Stroke

ORIGINAL CONTRIBUTION

Association of Net Water Uptake With Catastrophic Functional Outcome After Thrombectomy in Patients With Large Infarcts

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BACKGROUND: This study aimed to investigate whether net water uptake (NWU) is associated with 3-month catastrophic functional outcome (modified Rankin Scale score, 5–6) and to develop predictive models with preprocedural factors, including NWU, in patients with large infarcts who underwent endovascular thrombectomy.

METHODS: This multicenter observational cohort study conducted in Korea included patients with anterior circulation stroke and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≤5 receiving endovascular thrombectomy between 2015 and 2023. NWU, a quantitative imaging biomarker reflecting the degree of hypoattenuation on noncontrast computed tomography, was measured across the entire ASPECTS region (ASPECTS10-NWU), and its association with catastrophic functional outcome was assessed using a mixed-effects logistic regression model, adjusting for age, sex, prestroke modified Rankin Scale score, baseline National Institutes of Health Stroke Scale score, baseline ASPECTS, onset-to-baseline noncontrast computed tomography time, and intravenous tissue-type plasminogen activator, with hospital included as a random effect. Moreover, a predictive model has been developed with preprocedural factors that were significant covariates from the mixed-effects logistic regression analysis.

RESULTS: A total of 255 patients were included (mean age, 71.0±12.6 years; 54.9% male). The median ASPECTS10-NWU was 3.0% (interquartile range, 1.9%–4.1%). Higher ASPECTS10-NWU was independently associated with catastrophic functional outcome (adjusted odds ratio, 1.70 [95% CI, 1.33–2.17]; *P*<0.001). The model integrating ASPECTS10-NWU with preprocedural variables suggested predicted catastrophic functional outcome probabilities; as ASPECTS10-NWU and baseline National Institutes of Health Stroke Scale score increased, the marginal probability of catastrophic functional outcome increased in all age (<80 and ≥80 years) and prestroke modified Rankin Scale score (0–1 and 2–4) groups, with the patients aged ≥80 years and with prestroke modified Rankin Scale score of 2 to 4 having higher outcome probability.

CONCLUSIONS: Elevated ASPECTS10-NWU is strongly associated with catastrophic functional outcome in patients with large infarcts treated with endovascular thrombectomy. Integrating the ASPECTS10-NWU with clinical variables may provide patient-specific prognostication that may assist clinicians in decision-making for endovascular thrombectomy in large infarcts.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: biomarkers ■ ischemic stroke ■ neuroimaging ■ prognosis ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early Computed Tomography Score
CT	computed tomography
CTP	computed tomography perfusion
EVT	endovascular thrombectomy
HU	Hounsfield unit
ICH	intracerebral hemorrhage
IQR	interquartile range
mRS	modified Rankin Scale
NCCT	noncontrast computed tomography
NIHSS	National Institutes of Health Stroke Scale
NWU	net water uptake
OR	odds ratio

Six recent randomized clinical trials have demonstrated the efficacy and safety of endovascular thrombectomy (EVT) in patients with Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≤5.[1–6] However, the rates of bedridden state or death (modified Rankin Scale [mRS] score, 5 or 6) at 3 months remained high (33%–50%) despite EVT.[1–6] Moreover, 3 of these trials have reported higher rates of hemorrhagic transformation in the EVT group,[1–3] suggesting potential harm of EVT in patients with large infarcts. Given these challenges, physicians should consider various clinical and radiographic factors and provide realistic expectations to patients and their families when deciding whether to proceed with EVT in this population.

Net water uptake (NWU) is a biomarker that measures the degree of ischemic brain tissue damage based on hypoattenuation observed on computed tomography (CT).[7] Compared with ASPECTS, which rates only the presence or absence of ischemic injury in predefined brain regions,[8] NWU provides a quantitative assessment of ischemic severity.[7] This biomarker has shown significant clinical utility in predicting outcomes, such as cerebral edema development, intracranial hemorrhage, and functional outcome after EVT.[9–13] As a novel radiographic marker, NWU holds potential prognostic value in patients with large infarcts treated with EVT, a population at high risk for symptomatic intracranial hemorrhage and malignant cerebral edema, which are both associated with devastating outcomes but have been underexplored.

This study aimed to investigate whether NWU is associated with catastrophic functional outcome (defined as an mRS score, 5 or 6) and to develop predictive models with preprocedural factors, including NWU, in patients with large infarcts treated with EVT to support informed decision-making for EVT in this population.

METHODS

Study Population

We retrospectively identified consecutive patients with acute ischemic stroke treated with EVT at 4 academic and regional stroke centers from prospectively maintained institutional stroke registry databases (from January 2015 to December 2023 at Kyungpook National University Hospital, Seoul National University Bundang Hospital, and Dongguk University Ilsan Hospital, and from January 2020 to December 2023 at Keimyung University Dongsan Hospital). The inclusion criteria are given as follows: (1) age ≥18 years; (2) large vessel occlusion in the anterior circulation (intracranial internal carotid artery, M1 segment of the middle cerebral artery, or tandem occlusion) confirmed by initial CT angiography or magnetic resonance angiography; (3) onset-to-arrival time ≤24 hours; (4) a baseline National Institutes of Health Stroke Scale (NIHSS) score ≥6; and (5) ASPECTS ≤5 on baseline noncontrast CT (NCCT), as rated by board-certified stroke neurologists at each participating institution, blinded to other clinical data. We excluded patients with (1) no baseline NCCT data before EVT, (2) a large preexisting ischemic or hemorrhagic infarction, (3) poor image quality at baseline NCCT, and (4) a prestroke mRS score of 5. The institutional review board of each institution approved the study protocol (KNUH 2025-03-020, B-2504-968-101, DUIH 2025-03-010, and DSMC 2025-03-032). The need for informed consent was waived, owing to the retrospective study design and data anonymity. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[14] The data supporting the study findings are available from the corresponding author upon reasonable request.

Clinical Data and Outcome Measurements

Baseline patient demographics, procedural variables, and outcome variables, including prestroke mRS score, baseline NIHSS score, modified Thrombolysis in Cerebral Infarction score,[15] and mRS score at 3 months, were extracted from each institutional stroke registry or electronic medical record. Through a Web-based education system (https://k-stroke-academy.co.kr/), physicians and nurses at the participating centers were trained and certified to assess mRS scores and NIHSS scores. The mRS score at 3 months after the index stroke was obtained prospectively by dedicated coordinators during patients' routine clinic visits or via telephone interviews with patients or their next of kin. Hemorrhagic transformation and cerebral edema were assessed on follow-up CT or magnetic resonance imaging after EVT at ≈24 hours. Hemorrhagic transformation was classified into hemorrhagic infarction type 1, hemorrhagic infarction type 2, parenchymal hematoma type 1, and parenchymal hematoma type 2. Symptomatic intracerebral hemorrhage (ICH) was defined as parenchymal hematoma type 2 combined with neurological worsening ≥4 on the NIHSS score from baseline.[16,17] Cerebral edema was defined as mild (focal brain swelling up to one-third of the hemisphere), moderate (focal brain swelling involving greater than one-third of the hemisphere), or severe (focal brain swelling causing midline shift).[18]

NWU Measurement

All patients underwent comprehensive stroke imaging upon admission according to the institutional protocols. The baseline

NCCT protocols were 80 to 120 kV, 90 to 600 mA, a field of view of 156 to 270 mm, and 2- to 5-mm slice reconstruction. NWU was measured using a validated software tool with automated processing (JLK-CTL, JLK, Inc, Seoul, Republic of Korea; Figure 1).[19] To mitigate confounding effects from outliers, such as artifacts, hemorrhage, chronic infarcts, and cerebrospinal fluid spaces, a preprocessing procedure was performed. Specifically, intensity windowing with a center value of 40 Hounsfield units (HU) and a width of 40 HU was applied, followed by the exclusion of voxels in each region that deviated by >10 HU from the median. The NWU of the whole ASPECTS region (ASPECTS10-NWU) was calculated as follows. The mean HU values of all 10 ASPECTS regions for the ipsilesional (HU_{lesion}) and contralesional sides (HU_{normal}) were measured using a validated algorithm, and ASPECTS10-NWU was presented as the percentage difference in mean HU value between the ipsilesional and contralesional hemispheres according to equation (1). Because HU decreases with increasing severity and duration of ischemia, and no clear threshold of HU was set for ischemia, we used the entire ASPECTS region to define the NWU rather than a visually evident hypoattenuated lesion on NCCT.[20,21] To avoid inaccurate segmentation of the ASPECTS regions, all ASPECTS10-NWU measurements were verified by experienced stroke neurologists (D.-S.G. and N.K.).

$$\text{ASPECTS10-NWU (\%)}=[1-(HU_{lesion}/HU_{normal})]\times 100. \quad (1)$$

Statistical Analysis

Data are presented as mean±SD, median (interquartile range [IQR]), or number (proportion), as appropriate.

To evaluate the association of the ASPECTS10-NWU with stroke outcomes, we used a mixed-effects logistic regression

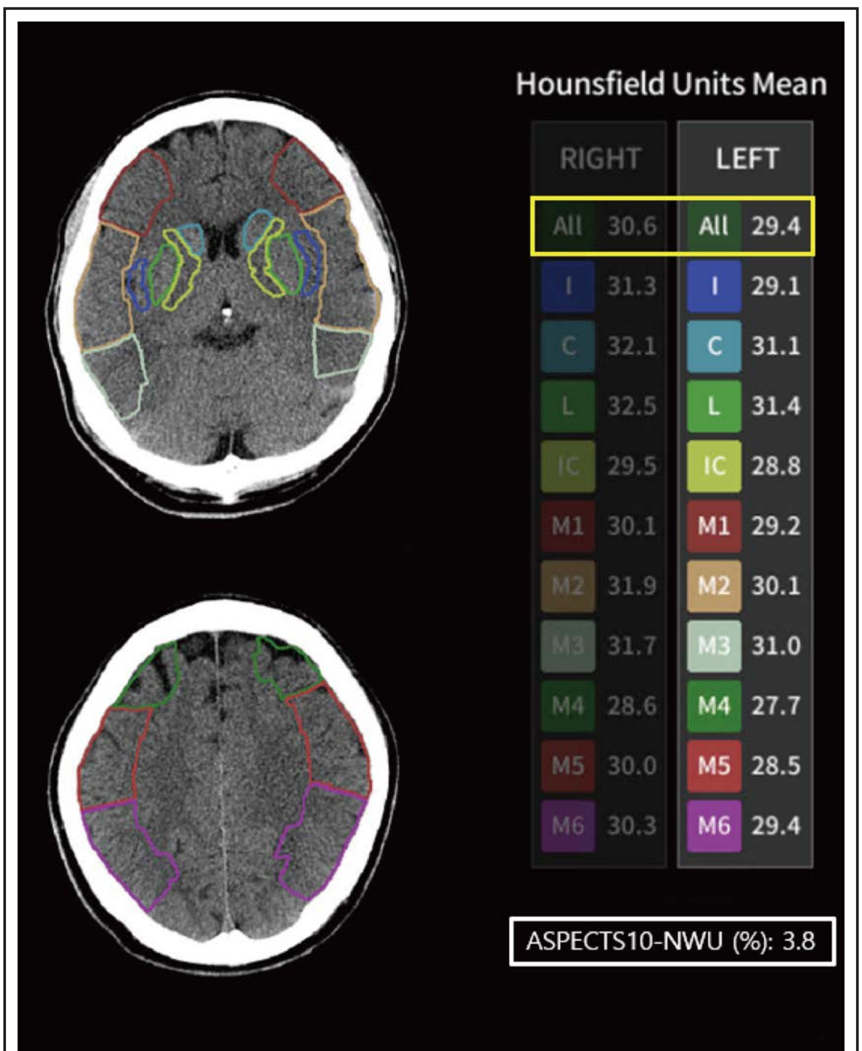

Figure 1. Quantification of Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 10-net water uptake (NWU). ASPECTS10-NWU was measured from baseline noncontrast computed tomography. The mean Hounsfield units (HU) values were automatically measured across all 10 ASPECTS regions in the ipsilesional (HU_{lesion}) and contralesional sides (HU_{normal}) using a validated algorithm (highlighted by the yellow box). ASPECTS10-NWU was calculated as the percentage difference in mean HU value between the ipsilesional and contralesional hemispheres using the following equation: ASPECTS10-NWU (%)=(1−[HU_{lesion}/HU_{normal}])×100.

model to account for clustering by hospital. The primary outcome was a 3-month catastrophic functional outcome (defined as an mRS score, 5 or 6). The secondary outcomes included a 3-month favorable functional outcome (defined as an mRS score, 0–3), any hemorrhagic transformation, symptomatic ICH, and moderate-to-severe cerebral edema. Because of the small sample size, we constructed a prespecified multivariable model (ASPECTS10-NWU model) with clinically important preprocedural variables (age, sex, prestroke mRS score, baseline NIHSS score, baseline ASPECTS, onset-to-baseline NCCT time, and intravenous tissue-type plasminogen activator).[13] Cases with missing data for the primary (n=0) and secondary outcomes (3-month mRS score, 0–3 [n=0], any hemorrhagic transformation [n=6], symptomatic ICH [n=6], and moderate-to-severe cerebral edema [n=6]) were excluded from the analyses. The resulting predicted probabilities of 3-month catastrophic and favorable functional outcomes were also plotted against ASPECTS10-NWU. Subgroup analyses were performed to investigate whether the association between the ASPECTS10-NWU and outcomes differed according to age, sex, prestroke mRS score, baseline NIHSS score, baseline ASPECTS, occlusion site, lesion side, prior stroke, onset-to-baseline NCCT time, and intravenous tissue-type plasminogen activator. Mixed-effects logistic regression analyses with the abovementioned predefined covariates were performed.

To investigate the additive prognostic value of NWU in predicting catastrophic functional outcome, we compared 2 mixed-effects logistic regression models: the ASPECTS10-NWU model, which included the ASPECTS10-NWU variable along with the same aforementioned clinically important preprocedural covariates (including baseline ASPECTS), and the ASPECTS model, which contained the identical covariates except for the exclusion of the ASPECTS10-NWU variable. The model performances were evaluated using a receiver operating characteristic curve analysis, and the area under the curve was estimated with internal validation via 1000 bootstrap replications. The difference in areas under the curve between the 2 models was assessed using the DeLong test.

Predictive models for 3-month catastrophic and favorable functional outcomes were developed using preprocedural factors that were significant covariates from the mixed-effects logistic regression analyses. Data were analyzed using the STATA software (version 18.0; STATA Corp, College Station, TX) and R, version 3.5.3 (R Foundation for Statistical Computing). Statistical significance was set at $P<0.05$.

RESULTS

Baseline Characteristics

A total of 255 patients with APSECTS of ≤5 who received EVT were included in this study (Figure S1). Their mean age was 71.0±12.6 years, and 54.9% were male (n=140). The median ASPECTS10-NWU was 3.0% (IQR, 1.9%–4.1%; Table 1). The distribution of ASPECTS10-NWU across each ASPECTS is presented in Figure S2. Patients with identical ASPECTS can exhibit markedly different ASPECTS10-NWU values. Those with significant disabilities before admission (prestroke mRS score, 2–4) were 21.6% (n=55). The median baseline

Table 1. Baseline, Imaging, Procedure, and Outcome Variables in 255 Patients With Acute Ischemic Stroke With ASPECTS Score of ≤5 Treated With Endovascular Thrombectomy

	All (n=255)
ASPECTS10-NWU, %	3.0 (1.9–4.1)
Range of ASPECTS10-NWU, %	0.0–10.9
Age, y	71.0±12.6
Male	140 (54.9)
Prestroke mRS score	
0–1	200 (78.4)
2–4	55 (21.6)
Baseline NIHSS score	18 (15–21)
ASPECTS on NCCT	4 (3–5)
Stroke mechanism	
LAA	36 (14.1)
Cardioembolism	159 (62.4)
Other determined/undetermined	60 (23.5)
Occlusion site	
Intracranial ICA	114 (44.7)
MCA M1	124 (48.6)
Tandem	17 (6.7)
Lesion side	
Left	95 (37.3)
Right	160 (62.8)
Hypertension	169 (66.3)
Diabetes	77 (30.2)
Hyperlipidemia	93 (36.5)
Atrial fibrillation	151 (59.2)
MI or angina	35 (13.7)
Prior stroke	53 (20.8)
Smoking	68 (26.7)
Workflow Times	
Onset-to-door time, h	3.3 (1.3–5.9)
Onset-to-baseline NCCT, h	3.5 (1.7–6.1)
Onset-to-puncture time, h	4.6 (2.6–7.2)
Onset-to-recanalization time, h	5.4 (3.6–8.6)
Baseline NCCT-to-puncture time, h	0.8 (0.5–1.2)
Baseline NCCT-to-recanalization time, h	1.7 (1.3–2.4)
Intravenous tissue-type plasminogen activator	113 (44.3)
mTICI	
0–2a	29 (11.4)
2b–3	226 (88.6)
Outcomes	
3-mo mRS score	4 (2–5)
3-mo mRS score, 5–6	97 (38.0)
3-mo mRS score, 0–3	105 (41.2)
Hemorrhagic transformation*	
Hemorrhagic infarction type 1	38/249 (15.3)
Hemorrhagic infarction type 2	56/249 (22.5)
Parenchymal hematoma type 1	26/249 (10.4)
Parenchymal hematoma type 2	34/249 (13.7)
Symptomatic ICH*	19/249 (7.6)
Moderate-to-severe cerebral edema*	109/249 (43.8)

Variables are presented as mean±SD, median (interquartile range), or absolute number (proportion). ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; ICA, internal carotid artery; ICH, intracerebral hemorrhage; LAA, large artery atherosclerosis; MCA, middle cerebral artery; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; and NWU, net water uptake.

* Patients lacking follow-up CT or MRI after endovascular thrombectomy at ≈24 h (n=6) were excluded.

NIHSS score and ASPECTS were 18 (IQR, 15–21) and 4 (IQR, 3–5), respectively. The median onset-to-baseline NCCT was 3.5 (IQR, 1.7–6.1) hours. A final modified Thrombolysis in Cerebral Infarction grade of 2b or 3 was achieved in 88.6% of the patients (n=226; Table 1).

Outcomes

Catastrophic functional outcome (mRS score, 5–6) at 3 months was observed in 97 patients (38%), and favorable functional outcome (mRS score, 0–3) at 3 months was observed in 105 patients (41.2%; Table 1). Any hemorrhagic transformation occurred in 61.8% (154/249; 6 patients lacking follow-up CT or magnetic resonance imaging after EVT at ≈24 hours were excluded), and the overall rate of symptomatic ICH was 7.6% (19/249). Moderate-to-severe cerebral edema was observed in 43.8% of the patients (109/249).

Association of ASPECTS10-NWU With Stroke Outcomes

In mixed-effects logistic regression analyses, higher ASPECTS10-NWU was associated with higher rates of catastrophic functional outcome at 3 months (odds ratio [OR], 1.86 [95% CI, 1.50–2.30]; P<0.001; Table 2). After adjustment for covariates, ASPECTS10-NWU showed an independent association with catastrophic functional outcomes at 3 months (adjusted OR, 1.70 [95% CI, 1.33–2.17]; P<0.001; Table 2; Table S1). ASPECTS10-NWU was also independently associated with secondary outcomes including 3-month favorable functional outcome (adjusted OR, 0.69 [95% CI, 0.54–0.87]; P=0.002; Table 2; Table S1), any hemorrhagic transformation (adjusted OR, 1.37 [95% CI, 1.09–1.72]; P=0.006), symptomatic ICH (adjusted OR, 1.59 [95% CI, 1.13–2.24]; P=0.008), and moderate-to-severe cerebral edema (adjusted OR, 1.48 [95% CI, 1.19–1.84]; P=0.001; Table 2).

The predicted probabilities of functional outcomes at 3 months against ASPECTS10-NWU from the same mixed-effects logistic regression models are shown in Figure S3. As the ASPECTS10-NWU increased, the predicted probability of a catastrophic functional outcome increased, whereas the likelihood of achieving a favorable functional outcome declined. At an ASPECTS10-NWU of 4.0%, corresponding approximately to the highest 25th percentile, ≈60% of patients experienced a catastrophic outcome, whereas <30% had a favorable outcome. At an ASPECTS10-NWU of 6.0%, near the highest fifth percentile, the proportion of catastrophic outcomes increased to ≈75%, whereas favorable outcomes decreased to <20%.

Subgroup Analyses

Subgroup analyses showed that ASPECTS10-NWU consistently affected catastrophic functional outcome at 3 months across all subgroups although the CIs for OR of subgroups for prestroke mRS score of 2 to 4, baseline ASPECTS score of 0 to 2, and presence of prior stroke marginally crossed 1.0 (Figure S4).

Comparison of the ASPECTS10-NWU and ASPECTS Models

In the receiver operating characteristic curve analyses with catastrophic functional outcome as the dependent variable, the area under the curve of the ASPECTS model was 0.76 (95% CI, 0.70–0.82; P<0.001; Figure 2). Whether the ASPECTS10-NWU model, adding the ASPECTS10-NWU variable to the ASPECTS model, would lead to improved predictive power for catastrophic functional outcome was tested, and its area under the curve was 0.82 (95% CI, 0.76–0.87; P<0.001), significantly outperforming the ASPECTS model (P=0.003; Figure 2).

Predictive Models for 3-Month Catastrophic and Favorable Functional Outcomes

Predictive models for 3-month catastrophic and favorable functional outcomes included only significant covariates from both multivariable mixed-effects logistic regression

Table 2. Associations Between ASPECTS10-NWU and Outcomes in Patients With Acute Ischemic Stroke With ASPECTS Score of ≤5 Treated With Endovascular Thrombectomy

	Univariable analysis, OR (95% CI)	P value	Multivariable analysis,* OR (95% CI)	P value
3-mo mRS score, 5–6	1.86 (1.50–2.30)	<0.001	1.70 (1.33–2.17)	<0.001
3-mo mRS score, 0–3	0.62 (0.51–0.76)	<0.001	0.69 (0.54–0.87)	0.002
Any hemorrhagic transformation†	1.28 (1.07–1.54)	0.008	1.37 (1.09–1.72)	0.006
Symptomatic ICH†	1.52 (1.15–2.00)	0.003	1.59 (1.13–2.24)	0.008
Moderate-to-severe cerebral edema†	1.66 (1.37–2.02)	<0.001	1.48 (1.19–1.84)	0.001

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; NWU, net water uptake; and OR, odds ratio.

*Data were adjusted for age, sex, prestroke mRS score, baseline NIHSS score, baseline ASPECTS, onset-to-baseline NCCT time, and intravenous tissue-type plasminogen activator.

†Patients lacking follow-up CT or MRI after endovascular thrombectomy at ≈24 h (n=6) were excluded from the analysis.

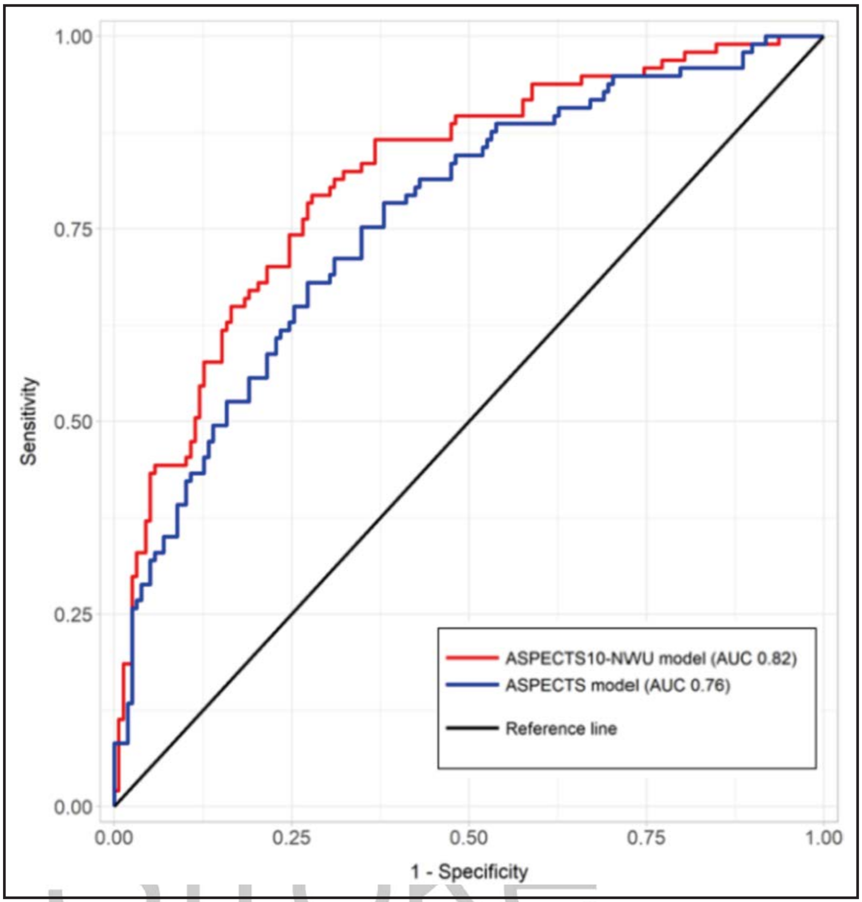

Figure 2. Receiver operating characteristic curve analysis for predicting catastrophic functional outcome.
With an area under the curve (AUC) of 0.82 (95% CI, 0.76–0.87), the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 10-net water uptake (NWU) model significantly outperformed the ASPECTS model (AUC, 0.76 [95% CI, 0.70–0.82]; *P*=0.003). The ASPECTS model was developed using a mixed-effects logistic regression model and included baseline ASPECTS, age, sex, prestroke modified Rankin Scale score, baseline National Institutes of Health Stroke Scale score, onset-to-baseline noncontrast computed tomography time, and intravenous tissue-type plasminogen activator, accounting for clustering by hospital. The ASPECTS10-NWU model included ASPECTS10-NWU and all variables of the ASPECTS model.

models, that is, ASPECTS10-NWU, age, and baseline NIHSS score (Table S1). The predicted probabilities were derived from a new mixed-effects logistic regression model (Table S2). Figure 3A illustrates the association of ASPECTS10-NWU, age, and baseline NIHSS score with the predicted probability of a catastrophic functional outcome at 3 months. As ASPECTS10-NWU and baseline NIHSS score increased, the marginal probability of the outcome increased in both age groups (<80 and ≥80 years) with the patients aged ≥80 years having a higher probability of catastrophic functional outcome than those aged <80 years. In terms of the predicted probability of a favorable functional outcome at 3 months, as the ASPECTS10-NWU and baseline NIHSS scores increased, the marginal probability of the outcome decreased in both age groups with the patients aged ≥80 years having a lower probability of a favorable functional outcome (Figure 3B).

We also developed another predictive model for the 3-month catastrophic outcome with significant covariates from the multivariable mixed-effects logistic regression model for the outcome: ASPECTS10-NWU, age, prestroke mRS score, and baseline NIHSS score (Table S1). As the ASPECTS10-NWU and baseline NIHSS scores increased, the marginal probability of the outcome increased in all age (<80 and ≥80 years) and prestroke mRS score (0–1 and 2–4) groups, with patients aged ≥80 years and those with prestroke mRS score of 2 to 4 having a higher probability of catastrophic functional outcomes (Figure 4; the predicted probability was derived from the new mixed-effects logistic regression model in Table S3).

DISCUSSION

ASPECTS10-NWU was significantly associated with a 3-month catastrophic functional outcome in patients with acute ischemic stroke with ASPECTS ≤5 treated with EVT. Moreover, it was negatively associated with a

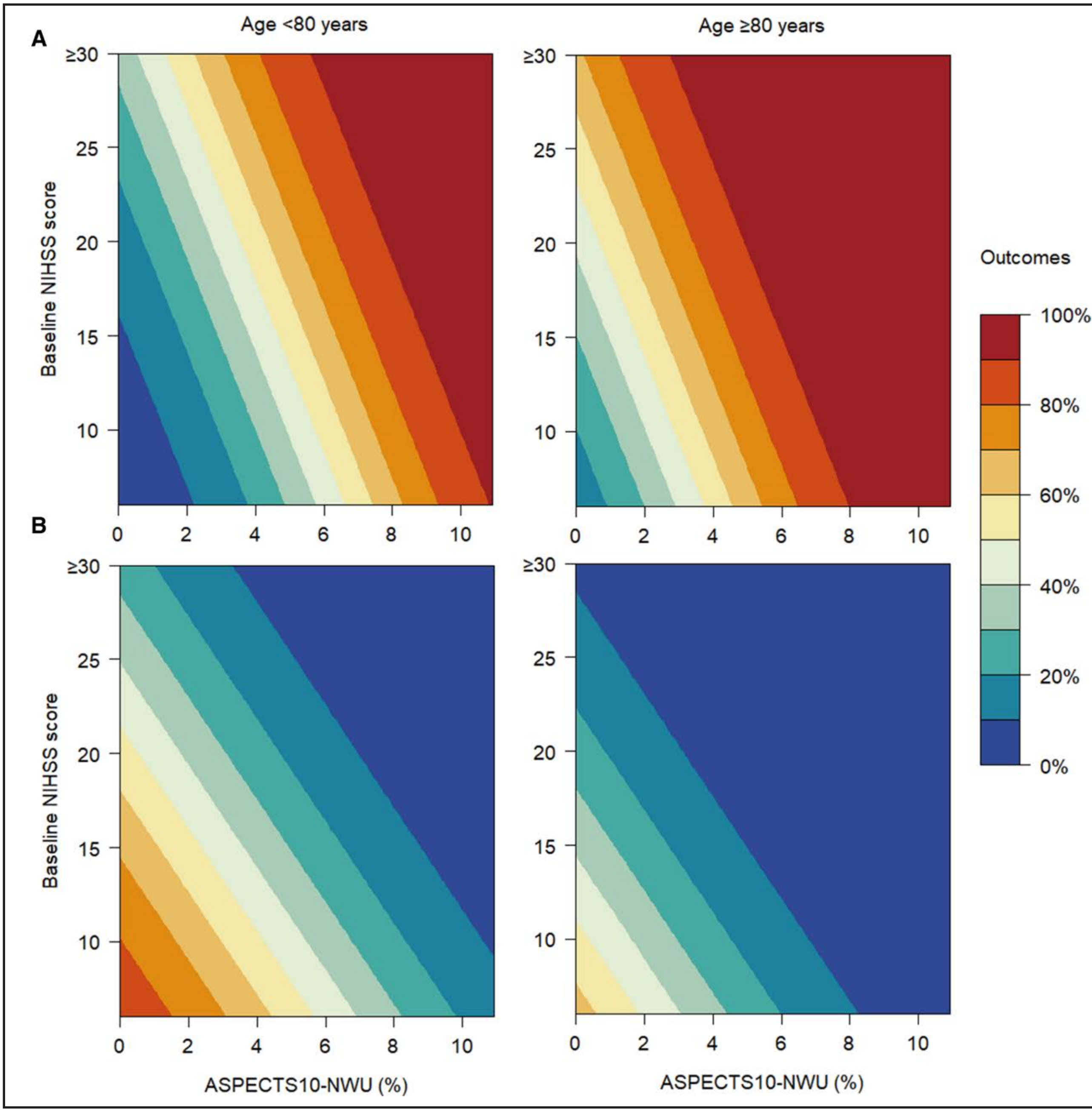

Figure 3. **XXX.**
Predicted probabilities for 3-month (**A**) catastrophic (modified Rankin Scale [mRS] score, 5 or 6) and (**B**) favorable (mRS score, 0–3) functional outcomes associated with Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 10-net water uptake (NWU), age, and baseline National Institutes of Health Stroke Scale (NIHSS) score in patients with acute ischemic stroke with ASPECTS ≤5 treated with endovascular thrombectomy. The predicted probabilities were derived from mixed-effects logistic regression models in Table S2.

3-month favorable functional outcome. As it increased, the likelihood of a catastrophic functional outcome increased, whereas the possibility of achieving a favorable functional outcome declined. In predicting functional outcomes after EVT in patients with large infarcts, the ASPECTS10-NWU in conjunction with age, baseline NIHSS score, and prestroke mRS score were the most informative. Our findings on the probability of catastrophic and favorable functional outcomes could guide clinical decisions regarding EVT in this patient population, which has poor clinical outcomes despite EVT.

The NWU reflects the pathophysiological process of infarction that disrupts water homeostasis with cytotoxic, ionic, and vasogenic edema, with subsequent blood-brain barrier breakdown.[9,10,22,23] Elevated NWU may also contribute to hemorrhagic transformation, as increased blood-brain barrier permeability makes the tissue more susceptible to reperfusion injury after

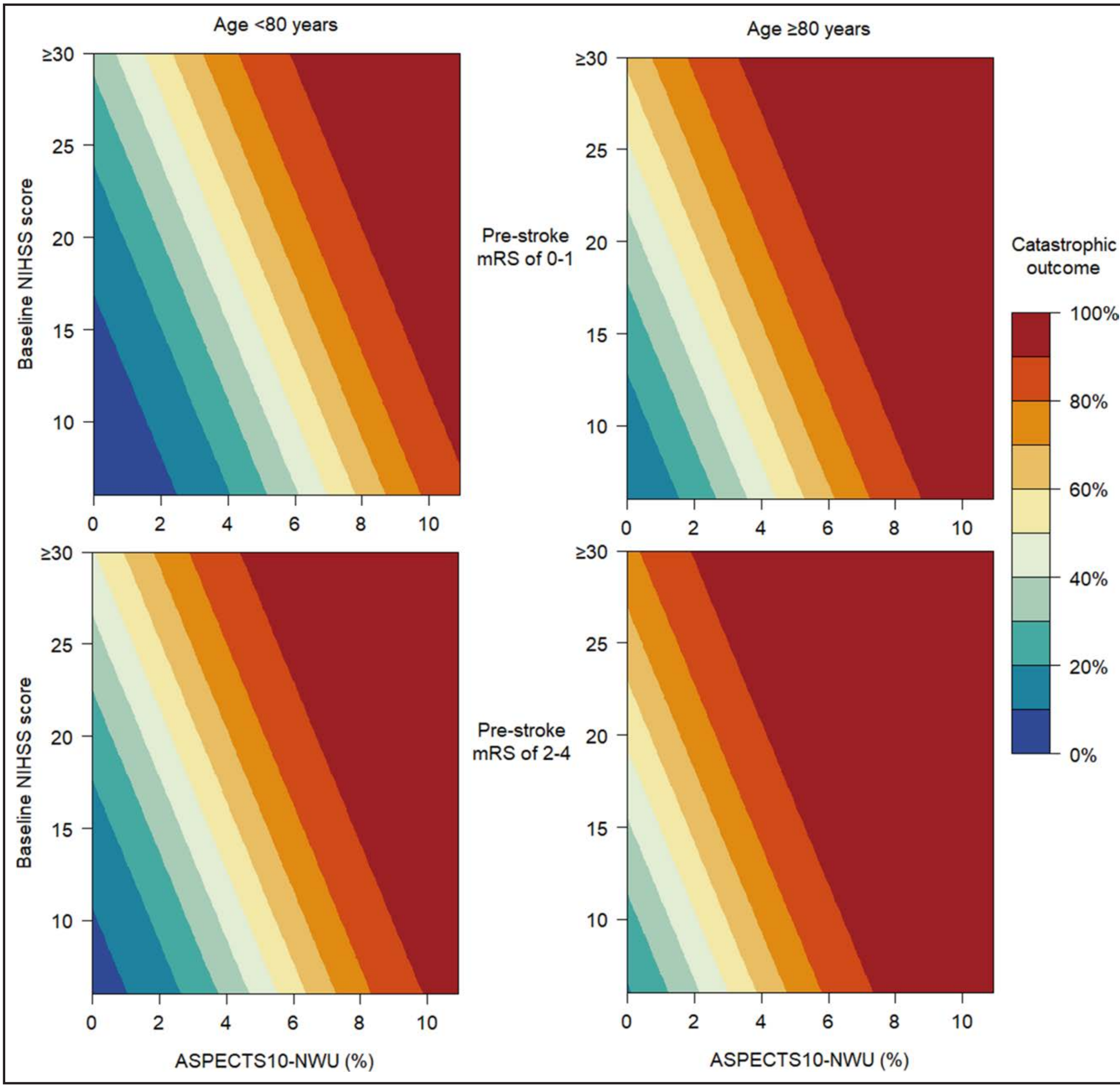

Figure 4. Predicted probability for 3-month catastrophic functional outcome (modified Rankin Scale [mRS] score, 5 or 6) associated with Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 10-net water uptake (NWU), age, prestroke mRS score, and baseline National Institutes of Health Stroke Scale (NIHSS) score in patients with acute ischemic stroke with ASPECTS ≤5 treated with endovascular thrombectomy.
The predicted probability was derived from a mixed-effects logistic regression model in Table S3.

EVT.[11,12] Consistent with this, our results demonstrated independent associations of ASPECTS10-NWU with moderate-to-severe cerebral edema and symptomatic ICH in large infarcts after EVT, which may partly account for its correlation with catastrophic functional outcome. In addition, the NWU, which quantitatively reflects the severity of ischemic injury, offers theoretical advantages over the ASPECTS, which only provides a binary assessment of ischemic involvement for more precise prognostication. The additional implementation of the ASPECTS10-NWU in the ASPECTS model improved the predictive power for catastrophic functional outcome (Figure 2).

Given the overall poor prognosis with high mortality rates or a bedridden state, the question arises as to whether all patients with large infarcts should undergo EVT although a poor prognosis does not generally preclude the treatment effect of EVT. As a novel radiographic predictor of stroke outcomes, NWU may provide realistic expectations for patients (if capable) or their next of kin. With increasing ASPECTS10-NWU, which is associated with more severe hypoperfusion and, therefore, least likely to revert from ischemia after EVT,[21] the proportion of patients with catastrophic functional outcome continued to increase, with approximately 3 of 4 patients having a catastrophic outcome at an ASPECTS10-NWU of 6.0% (Figure S3). However, the results should be interpreted with caution, and patient selection for EVT based on this variable alone should be avoided, as CIs for catastrophic outcome are wide (eg, ranging from 55% to 95% at an ASPECTS10-NWU of 6.0%), and few patients with high ASPECTS10-NWU may still benefit from EVT.

Rather, the decision to perform EVT for large infarcts should be individualized, and our study reconfirmed that age, baseline NIHSS score, and prestroke mRS score are important clinical predictors of catastrophic functional outcome. Older patients have a poor prognosis, likely mediated by high comorbidity burden and frailty.[24,25] Severe baseline NIHSS score, in relation to a large ischemic core volume and poor collateral status, was associated with poor functional outcomes.[26,27] Patients with prestroke disability at best lived with the same disability after stroke. They also had higher rates of nosocomial infections and withdrawal of care.[28,29] Collectively, these factors may have contributed to the worse outcomes. With the integration of these key preprocedural variables and ASPECTS10-NWU, the predictive models proposed in this study with improved prognostic accuracy would help facilitate personalized clinical judgments. For instance, at an ASPECTS10-NWU of 6.0%, patients aged ≥80 years with a baseline NIHSS score of 15 had a very high likelihood, with a predicted probability reaching 80% to 90%, of experiencing a catastrophic functional outcome, while their chances of achieving a favorable functional outcome were exceptionally low, falling <10% (Figure 3). If these patients also had a prestroke mRS score of 2 to 4, the predicted probability of a catastrophic functional outcome escalated even further, exceeding 90% (Figure 4). By contrast, despite a substantial risk of catastrophic outcomes (60%–70%), patients aged <80 years with the same ASPECTS10-NWU and NIHSS scores still exhibited a 20% to 30% probability of achieving a favorable functional outcome (Figure 3). These individualized probability estimates can be used to inform transparent evidence–based conversations among clinicians, patients (if capable), and patients' families when weighing the potential benefits and risks of EVT.

This study used a modified approach to measure the NWU (ASPECTS10-NWU). Previously established methods include CT perfusion (CTP)-NWU,[13] which measures NWU within CTP-defined infarct core regions, and ASPECTS-NWU,[30] which assesses NWU based solely on affected ASPECTS regions. Unlike these methods, the ASPECTS10-NWU reflects the overall attenuation difference across all ASPECTS regions of both hemispheres rather than restricting analysis to regions classified as ischemic core, which inevitably includes both severely hypodense and relatively preserved tissues, resulting in lower NWU values compared with CTP-NWU or ASPECTS-NWU. However, the following points strengthen the rationale for our approach in the context of large ischemic core patients. First, there is no definitive HU threshold on NCCT that reliably defines ischemic core.[20,21] Even hypodense lesions can be reversible after successful reperfusion therapy.[22] The same limitation applies to CTP: although a relative cerebral blood flow <30% is widely used as a surrogate for ischemic core, this threshold may overestimate infarct volume in early presenting patients undergoing EVT.[21,31] Therefore, a single threshold for ischemic core cannot adequately reflect the probabilistic relationship between the degree of hypodensity or hypoperfusion and the risk of infarction. Moreover, NWU analyses have shown that even mildly hypoperfused regions can develop cerebral edema or symptomatic intracranial hemorrhage,[10,11] suggesting that regions with relatively preserved perfusion are not necessarily benign and even modest ischemic stress can disrupt the blood-brain barrier and contribute to adverse outcomes. Furthermore, we only included patients with internal carotid artery, M1 segment of the middle cerebral artery, or tandem occlusion and ASPECTS ≤5. Thus, the ipsilesional hemisphere consisted primarily of hypoperfused and infarcted tissue, with minimal contribution from normal parenchyma, thereby reducing the potential dilution effect. In accordance with previously established methods,[32] the ASPECTS10-NWU demonstrated significant associations with clinical outcomes.

The strength of our study lies in the ASPECTS10-NWU, which can be measured without advanced imaging modalities (only with NCCT) with a processing time of only 1 to 3 minutes.[19] Predictive models developed with ASPECTS10-NWU and preprocedural variables could provide clinicians with real-time guidance for EVT decisions without time delay. Moreover, calculating NWU from the whole ASPECTS area may reduce variability caused by different definitions of affected regions among raters or software platforms. In addition, our cohort included patient groups aged ≥80 years and those with prestroke mRS scores of 2 to 4, populations often underrepresented in randomized clinical trials but commonly observed in clinical practice. Thus, our predictive models may offer more applicable prognostic insights for real-world patients with large infarcts undergoing EVT. However, this study has some limitations. First, the retrospective study design may have introduced a selection bias. Although we included patients with unrestricted infarct size (up to ASPECTS score of 0), only 15.7% of patients had an ASPECTS score of 0 to 2. Second, the lack of a medical treatment-only control group limited the ability to assess the treatment effect size of EVT for large infarcts across the ASPECTS10-NWU. Third, although the ASPECTS10-NWU showed consistent directions for catastrophic functional outcome across all subgroups, owing to the small number of cases, its usefulness should be validated in those with a prestroke mRS score of 2 to 4, a baseline ASPECTS score of 0 to 2, and the presence of prior stroke. Fourth, because the ASPECTS only evaluates ischemic changes within the middle cerebral artery territory, the ASPECTS10-NWU may underestimate the extent of ischemic injury in patients with internal carotid artery occlusion, where infarcts may extend beyond the middle cerebral artery territory. Nevertheless, ASPECTS10-NWU showed an independent association with catastrophic outcome in a subgroup of patients with intracranial internal carotid artery occlusion. Future research employing more elaborate methods to assess NWU in this subgroup is warranted. Fifth, direct comparisons of ASPECTS10-NWU with other NWU measurement methods, including CTP-NWU and ASPECTS-NWU, were beyond the scope of this study. Therefore, we cannot determine which method offers greater predictive accuracy for catastrophic functional outcomes. Further studies are needed to address this question. Last, as this study included only Korean patients with large infarcts, the results may not be generalizable to other ethnic groups or to patients with smaller infarcts.

In conclusion, an elevated ASPECTS10-NWU was strongly associated with catastrophic functional outcome in patients with large infarcts treated with EVT. Our predictive models integrating ASPECTS10-NWU, age, baseline NIHSS score, and prestroke mRS score provided valuable prognostic insights that may assist clinicians in the decision-making for EVT in large infarcts.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S4

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