The Canadian Journal of Neurological Sciences (2023), **50**, 268–273
doi:10.1017/cjn.2022.9

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Brief Communication

How to Define Fast and Slow Progressors in Any-Type Occlusion Acute Ischemic Stroke

Ali Z. Nomani[1,2], Jeremy L. Rempel[3], Khurshid A. Khan[1], Ashfaq Shuaib[1] and Glen C. Jickling[1]

[1]Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada, [2]Department of Medicine, Division of Neurology, Red Deer Regional Hospital, Red Deer, Alberta, Canada and [3]Department of Radiology, University of Alberta, Edmonton, Alberta, Canada

ABSTRACT: The variable rate of infarct progression in acute ischemic stroke as assessed by various thresholds excludes a substantial proportion of patients due to time or core constraints. We evaluated 106 patients with any-type occlusion to compare these thresholds and assessed performance of hypoperfusion index (HI) for fast and slow rate of infarct progression. Seven (12.5%) were classified fast progressors and 23 (46%), 25 (50%), 12 (24%), and 33 (66%) slow progressors using different core and time criteria. In comparison, HI categorized 100% ($n = 106$) of cohort with optimal cutoff 0.5 for any-type occlusion (slow progressors: HI ≤ 0.5), sensitivity/specificity 100%/91%, AUC 0.94, and indicative of eligibility for reperfusion and clinical outcomes (median 90-day modified Rankin Scale; 2 for HI ≤ 0.5 versus 5). Estimation of progressors by HI seems comprehensive but needs external validation.

RÉSUMÉ : Comment définir les accidents vasculaires cérébraux ischémiques d'évolution rapide et ceux d'évolution lente, quel que soit le type d'oblitération? La variabilité de la vitesse d'évolution des accidents vasculaires cérébraux ischémiques, estimée d'après différents seuils, écarte une bonne proportion de patients en raison de contraintes de temps ou de zone d'infarctus. Aussi avons-nous évalué l'état de 106 patients ayant subi un AVC, quel que soit le type d'oblitération, afin de comparer ces seuils avec la performance de l'indice d'hypoperfusion (IH) au regard de la vitesse d'évolution, rapide ou lente, des infarctus. Ainsi, selon les critères utilisés de zone d'infarctus et de temps, 7 patients (12,5 %) ont été classés en évolution rapide, tandis que 23 (46 %), 25 (50 %), 12 (24 %) et 33 (66 %) autres patients ont été classés en évolution lente. Par comparaison, l'IH a permis de classer 100 % des patients faisant partie de la cohorte (n = 106), à l'aide d'un seuil optimal de 0,5 pour tout type d'oblitération (en évolution lente : IH $\leq$ 0,5) : taux de sensibilité et de spécificité de 100 % et de 91 %, respectivement; surface sous la courbe de -0,94; indicateur d'admissibilité à la reperfusion et résultats cliniques (échelle de Rankin modifiée : valeur médiane au bout de 90 jours; 2 pour l'IH $\leq$ 0,5 contre 5). Il semble donc que l'appréciation de la vitesse d'évolution des AVC ischémiques d'après l'IH soit globale, mais une validation externe s'impose.

Keywords: Hypoperfusion index; Hypoperfusion intensity ratio; Stroke progression; Rate of infarct growth; Acute ischemic stroke

(Received 15 June 2021; final revisions submitted 19 December 2021; date of acceptance 15 January 2022; First Published online 11 March 2022)

The rate of infarct core progression after arterial occlusion in acute ischemic stroke (AIS) is a variable and dynamic process.[1,2] It is difficult to determine whether a patient with AIS will progress quickly to their final volume of infarct or will do so gradually.[2] Various methods and thresholds have been described to designate patients as fast or slow progressors.[2–4]

The conventional and commonly used core and time thresholds to define progression are core >70 mL within 6 hours of stroke onset for fast and <30 mL between 6–24 hours for slow progressors.[1,2] Alternatively, using core-to-time ratio also called as early infarct growth rate (EIGR), slow progressors are defined as those with EIGR of <1 and fast as >20 (mL/hour) or alternatively ~1 as slow and ~10 (mL/hour) as fast progressors.[3,4]

The core and time threshold-based definitions exclude a substantial proportion of stroke patients due to inherent nature of description. A relatively recent method to estimate infarct growth is by measuring hypoperfusion index (HI), which is a combination of degree of hypoperfusion marked on an 11-point scale (0–1, 0.1 each), and is correlated with collaterals, patient eligibility for thrombectomy, and functional outcomes in large vessel occlusion (LVO). It is automated and convenient.[5–8] We evaluated 106 stroke patients with any-type occlusion (proximal or distal) in internal carotid artery (ICA)/middle cerebral artery territory to compare different ways to define fast and slow progressors and assessed performance of HI to differentiate between fast and slow rate of core progression in AIS.

The medical records and imaging of 106 prospectively recruited patients with anterior circulation acute ischemic stroke were analyzed after approved by the Health Ethics Committee of the University of Alberta. Patients were

Corresponding author: Ali Nomani, MD, FCSC, MSc, FCPS, RPNI, Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada. Email: anomani@ualberta.ca

Cite this article: Nomani AZ, Rempel JL, Khan KA, Shuaib A, and Jickling GC. (2023) How to Define Fast and Slow Progressors in Any-Type Occlusion Acute Ischemic Stroke. *The Canadian Journal of Neurological Sciences* **50**: 268–273, https://doi.org/10.1017/cjn.2022.9

© The Author(s), 2022. Published by Cambridge University Press on behalf of Canadian Neurological Sciences Federation

https://doi.org/10.1017/cjn.2022.9 Published online by Cambridge University Press

successively selected from a pool of patients with ischemic deficits on CT Perfusion (CTP), which was acquired within 24 hours of symptom onset on post-processed FDA-approved RAPID (Rapid processing of perfusion and diffusion; iSchemaView, California, USA) software for estimation of core and mismatch. The perfusion deficit was defined using Tmax > 6 seconds. Core was identified by relative cerebral blood flow (CBF) <30% compared to that in normal tissue. Mismatch was defined as hypoperfused tissue within Tmax > 6 seconds that was out of the core (CBF > 30%).[9] Mismatch ratio was calculated by dividing total perfusion deficit by core volume. Hypoperfusion index was calculated automatically on dividing Tmax > 10 seconds by Tmax > 6 seconds on RAPID.[6]

Using core and time thresholds, we defined fast progressors as patients with ischemic core >70 mL in early tier after stroke onset (0–6 hours) using cutoff extrapolated from stroke trials of CTP in patients with LVO.[1,2]

For slow progressors, we evaluated following definitions based on criteria used by CTP stroke trials; DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo), DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3), EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits), and TIMELESS (Thrombolysis in imaging eligible late window patients (4.5–24 hours) to evaluate the efficacy and safety of tenecteplase).[1,10–13]

Definition "A": In patients with LVO, slow progressors were defined as patients with ischemic core ≤30 mL in the late tier after stroke onset (6–24 hours).[1]

Definition "B": In patients with LVO, slow progressors were defined as patients with ischemic core ≤50 mL in the late tier after stroke onset (6–24 hours).[11]

Definition "C": In patients with or without LVO (any occlusion type), slow progressors were defined as patients with ischemic core <70 mL, mismatch ratio >1.2, mismatch >10 mL, in the late tier after stroke onset (6–9 hours).[12]

Definition "D": In patients with ICA, M1, M2 occlusions, slow progressors were defined as patients with ischemic core ≤70 mL, mismatch ≥15 mL, and ratio ≥1.8 in the late tier after stroke onset (6–24 hours).[10,11,13]

Group of patients at 0–6 hours was called "early tier" and 6–24 hours as "late tier." LVOs were defined as ICA/M1 occlusions. LVOs and distal occlusions were identified by certified radiologist.[10,11] Outcomes were analyzed on modified Rankin Scale (mRS).

Quantitative data were summarized as median (IQR-interquartile range) due to non-normality (Shapiro-Wilk). Wilcoxon rank sum and x^2/Fischer's exact test were used for comparison as appropriate. The rate of core progression was determined using core-to-time ratio, that was dichotomized by > or ≤0.1–mL/minute as fast or slow, respectively.[3–5] HI was compared to rate of core progression, and the best-fitting model (cutoff) was determined using receiver operating characteristic to determine sensitivity and specificity of HI. Data analysis was conducted using STATA 16.0 (StataCorp LLC Texas, USA) and *p*-value <0.05 considered significant.

A total of 106 patients were analyzed, whose baseline characteristics are shown in Table 1. The median (IQR) core volume was 9 (0–37) mL, mismatch was 81 (40–113) mL, mismatch ratio was 3.2 (2.2–9.0), and HI was 0.4 (0.2–0.6). Ischemic core was ≤10 mL in 57 (53.7%), ≤30 mL in 76 (71.69%), ≤50 mL in 89 (83.96%), and ≤70 mL in 93 (87.73%) patients. Fifty-six (52.8%) were in early tier. Seventy-eight (73.5%) had LVO. Patient distribution across the cohort is shown in Figure 1.

Table 1: Baseline characteristics

Characteristics	Value
Age, median (IQR) (years)	74 (62–85)
Gender (male), *n* (%)	68 (64.1)
Comorbidities	
Hypertension, *n* (%)	64 (60.3)
Diabetes Mellitus, *n* (%)	20 (18.8)
Coronary Artery Disease, *n* (%)	21 (19.8)
Previous Stroke, *n* (%)	8 (7.5)
Previous Transient Ischemic Attack, *n* (%)	9 (8.4)
Current Smoking, *n* (%)	21 (19.8)
Atrial Fibrillation, *n* (%)	26 (24.5)
Hyperlipidemia, *n* (%)	36 (33.9)
Pre-stroke modified Rankin Scale, median (IQR)	0 (0–3)
NIHSS score, median (IQR)	14 (10–20)
Symptom onset to imaging, median (IQR) (minutes)	287 (105–636)
ASPECTS	
<5, *n* (%)	6 (5.6)
5–7, *n* (%)	13 (12.2)
8–10, *n* (%)	87 (82.1)
Occluded vessel	
Carotid T occlusion, *n* (%)	3 (2.8)
ICA occlusion, *n* (%)	18 (16.9)
M1 occlusion, *n* (%)	57 (53.7)
M2 occlusion, *n* (%)	18 (16.9)
Distal to M2, *n* (%)	10 (9.4)
Treatment	
IV Thrombolysis, *n* (%)	50 (47.1)
Endovascular Thrombectomy with or without thrombolysis, *n* (%)	49 (46.2)
Full Recanalization (TICI 3), *n* (%)	48 (45.2)
Hemorrhagic transformation	
Symptomatic, *n* (%)	2 (1.8)
Asymptomatic, *n* (%)	31 (29.2)

ICA = Internal Carotid Artery; NIHSS = National Institutes of Health Stroke Scale; ASPECTS = Alberta Stroke Program Early CT Score; IQR = Interquartile range; TICI = Thrombolysis In Cerebral Infarction; IV = Intravenous.

By using different criteria, the number of patients who could be classified as slow progressors by each definition was different, as shown in Figures 1 and 2. Seven (12.5%) were fast progressors in early tier and 23 (46%), 25 (50%), 12 (24%), and 33 (66%) were slow progressors in late tier according to criteria A, B, C, and D, respectively. Criteria "D" was most inclusive (31% slow by "D" versus 11–23% for others) as it incorporated nearly all patients from other definitions, covered all core thresholds, and included non-LVO (M2) occlusions as well, yet could not classify the rest ($n = 44$) (Figures 1 and 2).

https://doi.org/10.1017/cjn.2022.9 Published online by Cambridge University Press

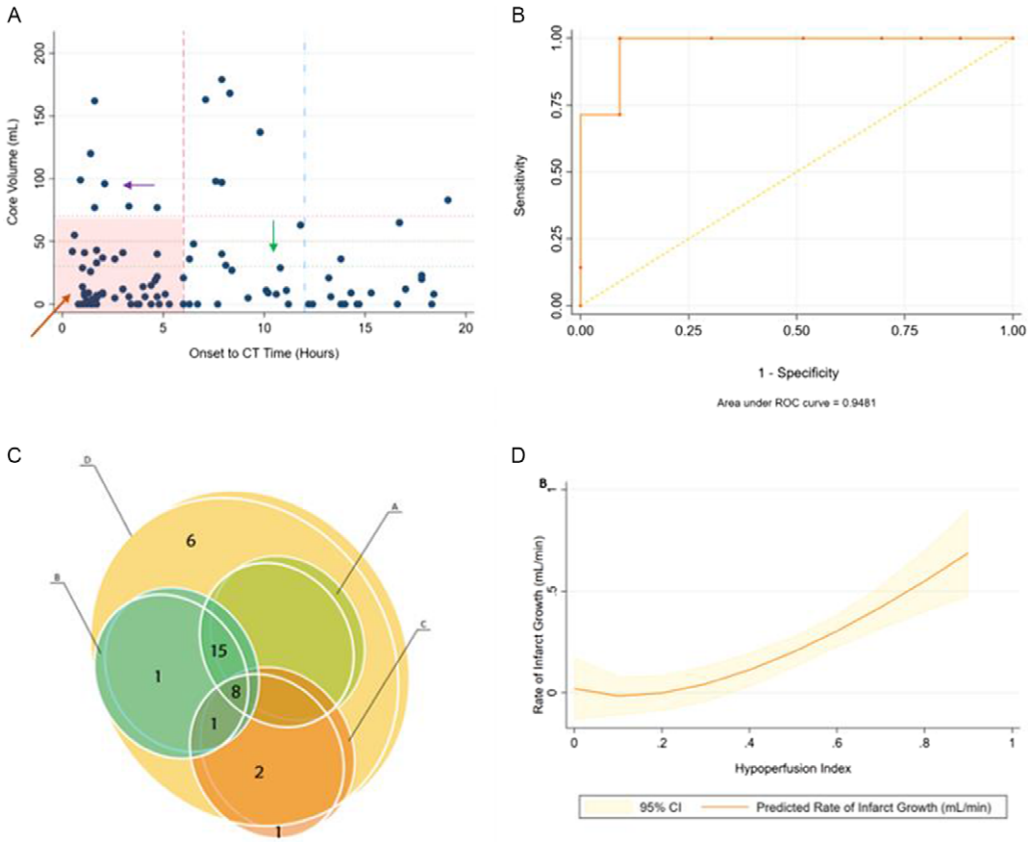

Figure 1: (A): Distribution of patient cohort. Onset to CT time in hours (x-axis) plotted against core volume in mL on CTP (y-axis). Top left (purple arrow) are fast progressing and bottom right (green arrow) are slow progressing. Bottom left (orange arrow) represents early presenting patients who do not meet conventional core and time threshold criteria to differentiate fast and slow progressors. (B): Receiver operating characteristic for predicting fast versus slow rate of core progression (core/time) using HI cutoff 0.5. Fast = >0.5, Slow = ≤0.5. (C): Mutual inclusion and exclusion of patients as slow progressors using different definition criteria A–D for slow progressors. Each circle shows the number of patients included by each definition (A–D) and shows if a patient is mutually inclusive or exclusive. Note that Definition D includes all patients from other definitions except 1. (D): Hypoperfusion Index (y-axis) versus Infarct Growth Rate that is, core/time (mL/min) (x-axis).

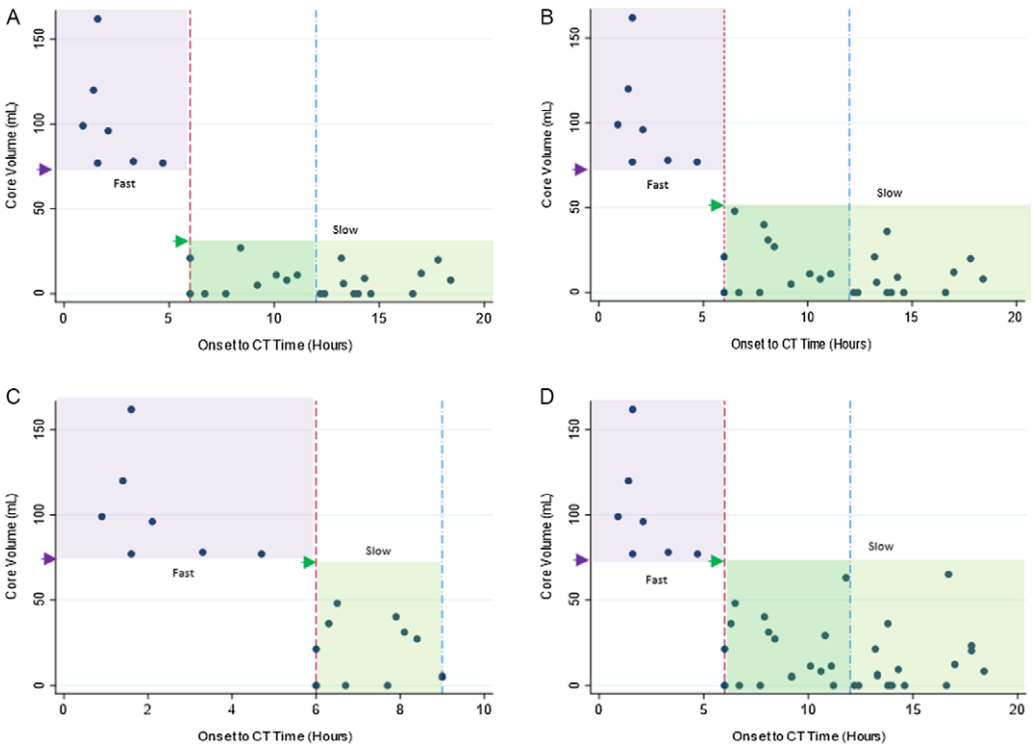

Figure 2: Distribution cohort using different definitions. Onset to CT Time in hours (x-axis) plotted against core volume in mL on CTP (y-axis). Small arrow heads points towards respective core volume cutoff used for each definition [lower limit for fast (dark purple arrow) and upper for slow (bright green arrow) progressor group]. Highlighted box areas represent progressor types (purple = fast, green = slow). (A): Definition "A." (B): Definition "B." (C): Definition "C." (D): Definition "D."

https://doi.org/10.1017/cjn.2022.9 Published online by Cambridge University Press

Table 2: Patient characteristics between fast and slow progressor type in each definition

Category	All	Fast	Slow	p-value
Definition A				
Total	30 (28.3)	7 (23.3)	23 (76.6)	–
Age, median (IQR) (years)	71.5 (49–95)	72 (63–83)	71 (61–80)	0.52
Gender (Male), *n* (%)	23 (76.6)	4 (57.1)	19 (82.6)	0.16
Symptom onset to imaging, median (IQR) (minutes)	583.5 (58–1106)	98 (58–287)	737 (353–1106)	0.001*
Core, median (IQR) (mL)	11 (0–162)	96 (77–162)	8 (0–48)	0.001*
Mismatch, median (IQR) (mL)	111 (32–232)	108 (34–161)	113 (32–232)	0.25
Mismatch ratio, median (IQR)	6.3 (2.5–12.4)	2.4 (1.5–2.5)	8.8 (6.3–15)	<0.001*
HI, median (IQR)	0.4 (0.2–0.6)	0.7 (0.6–0.7)	0.3 (0.2–0.5)	<0.001*
Rate of core progression, median (IQR) (mL/min)	0.01 (0–0.12)	0.80 (0.38–1.65)	0.008 (0–0.01)	<0.001*
Definition B				
Total	32 (30.1)	7 (21.8)	25 (78.1)	–
Age, median (IQR) (years)	72 (49–95)	72 (63–83)	72 (62–80)	0.56
Gender (Male), *n* (%)	24 (75)	4 (57.1)	20 (80)	0.21
Symptom onset to imaging, median (IQR) (minutes)	583.5 (58–1106)	98 (58–287)	737 (353–1106)	0.001*
Core, median (IQR) (mL)	11.5 (0–162)	96 (77–162)	8 (0–48)	0.001*
Mismatch, median (IQR) (mL)	109.5 (32–232)	108 (34–161)	112 (32–232)	0.38
Mismatch ratio, median (IQR)	5.9 (2.4–12.4)	2.4 (1.5–2.5)	7.2 (5.8–14.0)	<0.001*
HI, median (IQR)	0.4 (0.2–0.6)	0.7 (0.6–0.7)	0.3 (0.2–0.5)	<0.001*
Rate of core progression, median (IQR) (mL/min)	0.01 (0–0.10)	0.80 (0.38–1.65)	0.01 (0–0.02)	<0.001*
Definition C				
Total	19 (17.9)	7 (36.8)	12 (63.1)	–
Age, median (IQR) (years)	72 (36–88)	72 (63–83)	72.5 (62–79)	0.69
Gender (Male), *n* (%)	11 (57.8)	4 (57.1)	7 (58.3)	0.96
Symptom onset to imaging, median (IQR) (minutes)	361 (58–540)	98 (58–287)	400 (360–540)	0.001*
Core, median (IQR) (mL)	36 (0–162)	96 (77–162	13 (0–48)	0.001*
Mismatch, median (IQR) (mL)	89 (13–232)	108 (34–161)	70.5 (13–232)	0.52
Mismatch ratio, median (IQR)	2.4 (1.8–5.8)	2.4 (1.5–2.5)	5.8 (2.2–7.1)	0.03*
HI, median (IQR)	0.5 (0.3–0.7)	0.7 (0.6–0.7)	0.3 (0.1–0.5)	0.001*
Rate of core progression, median (IQR) (mL/min)	0.08 (0–0.73)	0.80 (0.38–1.65)	0.03 (0–0.07)	<0.001*
Definition D				
Total	40 (37.7)	7 (17.5)	33 (82.5)	–
Age, median (IQR) (years)	71.5 (28–95)	72 (63–83)	71 (61–78)	0.38
Gender (Male), *n* (%)	29 (78.7)	4 (57.1)	25 (75.7)	0.31
Symptom onset to imaging, median (IQR) (minutes)	644 (58–1106)	98 (58–287)	711 (353–1106)	0.001*
Core, median (IQR) (mL)	16 (0–162)	96 (77–162)	9 (0–65)	0.001*
Mismatch, median (IQR) (mL)	105 (15–232)	108 (34–161)	104 (15–232)	0.95
Mismatch ratio, median (IQR)	3.6 (2.3–8.8)	2.4 (1.5–2.5)	6.3 (2.9–12.4)	0.003*
HI, median (IQR)	0.4 (0.2–0.5)	0.7 (0.6–0.7)	0.4 (0.2–0.5)	<0.001*
Rate of core progression, median (IQR) (mL/min)	0.01 (0–0.08)	0.80 (0.38–1.65)	0.01 (0–0.04)	<0.001*

HI = hypoperfusion index.
*Significant.

HI was significantly different between fast and slow groups across all definitions (Table 2). HI for overall cohort was ≤0.5 in 77 (72.6%). For the overall cohort, the median (IQR) rate of core progression was 0.02 (0–0.06) in ≤0.1 and 0.28 (0.04–0.66) in >0.1 mL/minute core-to-time ratio groups, ($p < 0.001$). HI cutoff ≤0.5 (good) and >0.5 (poor) differentiated slow from fast rate of infarct progression in all-type occlusions, having sensitivity 100%, specificity 90.9%, and AUC 0.94 (Figure 1), with comparable baseline characteristics (supplementary table). Those with HI ≤ 0.5 (good) were more likely to receive thrombolysis, and/or

https://doi.org/10.1017/cjn.2022.9 Published online by Cambridge University Press

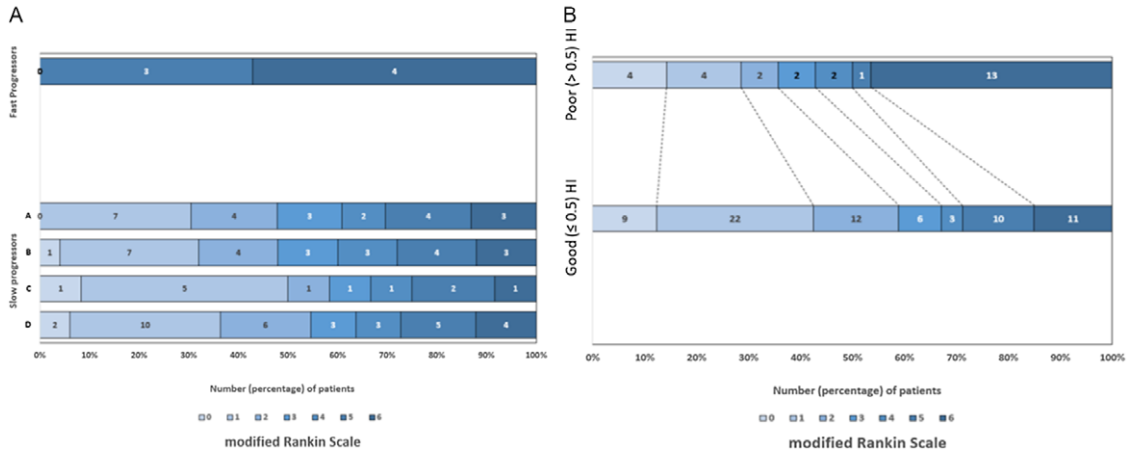

Figure 3: (A): Patient outcomes (modified Rankin Scale) in slow progressors (by different definitions) and fast progressors. (B): Patient outcomes in good (≤0.5) and poor (>0.5) hypoperfusion index groups in whole cohort.

thrombectomy and had better outcomes as compared to HI > 0.5 (poor), having median (IQR) 90-day mRS score 2 (1–5) and 5 (3–6) respectively, ($p = 0.02$) (supplementary table and Figure 3).

Our study indicated that ~13% patients in early tier were fast progressors, whereas 24–66% were slow progressors in late tier using different time and core constrained definitions. Although most inclusive, definition D could not account for distal occlusions due to the nature of description. In comparison, HI categorized 100% ($n = 106$) of the cohort with optimal cutoff 0.5 with good sensitivity and specificity to differentiate between slow and fast rate of core progression (core/time) in any-type occlusion. Using HI, ~73% were classified as having slow rate of core progression (HI ≤ 0.5) with more likelihood of attempted reperfusion and better outcomes.

Slow progressors are associated with reduced level of disability than fast progressors.[4] We have shown that by using <70 mL core criteria and including distal occlusions for slow progressors, we can identify more patients with slow progression who can potentially benefit from reperfusion than anticipated by earlier commonly used definitions. [14–16] This however needs external validation. HI-based estimation is easy and automated on standard CTP RAPID rather requiring cumbersome calculations.[5–8] The quick description of fast and slow infarct progression in various stroke sub-populations can help guide transfer and treatment decisions by anticipating rate of core progression and time of completion to infarction. However, the results should be interpreted considering limitations of CTP and its restricted availability. Although stroke progression is a dynamic process, HI has been shown to remain stable during patient transfers.[5,17,18] While our findings are likely to be applicable to clinical experience of similar high-volume comprehensive stroke centers, the observed proportions and relevance of fast and slow progressors, and transfer strategies may vary depending upon unique regional geography. Furthermore, given the small sample size, generalizability of results should be attempted with caution. Also, distal vessel occlusions accounted for 28% ($n = 30$) of cohort with most patients having LVOs, and therefore applicability to all type occlusions should be done judiciously and with care. However, the inclusive proportion of distal occlusions versus LVO in our study is much better than previous studies done in the setting of clinical trials and thus may represent true depiction of vessel occlusion types in clinical practice.[19,20] Future trials of HI can help validate its utility in patients with strokes of all type occlusions.

In conclusion, HI ≤ 0.5 differentiates slow from fast rate of infarct progression in AIS with any-type occlusion and may be indicative of eligibility for reperfusion and clinical outcomes. Estimation of progressors by HI seems comprehensive but needs external validation.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.9

Acknowledgements. None.

Disclosures. A.Z. Nomani, J. L. Rempel, K. A. Khan and A. Shuaib report no disclosure. G.C. Jickling reports receiving grant funding from CIHR, HSF, CFI, NIH and UHF.

Statement of Authorship. AZN and GCJ contributed equally in the conception and design of study, and acquisition of data. AZN, JLR, KAK, AS and GCJ equally contributed in analysis and interpretation of data, drafted manuscript, reviewed manuscript, and gave final approval of version for publication.

References

1. Rocha M, Jovin TG. Fast versus slow progressors of infarct growth in large vessel occlusion stroke: clinical and research implications. Stroke. 2017;48:2621–7. DOI 10.1161/STROKEAHA.117.017673.
2. Rocha M, Desai SM, Jadhav AP, Jovin TG. Prevalence and temporal distribution of fast and slow progressors of infarct growth in large vessel occlusion stroke. Stroke. 2019;50:2238–40. DOI 10.1161/STROKEAHA.118.024035.
3. Sarraj A, Hassan AE, Grotta J, et al. Early infarct growth rate correlation with endovascular thrombectomy clinical outcomes: analysis from the SELECT study. Stroke. 2021;52:57–69. DOI 10.1161/STROKEAHA.120.030912.
4. Seo WK, Liebeskind DS, Yoo B, et al. Predictors and functional outcomes of fast, intermediate, and slow progression among patients with acute ischemic stroke. Stroke. 2020;51:2553–7. DOI 10.1161/STROKEAHA.120.030010.
5. Guenego A, Mlynash M, Christensen S, et al. Hypoperfusion ratio predicts infarct growth during transfer for thrombectomy. Ann Neurol. 2018;84:616–20. DOI 10.1002/ana.25320.
6. Olivot JM, Mlynash M, Inoue M, et al. Hypoperfusion intensity ratio predicts infarct progression and functional outcome in the DEFUSE 2 Cohort. Stroke. 2014;45:1018–23. DOI 10.1161/STROKEAHA.113.003857l.
7. Guenego A, Marcellus DG, Martin BW, et al. Hypoperfusion intensity ratio is correlated with patient eligibility for thrombectomy. Stroke. 2019;50:917–22. DOI 10.1161/STROKEAHA.118.024134.

8. Guenego A, Fahed R, Albers GW, et al. Hypoperfusion intensity ratio correlates with angiographic collaterals in acute ischaemic stroke with M1 occlusion. Eur J Neurol. 2020;27:864–70. DOI 10.1111/ene.14181.
9. Straka M, Albers GW, Bammer R. Real-time diffusion-perfusion mismatch analysis in acute stroke. J Magn Reson Imaging. 2010;32:1024–37. DOI 10.1002/jmri.22338.
10. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378:708–18. DOI 10.1056/NEJMoa1713973.
11. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378:11–21. DOI 10.1056/NEJMoa1706442.
12. Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med. 2019;380:1795–803. DOI 10.1056/NEJMoa1813046.
13. Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS). ClinicalTrials.gov Identifier: NCT03785678. Available at: https://clinicaltrials.gov/ct2/show/NCT03785678
14. Dorn F, Lockau H, Stetefeld H, et al. Mechanical thrombectomy of M2-occlusion. J Stroke Cerebrovasc Dis. 2015;24:1465–70. DOI 10.1016/j.jstrokecerebrovasdis.2015.04.013.
15. Grossberg JA, Rebello LC, Haussen DC, et al. Beyond large vessel occlusion strokes: distal occlusion thrombectomy. Stroke. 2018;49:1662–8. DOI 10.1161/STROKEAHA.118.020567.
16. Sarraj A, Sangha N, Hussain MS, et al. Endovascular therapy for acute ischemic stroke with occlusion of the middle cerebral artery M2 segment. JAMA Neurol. 2016;73:1291–6. DOI 10.1001/jamaneurol.2016.2773.
17. Broocks G, Rajput F, Hanning U, et al. Highest lesion growth rates in patients with hyperacute stroke: when time is brain particularly matters. Stroke. 2019;50:189–92. DOI 10.1161/STROKEAHA.118.023457.
18. Vagal A, Wintermark M, Nael K, et al. Automated CT perfusion imaging for acute ischemic stroke: pearls and pitfalls for real-world use. Neurology. 2019;93:888–98. DOI 10.1212/WNL.0000000000008481.
19. Goyal M, Ospel JM, Menon BK, Hill MD. MeVO: the next frontier? J Neurointerv Surg. 2020;12:545–7. DOI 10.1136/neurintsurg-2020-015807.
20. Nomani AZ, Tatuene JK, Rempel JL, et al. Association of CT-based hypoperfusion index with ischemic core enlargement in patients with medium and large vessel stroke. Neurology. 2021;97:e2079–87. DOI 10.1212/wnl.0000000000012855.

https://doi.org/10.1017/cjn.2022.9 Published online by Cambridge University Press