A retrospective cohort study was conducted involving 298 patients with LVO-AIS from two comprehensive stroke centres. Patients were divided into two groups based on BUN/Cr ratio: ≤20 (n=205) and >20 (n=93). Primary outcomes included 90-day mortality and unfavourable functional outcomes, defined as a modified Rankin Scale score of 3–6. Secondary outcomes included the successful reperfusion, haemorrhagic transformation and National Institutes of Health Stroke Scale score at discharge.

Results Patients with a BUN/Cr ratio >20 had significantly higher 90-day mortality (35% vs 13%, p<0.001) and this association remained significant after adjusting for confounding factors (OR 2.20; 95% CI 1.11 to 4.39; p=0.024). However, VCS was not significantly associated with unfavourable functional outcomes at 90 days (OR 1.28; 95% CI 0.67 to 2.51; p=0.46). Age and initial stroke severity were more strongly associated with long-term functional outcomes.

Conclusions VCS is associated with higher odds of 90-day mortality in patients with LVO-AIS but not with unfavourable functional outcomes. These findings suggest the need for further research into the role of hydration management in improving survival in patients with AIS, potentially informing future treatment protocols.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ An elevated blood urea nitrogen to creatinine (BUN/Cr) ratio is a marker of volume contracted state (VCS) and has been associated with adverse outcomes in acute ischaemic stroke (AIS) patients. Previous studies suggest that VCS may influence mortality and functional recovery, but its specific impact on patients with large vessel occlusion (LVO) remains underexplored.

WHAT THIS STUDY ADDS

⇒ This study identifies that VCS (BUN/Cr ratio >20) is independently associated with a significantly higher 90-day mortality rate in patients with LVO-AIS. However, VCS does not show a significant association with unfavourable functional outcomes at 90 days after adjusting for confounding factors such as age and initial stroke severity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that addressing VCS through targeted hydration strategies during AIS management could improve survival rates. Future research should focus on prospective trials to evaluate the impact of hydration correction on outcomes, potentially informing treatment protocols and guidelines.

INTRODUCTION

Stroke is the second leading cause of death and disability globally,[1] among the different types of strokes, acute ischaemic stroke (AIS) is the most common.[2] AIS results from sudden occlusion in a cerebral blood vessel, leading to hypoperfusion of a brain territory, and the underlying mechanisms of AIS are influenced by complex interactions between the brain's blood flow and overall cardiovascular dynamics.[3 4] The role of dehydration status, or more specifically volume contracted state (VCS), in cerebral infarction, is thought to be multifactorial. Dehydration reduces intravascular volume and increases blood viscosity, both of which may contribute to diminished cerebral perfusion in the setting

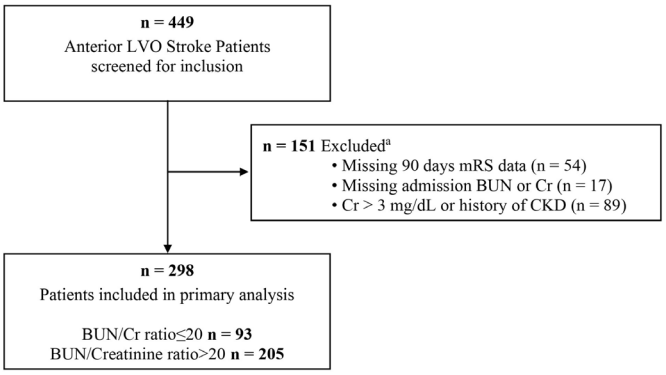

Figure 1 Patients selection flowchart. [a]Multiple selection of patients possible. BUN/Cr, blood urea nitrogen to creatinine; LVO, large vessel occlusion; mRS, modified Rankin Scale.

of impaired autoregulation. Elevated haematocrit levels have been correlated with larger infarct sizes in patients experiencing cerebral infarction.[5] Furthermore, VCS has been associated with an increased incidence of recurrent embolic strokes and thrombotic events, including venous thromboembolism, following an acute stroke.[6 7]

The blood urea nitrogen to creatinine ratio (BUN/Cr) is a commonly utilised indirect indicator for evaluating VCS, BUN/Cr ratio has been applied in various studies to assess VCS.[6 8 9] Both BUN and Cr are key markers in evaluating renal function and are frequently included in electrolyte panels for patients experiencing cerebral infarction. Its potential value as a VCS marker would be significant if it could reliably predict adverse outcomes in patients with AIS.[6] In this study, we use an elevated BUN/Cr ratio (>20) as a surrogate biomarker of VCS, recognising that it is one of the several potential clinical or biochemical indicators of volume contraction.[10 11] Thus, the primary aim of this study was to investigate the association between VCS and clinical outcomes in patients with AIS.

METHODS

Population and study design

This prospectively collected, retrospectively reviewed cohort study was conducted at two comprehensive stroke centres within the Johns Hopkins Medical Enterprise: Johns Hopkins Hospital—East Baltimore and Bayview Medical Campus.[12–28] We identified consecutive patients from a continuously maintained database from 22 August 2018 to 18 October 2022. The study was approved by the Institutional Review Board and was conducted in accordance with the Declaration of Helsinki and HIPAA regulations. Informed consent was waived due to the retrospective nature of the study. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology checklist guidelines for observational studies.[29]

The study included participants who met the following criteria: (a) adult individuals diagnosed with AIS resulting from a large vessel occlusion (LVO) in the anterior circulation, defined as occlusions in the internal carotid artery, M1 segment or proximal M2 segment of the middle cerebral artery, as confirmed by CT angiography; (b) availability of BUN and creatinine levels at the time of admission and (c) available 90-day modified Rankin Scale (mRS) scores for outcome assessment. Patients were excluded if they had chronic kidney disease or if their creatinine levels exceeded 3 mg/dL on admission, to ensure that the BUN/Cr ratio reliably reflected VCS rather than renal impairment or baseline renal dysfunction.

Data collection

The data were obtained from electronic health records and stroke centre databases. The gathered data encompassed patient characteristics such as age, gender and medical history, including risk factors for AIS (diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation). Additionally, the data included admission National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score, occlusion site and administration or performance of intravenous thrombolysis (IVT) or mechanical thrombectomy (MT). The levels of BUN and creatinine were measured as part of routine clinical care on patient arrival at the emergency department, prior to neuroimaging and any acute interventions. mRS scores at discharge and 90 days (90-day mRS) were determined by a stroke neurologist or certified stroke nurse per stroke centre standards.

The administration of IVT and the performance of MT were determined on a case-by-case basis, following a consensus appraisal by the stroke team according to our institution's protocols. However, reasons for not performing MT were not systematically recorded.

Imaging analysis and parameters

Non-contrast CT and CT angiography were performed using standard institutional protocols. The evaluation of all images was performed by experienced neuroradiologists (MH and VY, 3 and 10 years of experience, respectively). Discrepancies were resolved by consensus review.

Outcomes

The primary outcomes of this study were to examine the relationship between VCS and two key outcomes: mortality and unfavourable recovery, with unfavourable recovery defined as an mRS score of 3–6. Secondary outcomes included the extent of reperfusion, assessed by the Modified Thrombolysis in Cerebral Infarction (mTICI) scale, haemorrhagic transformation (HT) as defined by ECASS-2 criteria and the NIHSS score at discharge.

Statistical analysis

Categorical variables were summarised as frequencies and percentages, compared using the χ^2 test and Fisher's exact test where sample sizes were less than five. Continuous variables were presented as medians and IQRs, compared using the Mann-Whitney U test.

Table 1 Baseline characteristics of dichotomisation based on BUN/creatinine ratio≤20

Variable	Overall, N=298	BUN/creatinine ratio≤20 N=205	BUN/creatinine ratio>20 N=93	P value*
Age, median (IQR)	66 (55, 76)	64 (53, 73)	72 (63, 81)	<0.001
Sex, n (%)				0.018
Female	172 (58)	109 (53)	63 (68)	
Male	126 (42)	96 (47)	30 (32)	
Occlusion segment, n (%)				0.12
ICA	49 (16)	29 (14)	20 (22)	
M1	185 (62)	135 (66)	50 (54)	
M2	64 (21)	41 (20)	23 (25)	
Smoking status, n (%)	138 (46)	97 (47)	41 (44)	0.6
Alcohol use, n (%)	88 (30)	65 (32)	23 (25)	0.22
Hypertension, n (%)	222 (74)	152 (74)	70 (75)	0.84
Dyslipidaemia, n (%)	146 (49)	101 (49)	45 (48)	0.89
Diabetes, n (%)	71 (24)	42 (20)	29 (31)	0.045
Heart disease, n (%)	136 (46)	91 (44)	45 (48)	0.52
Atrial fibrillation, n (%)	95 (32)	59 (29)	36 (39)	0.088
History of stroke/TIA, n (%)	60 (20)	42 (20)	18 (19)	0.82
Chronic kidney disease, n (%)	0 (0)	0 (0)	0 (0)	
Sleep apnoea, n (%)	34 (11)	24 (12)	10 (11)	0.81
Admission glucose level, median (IQR)	119 (105, 144)	117 (104, 140)	125 (107, 160)	0.031
Premorbid modified Rankin Scale, median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	1.00 (0.00, 3.00)	<0.001
Admission NIHSS score, median (IQR)	14 (6, 20)	14 (6, 19)	16 (8, 21)	0.08
Occlusion laterality, n (%)				0.54
Left	158 (53)	106 (52)	52 (56)	
Right	138 (46)	98 (48)	40 (43)	
Bilateral	2 (0.7)	1 (0.5)	1 (1.1)	
ASPECTS, median (IQR)	9.00 (7.75, 10.00)	9.00 (8.00, 10.00)	10.00 (7.00, 10.00)	0.91
Tan score (0–3), median (IQR)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.75)	0.5

*Wilcoxon rank sum test; Pearson's χ^2 test; Fisher's exact test.
ASPECTS, Alberta Stroke Program Early CT Score; BUN, blood urea nitrogen; NIHSS, National Institutes of Health Stroke Scale.

Univariable logistic regression was initially employed to identify variables potentially associated with the primary outcomes, with a threshold p value of <0.1. Variables meeting this criterion were subsequently included in a multivariable logistic regression model. The findings from the logistic regression analyses were reported as ORs with corresponding 95% CIs. All p values were based on two-sided tests, and a p value of less than 0.05 was considered statistically significant.

R statistical software (V.4.3.0, R Project for Statistical Computing) and Rstudio statistical software (V.2023.03.0+386, Rstudio) were used for statistical analyses and data visualisation.

RESULTS

Patient characteristics

A total of 298 patients with AIS due to LVO were included in this study (figure 1). The cohort was divided based on their BUN/Cr ratio into two groups: BUN/Cr ≤20 (n=205) and BUN/Cr >20 (n=93). Patients in the BUN/Cr >20 group were significantly older, with a median age of 72 years (IQR 63–81), compared with 64 years (IQR 53–73) in the BUN/Cr ≤20 group (p<0.001). The BUN/Cr >20 group also had a higher proportion of women (68% vs 53%, p=0.018) and a greater prevalence of diabetes mellitus (31% vs 20%, p=0.045). No significant differences were observed between the two groups regarding other baseline characteristics, such as smoking status, hypertension or atrial fibrillation (table 1)

Table 2 Procedural and clinical outcome variables dichotomisation based on BUN/creatinine ratio≤20

Variable	Overall, N=298	BUN/creatinine ratio≤20 N=205	BUN/creatinine ratio>20 N=93	P value*
IVT administered, n (%)	98 (33)	71 (35)	27 (29)	0.34
MT attempted, n (%)	196 (66)	136 (66)	60 (65)	0.76
Type of thrombectomy, n (%)				0.86
Direct aspiration	98 (53)	70 (54)	28 (51)	
Stent retriever	23 (13)	15 (12)	8 (15)	
Combined	61 (33)	42 (33)	19 (35)	
Other	2 (1.1)	2 (1.6)	0 (0)	
Number of thrombectomy passes, median (IQR)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.84
Type of anaesthesia used, n (%)				0.4
General	181 (92)	127 (93)	54 (90)	
MAC	15 (7.7)	9 (6.6)	6 (10)	
Door to CT time (min), median (IQR)	28 (16, 47)	27 (17, 45)	31 (13, 52)	0.6
Door to needle time (min), median (IQR)	58 (42, 79)	58 (41, 77)	66 (45, 116)	0.22
Onset to groin puncture time (min), median (IQR)	253 (182, 401)	258 (171, 413)	237 (193, 332)	0.68
Groin puncture to first pass time (min), median (IQR)	22 (16, 30)	20 (15, 29)	24 (19, 33)	0.021
Door to reperfusion time (mins), median (IQR)	365 (220, 846)	367 (217, 739)	347 (235, 971)	0.49
Groin puncture to reperfusion time (min), median (IQR)	32 (22, 58)	31 (22, 57)	35 (23, 66)	0.24
Modified thrombolysis in cerebral infarction (mTICI) score, n (%)				0.84
0	10 (5.2)	8 (6.1)	2 (3.4)	
1	3 (1.6)	2 (1.5)	1 (1.7)	
2a	9 (4.7)	7 (5.3)	2 (3.4)	
2b	49 (26)	37 (28)	12 (20)	
2c	21 (11)	13 (9.8)	8 (14)	
3	99 (52)	65 (49)	34 (58)	
Haemorrhagic transformation (HT), n (%)	97 (35)	71 (36)	26 (30)	0.32
Type of HT if present, n (%)				0.46
HI1	15 (16)	13 (19)	2 (8.3)	
HI2	40 (44)	27 (40)	13 (54)	
PH1	20 (22)	16 (24)	4 (17)	
PH2	16 (18)	11 (16)	5 (21)	
Discharge NIHSS score, median (IQR)	4 (1, 12)	4 (1, 12)	4 (1, 14)	0.74

*Wilcoxon rank sum test; Pearson's χ^2 test; Fisher's exact test.
BUN, blood urea nitrogen; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale.

Procedural and clinical outcomes

As shown in table 2, there were no significant differences between the two groups in terms of procedural variables, including the administration of IVT (35% vs 29%; p=0.34), the performance of MT (66% vs 65%; p=0.76) or the type of anaesthesia used during MT (general anaesthesia in 93% vs 90%; p=0.40). However, patients with a BUN/Cr ratio >20 had a significantly longer groin puncture to first pass time (median, 24 min (IQR, 19–33) vs 20 min (IQR, 15–29); p=0.021). There were no significant differences in other time metrics, including door to CT time, door to needle time and door to reperfusion time.

Mortality

At 90 days, 60 patients (20%) had died. Univariable analysis demonstrated that an elevated BUN/Cr ratio (>20) was strongly associated with 90-day mortality (OR 3.63; 95% CI 2.02 to 6.57; p<0.001). The mortality rate in the BUN/Cr >20 group was 35% (33 out of 93 patients), compared with 13% (27 out of 205 patients) in the BUN/Cr ≤20 group (p<0.001). After adjusting for age, admission NIHSS score, and other relevant variables in the multivariable model, the BUN/Cr ratio>20 remained an independently associated with higher odds of mortality (OR 2.20; 95% CI 1.11 to 4.39; p=0.024). In addition,

Table 3 Patient cohort, univariable, multivariable model for association with 90 days mortality outcome

	Survival	Mortality	Univariable model		Multivariable model	
Variable	**N=238**	**N=60**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age, median (IQR)	64 (53, 73)	77 (66, 85)	1.06 (1.04 to 1.08)	<0.001	1.05 (1.03 to 1.08)	**<0.001**
Sex, n (%)						
Female	139 (58)	33 (55)	—			
Male	99 (42)	27 (45)	1.15 (0.65 to 2.03)	0.63		
Occlusion segment, n (%)						
ICA	41 (17)	8 (13)	—			
M1	148 (62)	37 (62)	1.28 (0.58 to 3.15)	0.56		
M2	49 (21)	15 (25)	1.57 (0.62 to 4.24)	0.35		
Smoking status, n (%)	115 (48)	23 (38)	0.66 (0.37 to 1.18)	0.17		
Alcohol use, n (%)	77 (32)	11 (18)	0.47 (0.22 to 0.92)	0.036	0.50 (0.21 to 1.10)	0.1
Hypertension, n (%)	173 (73)	49 (82)	1.67 (0.85 to 3.57)	0.16		
Dyslipidaemia, n (%)	115 (48)	31 (52)	1.14 (0.65 to 2.02)	0.64		
Diabetes, n (%)	53 (22)	18 (30)	1.50 (0.78 to 2.78)	0.21	1.88 (0.87 to 4.05)	0.11
Heart disease, n (%)	109 (46)	27 (45)	0.97 (0.55 to 1.71)	0.91		
Atrial fibrillation, n (%)	70 (29)	25 (42)	1.71 (0.95 to 3.07)	0.071		
History of stroke/TIA, n (%)	50 (21)	10 (17)	0.75 (0.34 to 1.53)	0.45		
Chronic kidney disease, n (%)	0 (0)	0 (0)				
Sleep apnoea, n (%)	31 (13)	3 (5.0)	0.35 (0.08 to 1.03)	0.093		
Admission glucose level, median (IQR)	118 (104, 142)	124 (112, 152)	1.00 (1.00 to 1.01)	0.18		
BUN/creatinine ratio>20, n (%)	60 (25)	33 (55)	3.63 (2.02 to 6.57)	<0.001	2.20 (1.11 to 4.39)	**0.024**
Admission NIHSS score, median (IQR)	12 (5, 18)	19 (15, 22)	1.12 (1.08 to 1.17)	<0.001	1.11 (1.06 to 1.17)	**<0.001**
Occlusion laterality, n (%)						
Left	123 (52)	35 (58)	—			
Right	114 (48)	24 (40)	0.74 (0.41 to 1.31)	0.31		
Bilateral	1 (0.4)	1 (1.7)	3.51 (0.14 to 90.4)	0.38		
ASPECTS, median (IQR)	9.00 (8.00, 10.00)	8.50 (6.00, 10.00)	0.86 (0.76 to 0.97)	0.012	0.91 (0.78 to 1.07)	0.25
Tan score (0–3), median (IQR)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.79 (0.56 to 1.10)	0.16		
IVT administered, n (%)	81 (34)	17 (28)	0.77 (0.40 to 1.41)	0.4	0.94 (0.44 to 1.97)	0.88
MT attempted, n (%)	156 (66)	40 (67)	1.05 (0.58 to 1.94)	0.87	0.66 (0.31 to 1.44)	0.29

ASPECTS, Alberta Stroke Program Early CT Score; BUN, blood urea nitrogen; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

higher admission NIHSS scores were also independently associated with increased odds of mortality (OR 1.11; 95% CI 1.06 to 1.17; p<0.001) as was age (OR 1.05; 95% CI 1.03 to 1.08; p<0.001) (table 3).

Functional outcomes

The percentage of patients with unfavourable outcome was higher in the BUN/Cr >20 group (55%, 51 out of 93 patients) compared with the BUN/Cr ≤20 group (44%, 89 out of 205 patients), though this difference did not reach statistical significance (p=0.28) (figure 2). Univariable analysis revealed that a higher admission NIHSS score (OR 0.88; 95% CI 0.85 to 0.91; p<0.001), older age (OR 0.96; 95% CI 0.94 to 0.97; p<0.001) and a history of atrial fibrillation (OR 0.52; 95% CI 0.32 to 0.86; p=0.01) were associated with poor functional outcomes (mRS 3–6). In the multivariable analysis, the BUN/Cr ratio >20 was not significantly associated with unfavourable functional outcomes (OR 1.28; 95% CI 0.67 to 2.51; p=0.46) (table 4). However, age (OR 0.95; 95% CI 0.93 to 0.98; p<0.001) and admission NIHSS score (OR 0.90; 95% CI

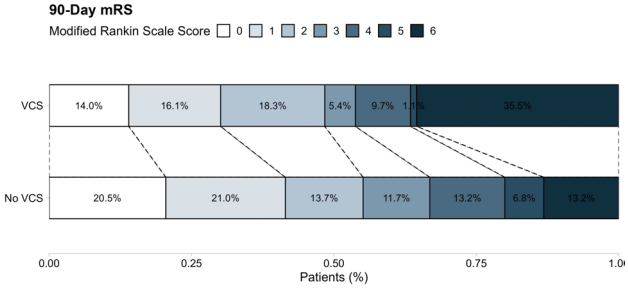

Figure 2 Distribution of 90-day modified Rankin Scale (mRS) scores among the patients with VCS and those without. VCS, volume contracted state.

Table 4 Patient cohort, univariable, multivariable model for association with 90 days favourable outcome (vs unfavourable outcome (mRS 3–6) as reference value)

	mRS 3–6	mRS 0–2	Univariable model		Multivariable model	
Variable	**N=140**	**N=158**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age, median (IQR)	72 (62, 82)	62 (52, 70)	0.96 (0.94 to 0.97)	<0.001	0.95 (0.93 to 0.98)	**<0.001**
Sex, n (%)						
Female	81 (58)	91 (58)	—			
Male	59 (42)	67 (42)	1.01 (0.64 to 1.60)	0.96		
Location arterial occlusion, n (%)						
ICA	22 (16)	27 (17)	—			
M1	90 (64)	95 (60)	0.86 (0.45 to 1.62)	0.64		
M2	28 (20)	36 (23)	1.05 (0.49 to 2.22)	0.9		
Smoking status, n (%)	63 (45)	75 (47)	1.10 (0.70 to 1.75)	0.67		
Alcohol use, n (%)	32 (23)	56 (35)	1.85 (1.12 to 3.11)	0.018	1.84 (0.98 to 3.52)	0.061
Hypertension, n (%)	116 (83)	106 (67)	0.42 (0.24 to 0.72)	0.002	0.71 (0.34 to 1.45)	0.35
Dyslipidaemia, n (%)	73 (52)	73 (46)	0.79 (0.50 to 1.24)	0.31		
Diabetes, n (%)	39 (28)	32 (20)	0.66 (0.38 to 1.12)	0.13	0.59 (0.27 to 1.27)	0.18
Heart disease, n (%)	77 (55)	59 (37)	0.49 (0.31 to 0.77)	0.002	0.73 (0.38 to 1.41)	0.35
Atrial fibrillation, n (%)	55 (39)	40 (25)	0.52 (0.32 to 0.86)	0.01	1.15 (0.55 to 2.43)	0.71
History of stroke/TIA, n (%)	31 (22)	29 (18)	0.79 (0.45 to 1.39)	0.42		
Sleep apnoea, n (%)	14 (10)	20 (13)	1.30 (0.64 to 2.74)	0.47		
Admission glucose level, median (IQR)	123 (110, 152)	116 (102, 139)	0.99 (0.99 to 1.00)	0.024	1.00 (0.99 to 1.00)	0.62
BUN/creatinine ratio>20, n (%)	48 (34)	45 (28)	0.76 (0.47 to 1.25)	0.28	1.28 (0.67 to 2.51)	0.46
Admission NIHSS score, median (IQR)	18 (13, 22)	10 (4, 16)	0.88 (0.85 to 0.91)	<0.001	0.90 (0.86 to 0.93)	**<0.001**
Occlusion laterality, n (%)						
Left	79 (56)	79 (50)	—			
Right	60 (43)	78 (49)	1.30 (0.82 to 2.06)	0.26		
Bilateral	1 (0.7)	1 (0.6)	1.00 (0.04 to 25.6)	>0.99		
ASPECTS, median (IQR)	9.00 (6.00, 10.00)	9.00 (8.00, 10.00)	1.19 (1.07 to 1.34)	0.003	1.15 (0.98 to 1.36)	0.1
Tan score (0–3), median (IQR)	1.00 (1.00, 2.00)	2.00 (1.00, 2.00)	1.48 (1.12 to 1.96)	0.006	1.17 (0.82 to 1.65)	0.39
IVT administered, n (%)	38 (27)	60 (38)	1.64 (1.01 to 2.70)	0.048	1.75 (0.92 to 3.38)	0.091
MT attempted, n (%)	96 (69)	100 (63)	0.79 (0.49 to 1.28)	0.34		

ASPECTS, Alberta Stroke Program Early CT Score; BUN, blood urea nitrogen; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale.

0.86 to 0.93; p<0.001) remained significantly associated with unfavourable functional outcomes (figure 1).

Secondary outcomes

HT occurred in 35% of the cohort (97 out of 298 patients), with no significant difference between the BUN/Cr >20 group (28%) and the BUN/Cr ≤20 group (34%, p=0.32). Among those who experienced HT, the distribution of haemorrhagic types did not differ significantly between the two groups, with HI2 being the most common type in both groups (40% in the BUN/Cr ≤20 group and 54% in the BUN/Cr >20 group, p=0.46) (table 5).

Successful reperfusion (mTICI 2b–3) was achieved in 89% of patients, with similar rates in the BUN/Cr >20 group (91%) and the BUN/Cr ≤20 group (88%, p=0.84). Complete reperfusion (mTICI 3) rates were also similar (58% vs 52%, p=0.84). In terms of discharge outcomes, there was no significant difference between the BUN/Cr ≤20 group (median 4 (IQR 1–12)) and the BUN/Cr >20 group (median 4 (IQR 1–14), p=0.74) (table 5).

DISCUSSION

In this cohort, we demonstrate that patients with a BUN/Cr ratio >20 had significantly higher mortality rates at 90 days as compared with the cohort without VCS (35% vs 13%, p<0.001) and was independently associated with higher odds of mortality after adjustment for confounders (OR 2.20; 95% CI 1.11 to 4.39; p=0.024). However, while a higher BUN/Cr ratio had worse recovery outcomes, it was not significantly associated with unfavourable functional outcomes at 90 days (OR 1.28; 95% CI 0.67 to 2.51; p=0.46).

Table 5 Secondary outcomes

Variable	Overall, N=298	BUN/creatinine ratio≤20 N=205	BUN/creatinine ratio>20 N=93	P value*
Modified thrombolysis in cerebral infarction (mTICI) score, n (%)				0.84
0	10 (5.2)	8 (6.1)	2 (3.4)	
1	3 (1.6)	2 (1.5)	1 (1.7)	
2a	9 (4.7)	7 (5.3)	2 (3.4)	
2b	49 (26)	37 (28)	12 (20)	
2c	21 (11)	13 (9.8)	8 (14)	
3	99 (52)	65 (49)	34 (58)	
Haemorrhagic transformation (HT), n (%)	97 (35)	71 (36)	26 (30)	0.32
Type of HT if present, n (%)				0.46
HI1	15 (16)	13 (19)	2 (8.3)	
HI2	40 (44)	27 (40)	13 (54)	
PH1	20 (22)	16 (24)	4 (17)	
PH2	16 (18)	11 (16)	5 (21)	
Discharge NIHSS score, median (IQR)	4 (1, 12)	4 (1, 12)	4 (1, 14)	0.74

*Wilcoxon rank sum test; Pearson's χ^2 test; Fisher's exact test.
BUN, blood urea nitrogen; NIHSS, National Institutes of Health Stroke Scale.

The underlying mechanisms behind our findings may stem from the intricate relationship between intravascular volume and the body's haemodynamic responses.[3 4] Maintaining proper intravascular volume during periods of disrupted autoregulation is essential for sustaining adequate blood flow, which is critical for delivering oxygen and ensuring the proper function of organs.[3 4] During VCS blood flow to vital organs including brain is significantly diminished, which can impair their function.[3 4 6] Additionally, VCS can lead to a reduction in cardiac output, further compromising cerebral perfusion.

The brain has a strong autoregulatory system that typically maintains stable cerebral blood flow even when systemic blood pressure fluctuates.[30] This autoregulatory system can be compromised by ischaemic stroke, resulting in a greater reliance on systemic blood pressure for cerebral perfusion. Consequently, in the context of VCS, a diminished intravascular volume may further reduce perfusion pressure and exacerbate ischaemic injury.[10 11] This impairment could make the brain more susceptible to reduced perfusion during an AIS period.[6] The combination of reduced cerebral blood flow and increased blood viscosity due to VCS can worsen ischaemic injury, leading to larger infarct sizes and a higher risk of mortality.

Furthermore, previous studies have demonstrated that dehydrated stroke patients have higher risk for earlier neurological deterioration, likely due to the decreased collateral blood flow and cerebral perfusion associated with VCS, resulting in ischaemic brain injury.[31] Infarct volume, a critical determinant of clinical severity in stroke patients, has been shown to progress in the context of VCS, as evidenced by both animal models and clinical studies.[32–34] Recent large-scale research has further linked VCS with a more severe stroke course and increased mortality, highlighting the complex relationship between poststroke hydration status and clinical outcomes.[11] However, clinical research specifically addressing how VCS predicts the evolution of the ischaemic core remains limited.

On the other hand, the trend towards an association between the VCS and unfavourable functional outcomes at 90 days, although not statistically significant, is consistent with a potential negative impact of VCS on functional recovery.[31] This finding likely reflects limited statistical power in our analysis rather than the absence of a true association, highlighting the need for larger studies to adequately evaluate this relationship.[6 10 35]

Our findings are consistent with those reported by Renner *et al*, who demonstrated that VCS at the admission was associated with higher odds of mortality but not associated with worse functional outcome.[11] Similarly, Li *et al* identified a BUN/Cr ratio >19.63 mg/dL as a significant predictor of elevated in-hospital mortality rates.[36] In contrast, other studies have established an association between VCS and unfavourable outcomes in AIS patients.[6 10 35]

Despite all of this, an important area that remains unresolved is whether the rapid correction of VCS in AIS patients could lead to decrease in mortality rate or improve clinical outcomes. In the acute setting, intravenous fluid administration is a common practice for AIS patients, based on the fact that VCS may reduce cerebral perfusion and worsen outcomes.[6 37] The 2018 American Heart Association/American Stroke Association guidelines for early management of AIS patients

recommend correcting hypotension and hypovolemia to maintain systemic perfusion necessary for organ function.[38] However, these guidelines acknowledge the lack of specific data on the appropriate volume and duration of parenteral fluid delivery, with the recommendations largely based on expert consensus rather than empirical evidence.

Despite the strong recommendation (class I) for maintaining adequate hydration, there is surprisingly little data on the actual hydration practices and their efficacy in the context of AIS, especially on mortality.[39 40] Addressing this gap would likely require a prospective trial. Furthermore, it remains unclear whether hydration strategies that go beyond achieving euvolemia, such as hyperdynamic haemodilution, could offer additional benefits in the acute phase of stroke. Given that nearly one-third of our study sample had a VCS, the potential for rapid VCS correction to improve clinical outcomes could be significant. Such findings would have important implications for the management of AIS and could lead to more targeted and effective treatment protocols.[6]

This study has several limitations including the use of a single institution, which may limit the results at other geographic locations. Additionally, our study focused on BUN/Cr ratio as a surrogate marker for VCS. We recognise that other markers, including hypotension, tachycardia and elevated haematocrit, could strengthen the assessment of VCS and its impact on outcomes and incorporating these markers in future studies may provide a more comprehensive understanding of VCS in AIS patients. The use of the BUN/Cr ratio of 20 was chosen a priori based on similar studies looking at markers for VCS, changes in this ratio would affect the number of patients marked as VCS and would affect results.[10 11] We did not control for medications which may affect this ratio such as diuretics. We did not measure the amount of intravascular fluid administered within the early ischaemic stroke period. Next, the data for potentially relevant variables, such as urine-specific gravity, urine sodium, serum bicarbonate, measured osmolality, and ejection fraction, are not routinely collected in stroke trials and therefore were not included in the analysis. Using a single measure at baseline likely does not fully reflect the dynamic situation of a patient with AIS. Moreover, detailed reasons for not pursuing MT were not consistently recorded and should be addressed in future studies. While we adjusted for common comorbid conditions known to influence outcomes after stroke, there are likely numerous unmeasured residual confounders, and VCS may simply reflect a marker of a more medically ill cohort of patients with stroke.

CONCLUSION

In conclusion, this study demonstrates a significant association between VCS, as indicated by BUN/Cr ratio >20, and increased mortality in patients with AIS due to LVO, though was not significantly associated with long-term functional outcomes, with factors such as age and initial stroke severity playing more critical roles. These results underscore the need for further research into this relationship and hydration strategies in AIS management. Studies to investigate the influence of prescribed hydration at the time of AIS are in process. Prospective studies will allow a better understand of this mechanistic relationship and allow us to potentially refine treatment protocols for this high-risk patient population.

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