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Elevated Hypoperfusion Intensity Ratio (HIR) observed in patients with a large vessel occlusion (LVO) presenting in the evening

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Abstract

Background: Circadian variability has been implicated in timing of stroke onset, yet the full impact of underlying biological rhythms on acute stroke perfusion patterns is not known. We

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Guarantors

A. Sreekrishnan serves as guarantor and accepts full responsibility for the design and analysis of the study as well as allocation of the study data.

Contributorship

Study conception and design: Anirudh Sreekrishnan, Sarah Lee, Gregory W Albers Data collection: Anirudh Sreekrishnan, Pierre Seners, Nicole Yuen, Jean-Marc Olivot, Maarten G Lansberg, Patrik Michel, Davide Strambo, Alexander Salerno, José Bernardo Escribano Paredes, Emmanuel Carrera

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Draft manuscript preparation: Anirudh Sreekrishnan, Pierre Seners, Gregory W Albers All authors reviewed the results and approved the final version of the manuscript.

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Ethics Approval and Informed Consent

The individual registry data was approved by the local ethics committee at each center. Data acquired from Switzerland, ethical commission approval and patient consent were not required according to current local and national legislation as all data were anonymized before analysis and as patient's refusal of scientific use of their data was duly honored. Study design and analysis of this cohort was approved by the Stanford institutional review board (IRB), assurance # FWA00000935 (SU), on 9/15/2022.

aimed to describe the relationship between time of stroke onset and perfusion profiles in patients with large vessel occlusion (LVO).

Methods: A retrospective observational study was conducted using prospective registries of four stroke centers across North America and Europe with systematic use of perfusion imaging in clinical care. Included patients had stroke due to ICA, M1 or M2 occlusion and baseline perfusion imaging performed within 24h from last-seen-well (LSW). Stroke onset was divided into eight hour intervals: (1) Night: 23:00–6:59, (2) Day: 7:00–14:59, (3) Evening: 15:00–22:59. Core volume was estimated on CT perfusion (rCBF <30%) or DWI-MRI (ADC <620) and the collateral circulation was estimated with the hypoperfusion intensity ratio (HIR = [Tmax>10s]/[Tmax>6s]). Non-parametric testing was conducted using SPSS to account for the non-normalized dependent variables.

Results: A total of 1506 cases were included (median age 74.9 years, IQR 63.0–84.0). Median NIHSS, core volumes, and HIR were 14.0 (IQR 8.0–20.0), 13.0mL (IQR 0.0–42.0), and 0.4 (IQR 0.2–0.6) respectively. Most strokes occurred during the Day (n = 666, 44.2%), compared to Night (n = 360, 23.9%), and Evening (n = 480, 31.9%). HIR was highest, indicating worse collaterals, in the Evening compared to the other timepoints (p = 0.006). Controlling for age and time to imaging, Evening strokes had significantly higher HIR compared to Day (p = 0.013).

Conclusion: Our retrospective analysis suggests that HIR is significantly higher in the evening, indicating poorer collateral activation which may lead to larger core volumes in these patients.

Keywords

Circadian Rhythm; Large Vessel Occlusion; Acute Stroke; Imaging

Introduction

Circadian rhythm is implicated in modulating various physiological processes from elements of the inflammatory system¹ to blood pressure variations,^{2,3} resulting in discrepancies in stroke incidence.⁴ Observational studies have outlined an increased incidence of both hemorrhagic and ischemic strokes in the mornings, 6:00 to 12:00, with a smaller secondary peak in the evening.^{5,6,7} Furthermore, it has been suggested that a higher proportion of lacunar strokes occur at night, 0:00 to 6:00.^{8,9,10}

Changes in the diurnal rhythm, as seen in daylight saving time transitions¹¹ or the initiation of Ramadan,¹² have been associated with changes in the incidence of strokes. Additionally, there may be differences in the efficacy of thrombolysis and the rates of hemorrhagic transformation based on the time of day.¹³ These studies suggest that timing of stroke onset can be a potential factor in the responsiveness to acute therapies and consequently impact stroke outcomes.

While there is observational data available regarding the relationship between stroke incidence and onset time, the association between underlying biological rhythms (e.g. circadian, diurnal, behavioral, etc.) and perfusion profiles is limited. Downstream to an acute intracranial occlusion, cerebral ischemic tissue can be schematically divided into ischemic core (i.e. the irreversibly injured tissue) and penumbra (i.e. the severely hypoperfused yet

salvageable tissue), which can be clinically estimated using CT or MRI. A prior study found that nighttime strokes have significantly larger ischemic core volumes than those presenting during the day, even when controlling for time to initial imaging.¹⁴ However, how stroke onset time may influence stroke evolution or the effectiveness of stroke therapies is unclear.

The goal of this large retrospective analysis was to examine a series of LVO cases with occlusion of the internal carotid artery (ICA) or first or second branch of the middle cerebral artery (M1 or M2), with available imaging in the form of CT perfusion (CTP) or MRI perfusion/diffusion (MR-DWI/PWI) conducted within 24 hours of the stroke onset. To reflect real-world clinical practice, we included cases from multiple national and international sites with prospective real-world databases. In conjunction with the Leducq Trans-Atlantic Network of Excellence On Circadian Effects in Stroke (LCN) Clinical Working Group,¹⁵ stroke onset was categorized *a priori* into eight hour intervals to compare various perfusion parameters based on stroke onset time. Our initial hypothesis, in line with prior work suggesting large ischemic cores presenting at night,¹⁴ was that nighttime strokes would exhibit poorer collaterals to help account for the larger core volumes observed in this time window.

Methods

Study Design and Data Sources

We retrospectively collected data from consecutive acute ischemic stroke patients extracted from prospective registries of four comprehensive stroke centers: (1) Stanford Hospital, Palo Alto, USA, (2) Rothschild Foundation Hospital, Paris, France, (3) Geneva University Hospital, Geneva, Switzerland, and (4) Lausanne University Hospital, Lausanne, Switzerland. All sites employed the systematic use of perfusion imaging in the evaluation of their stroke patients and include both thrombectomy-treated and untreated patients (Supplementary Table 1). Center 1 (Stanford Hospital) included both directly admitted patients or those transferred from an outside hospital with repeat perfusion imaging performed on arrival, whereas the other centers included only directly admitted patients. Patients included in analysis had LVO of either the ICA, M1 or M2 as well as baseline imaging conducted within 24 hours of symptom onset. The individual registry data was approved by the local ethics committee at each center if required by local and national legislation of the institution.

Clinical Data and Stroke Onset Time Allocation

The following variables were abstracted from medical records: patient age, sex, stroke etiology, vascular risk factors, National Institute of Health Stroke Scale (NIHSS) score on admission, intravenous thrombolysis use, baseline glucose. To account for differences in documentation across the various databases, stroke onset time was defined by specific parameters (Supplementary Table 2). A ‘witnessed stroke’ was defined as stroke with symptoms discovered within 60 minutes of last seen well (LSW), which was used as the ‘stroke onset time.’ An ‘unwitnessed stroke’ was any stroke where symptom discovery occurred greater than 60 minutes of LSW. In these cases, the midpoint between the two timepoints (LSW and symptom discovery) was used as the ‘stroke onset time.’ If the

discrepancy between LSW and the symptoms observed was greater than 12 hours, that case was excluded from the final analysis, because stroke onset time estimation was deemed too imprecise. Within the 'unwitnessed stroke' classification, there was a subgroup defined as 'wake-up stroke,' which was defined as a stroke where the LSW was prior to 0:00 and the symptoms noted was between 0:00 and 10:00. In line with the definition of 'unwitnessed stroke,' 'wake-up strokes' utilized the midpoint for stroke onset for the purposes of analysis and allocation. Time of stroke onset was then divided into three time-intervals, decided *a priori* in conjunction with the LCN Clinical Working Group,¹⁵ which is a working group tasked to create guidelines for standardized statistical analysis for projects involving stroke and circadian rhythm: (1) Night: 23:00–6:59, (2) Day: 7:00–14:59, and (3) Evening: 15:00–22:59. Onset-to-imaging time was defined as time between stroke onset and imaging start.

Radiographic Parameters

The following radiological variables were collected: (1) occlusion site, trichotomized as ICA, M1 or M2, (2) core (defined as an apparent diffusion coefficient $<620 \times 10^{-6} \text{ mm}^2/\text{s}$ on diffusion-weighted imaging or relative cerebral blood flow $<30\%$ on CT-perfusion), (3) time-to-maximum (Tmax) $>6\text{s}$ and $>10\text{s}$ volumes, (4) mismatch volume, defined as the difference between core volume and Tmax $>6\text{s}$, (5) mismatch ratio, defined as Tmax $>6\text{s}$ divided by the core volume and (6) leptomeningeal collateral status as evaluated by the Hypoperfusion Intensity Ratio (HIR), defined as the proportion of Tmax $>6\text{s}$ volume with Tmax $>10\text{s}$ (i.e., Tmax $>10\text{s}$ volume / Tmax $>6\text{s}$ volume). A greater HIR has previously been shown to be suggestive of poor collaterals.^{16,17} All diffusion-weighted imaging and perfusion imaging were processed by RAPID (iSchemaView, Menlo Park, CA). Artifacts were manually removed from core or Tmax maps whenever necessary.

Statistical Analysis

Continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, and categorical variables as frequency and percentages. As each outcome (i.e. Core, Tmax, HIR) were not normally distributed, the univariable relationship between time of stroke onset intervals and perfusion parameter was assessed using Kruskal-Wallis Independent-Samples Test followed by pair-wise comparisons using Bonferroni Correction for multiple testing. To adjust on potential confounders, multi-variable testing was then conducted using Quade Nonparametric Analysis of Covariance Model, adjusted for age and time to imaging. All statistical analysis was conducted using IBM SPSS v.28 software (SPSS Inc., Chicago, Illinois, USA).

Results

Out of the 1849 patients screened, a total of 1506 cases were included in the final analysis (Supplementary Figure 1). Of the 343 patients excluded, 301 cases were excluded due to the lack of or inadequate perfusion imaging and 42 cases due to a discrepancy between LSW and symptom onset exceeding 12 hours. Baseline characteristics were similar in the final cohort of included patients compared to excluded patients (Supplemental Table 3). Baseline clinical and imaging characteristics of patients included in the study are presented in Table 1. Stroke onset occurred at Night (23:00–6:59) in 360 (23.9%) patients, during the

Day (7:00–14:59) in 666 (44.2%), and in the Evening (15:00–22:59) in 480 (31.9%). The incidence of stroke according to the timing of stroke onset is displayed in Figure 1. There was a peak in stroke onset around 11:00 which steadily tapered off into the evening.

The comparison of baseline and radiological characteristics according to stroke onset timepoints is also presented in Table 1. The time to imaging was significantly longer at Night (median 380.0 min, IQR: 248.8–536.0) compared to either Day (median 172.0 min, IQR: 88.5–293.0) or Evening (median 190.0 min, IQR: 93.3–345.8) ($p < 0.001$). The median ischemic core volume was 13 mL (IQR 0.0–42.0) and the median HIR was 0.4 (IQR 0.2–0.6). In univariable testing, there was a significant association for ischemic core volume across timepoints ($p = 0.005$), specifically with smaller cores noted during the Day (median 10.0 mL, IQR: 0.0–35.0) compared to the Evening (median 16.8 mL, IQR: 0.0–50.9) (Figure 2, $p = 0.006$). There was also a trend in ischemic core volume differences between Day and Night (median 14.2 mL, IQR: 0.0–45.5) ($p = 0.08$). There were no differences observed for $T_{max} > 6s$ or $T_{max} > 10s$ in univariate testing. Trends for mismatch volume and mismatch ratio followed the inverse of what was observed for ischemic core (Table 1). For HIR, there was a significant association across timepoints ($p = 0.008$), specifically with a lower HIR at Night (median 0.4, IQR: 0.2–0.5) as compared to the Evening (median 0.4, IQR: 0.3–0.6) (Figure 3, $p = 0.009$); there was also a trend toward significance between Day (median 0.4, IQR: 0.2–0.6) and Evening ($p = 0.058$).

Since stroke onset had to be estimated among unwitnessed strokes, a sensitivity analysis was conducted to confirm these initial findings within the witnessed stroke population ($n = 1091$). The clinical characteristics of this sub-group is included in Supplementary Table 4 and 5. Among exclusively witnessed stroke, both ischemic core volume ($p = 0.023$) and HIR ($p = 0.028$) continued to remain significant across timepoints. Follow-up pair-wise comparisons, ischemic core volume was larger during the Evening (median 15.0 mL, IQR: 0.0–49.0) compared to during the Day (median 10.0, IQR: 0.0–35.0) ($p = 0.022$). Similarly, HIR was higher during the Evening (median: 0.4, IQR: 0.3–0.6) compared to the Day (median 0.4, IQR: 0.2–0.5) ($p = 0.023$).

We separately performed a secondary sensitivity analysis looking only at ischemic core volume among MRI perfusion scans ($n = 752$), given ischemic core volume is better estimated with MRI as compared to CTP. Of the 752 patients with MRI perfusion imaging, there was a significant difference in core based on timepoint ($p = 0.001$), with a higher ischemic core in the Evening compared to Day ($p = 0.006$) and Night compared to Day ($p = 0.008$), matching the original conclusion (Supplementary Table 6 & 7).

In multivariable non-parametric testing, using a model including age and time to imaging, differences in ischemic core volume across timepoints only trended toward significance ($p = 0.083$). However, in the same model, HIR was significant across timepoints ($p = 0.041$), with strokes occurring in the Evening showing significantly elevated HIR when compared to Day ($p = 0.013$).

Discussion

In our large retrospective analysis of over 1,500 patients across international sites, we found differences in imaging profiles based on stroke onset time. Specifically, our analysis suggests that strokes occurring in the evening (15:00–22:59) were associated with larger ischemic cores as well as higher HIR, indicating worse collaterals. While ischemic core volume only trended toward significance in our multivariable model, HIR was significant across timepoints in a model with age and time to scan.

A prior study has already suggested that ischemic core volumes may be larger in strokes that occur at night as compared with day.¹⁴ One of the major differences between the approach in prior work and this current analysis is the definition of respective time windows, with ‘Night’ defined in the previous work as 21:00–3:00,¹⁴ overlapping with our definition of ‘Evening’ (15:00–22:59) and ‘Night’ (23:00–6:59). We specifically chose our timepoints *a priori* based on time window definitions put forth by the LCN Clinical Working Group.¹⁵ However, subsequent analyses may potentially further refine the optimal time intervals to study. Despite the discrepancy in definitions, both these analyses suggest that ischemic core volumes seem to be larger for patients with stroke onset in the late evening/night. In line with these findings, we also observed an expected inverse trend in the penumbral volume (i.e. mismatch volume and mismatch ratio) to that of ischemic core (Table 1). Given that these values are derived from ischemic core volume and perfusion delay, which show differences by time, this was not an unexpected finding.

HIR has been shown to be a reliable indicator of cerebrovascular collaterals,^{16,17} with a higher HIR associated with faster ischemic core progression,^{18,19} development of malignant edema,²⁰ and poorer functional outcomes.^{18–21} In our analysis, we observed higher HIR values in the evenings (15:00–22:59), which suggests poorer collateral activation within this time window and potentially explains the larger ischemic core volumes observed at this timepoint as well.

There is ongoing work to better understand the connection between instability of collaterals, size in ischemic core, and their relationship with an underlying circadian or diurnal rhythm. Pre-clinical mouse models have supported our findings of larger ischemic core volumes during the ‘inactive’ period.²² Potential mechanisms that have been proposed connect to other phenomena that oscillate over a 24 hour period including blood pressure,^{1,2} cerebral blood flow,^{22,23} mitochondrial function,²³ and hormone secretion.^{1,2} It has been specifically noted that there are differences in blood flow within a stroke penumbra in animal models during the day and night.²² Despite an incomplete understanding of the physiological basis, these results suggest that therapeutic interventions, such as thrombolysis and thrombectomy, may be less effective when performed in patients with stroke onset in the late evening. Further research will be required to assess if clinical outcomes differ based on stroke onset time.

Limitations of this analysis include the retrospective design, with limited variables used as part of the data collection and analysis. These limitations were necessary step to increase the sample size and to ensure standardization in reporting. Additionally, we instituted an

assumption to estimate stroke onset in this patient cohort, using the midpoint between LSW and symptoms observed for unwitnessed strokes, which is in line with some prior studies.²⁴ Because stroke onset can be more ambiguous especially in the night (Table 1), this assumption was necessary to account for patients presenting in the late evening and early morning without an exact stroke onset time. However, other studies have taken alternative approaches,^{25,26} such as defining stroke onset as one hour prior to symptoms observed. Because we chose a midpoint for this analysis, we had 75 (5.0%) cases where the LSW and symptoms observed spanned across a given cut-off (i.e. LSW 5:55 and symptoms observed 8:05). Consequently, we performed a sensitivity analysis to show that our central findings were replicated when we looked at the subset of strokes with witnessed stroke onset (n = 1091), though the sample size of patients especially in the night was reduced.

We also choose to combine both CTP and MR-DWI/PWI data to account for preferences in clinical practice across different centers that employ a preference toward one modality in evaluation versus a mixture of the two modalities (Supplemental Table 1). This approach is supported by multiple studies^{27,28} that have found a high correlation among basic perfusion characteristics between these two imaging modalities, however this has not examined exclusively for HIR. Reassuringly in a separate sensitivity analysis of ischemic core volume among exclusively MRI perfusion scans, we saw similar significant results that matched our initial conclusions.

Another impact to generalizability is the inclusion of baseline imaging up to 24 hours from LSW, understanding that perfusion profiles may vary the further removed from stroke onset. Despite this broad inclusion criteria, our median onset-to-imaging time was under 4 hours, with an interquartile range between 1.7 and 6.4 hours. Additionally, 91% of all imaging included in this analysis occurred within 10 hours from LSW (Supplementary Figure 2) and was a variable accounted for in the final multivariable model. We also compared our final cohort to patients excluded from the initial analysis, due to lack of perfusion imaging or discrepancy in LSW, and did not find systemic differences based on age, NIHSS, or ASPECT Score (Supplementary Table 3).

Despite these limitations, this analysis is the largest to offer insight into the association between time of stroke onset and perfusion imaging profiles. These results suggest that elements critical to the effectiveness of current interventions, including the robustness of collaterals, may vary based on time of day and could be influenced by alterations in the sleep-wake cycle. Further steps are already underway to validate these findings in additional cohorts as well as develop registries to obtain more granular information on the interaction of sleep-wake cycles and stroke occurrence. In summary, this is first analysis of its kind suggesting that collaterals vary based on stroke onset time and support prior data suggesting an interaction between circadian rhythm and factors that mediate stroke evolution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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JJ. Heit is a consultant for Medtronic and MicroVention and a member of the iSchemaView Medical and Scientific Advisory Board.

All other authors have nothing to declare.

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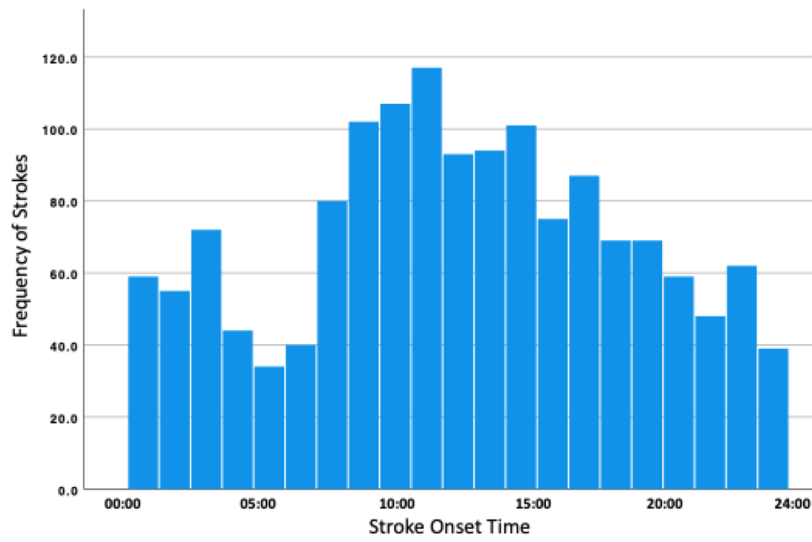


Figure 1. Distribution of large vessel occlusions (LVOs) based on stroke onset time.

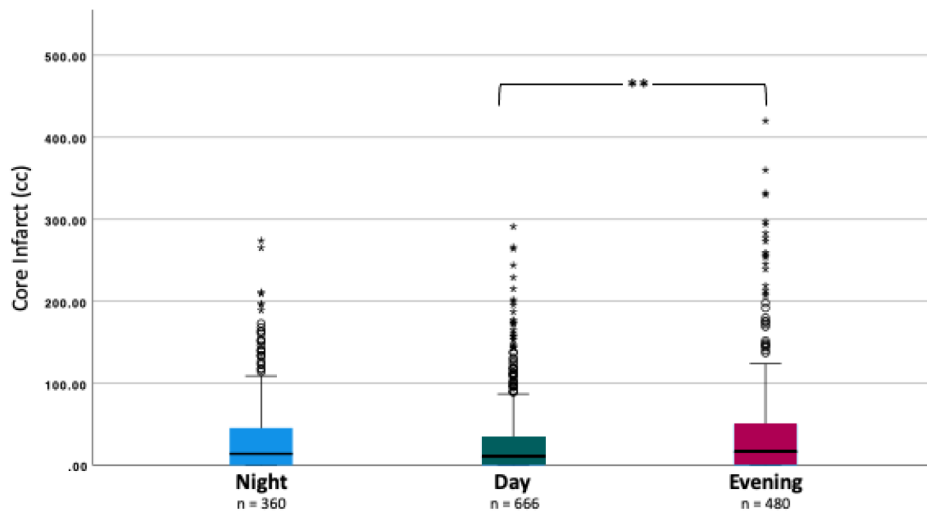


Figure 2. Distribution of ischemic core of LVOs based on stroke onset time, Night (23:00–6:59), Day (7:00–14:59), Evening (15:00–22:59). ** $p < 0.001$ using Kruskal-Wallis Independent-Samples Test.

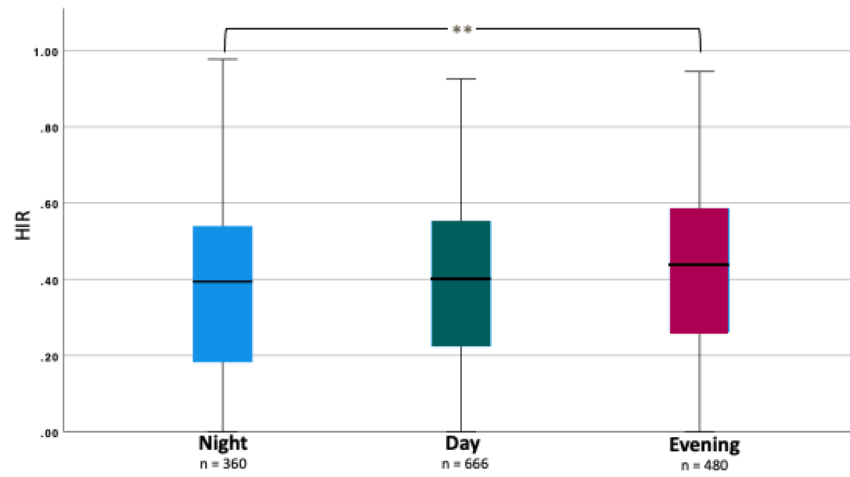


Figure 3. Distribution of HIR of LVOs based on stroke onset time, Night (23:00–6:59), Day (7:00–14:59), Evening (15:00–22:59). ** $p < 0.01$ using Kruskal-Wallis Independent-Samples Test.

Table 1.

Clinical presentation and radiographic features of the total cohort, subdivided into stroke onset times, Night (23:00–6:59), Day (7:00–14:59), Evening (15:00–22:59).

	Total Cohort n = 1506	Night n = 360	Day n = 666	Evening n = 480
Age, mean years (IQR)	74.9 (63.0–84.0)	73.0 (61.8–82.6) ¹	76.0 (64.3–85.6) ^{1,2}	73.9 (61.5–82.8) ²
NIHSS, median (IQR)	14.0 (8.0–20.0)	14.0 (8.0–20.0)	14.0 (7.0–20.0)	15.0 (8.0–20.0)
Blood Glucose, median mg/dL (IQR)	120.6 (104.4–151.0)	120.0 (104.3–151.0)	120.6 (104.4–151.4)	120.7 (104.4–150.0)
<i>Occlusion Site</i> , n (%)				
ICA	290 (19.3)	79 (21.9)	114 (17.1)	97 (20.2)
M1	716 (47.5)	174 (48.3)	327 (49.1)	215 (44.8)
M2	500 (33.2)	107 (29.7)	225 (33.8)	168 (35.0)
Wake-up Stroke, n (%)	256 (17.0)	208 (57.8)	41 (6.2)	7 (1.5)
<i>Medical History</i> [*] , n (%)				
Hypertension	932 (61.9)	219 (60.8)	423 (63.5)	290 (60.4)
Diabetes	297 (19.7)	72 (20.0)	136 (20.4)	89 (18.5)
Dyslipidemia	700 (46.5)	166 (46.1)	307 (46.1)	227 (47.3)
Witnessed Stroke, n (%)	1091 (72.4)	89 (24.7)	591 (88.7)	411 (85.6)
<i>Type of Acquisition</i> , n (%)				
MRI Perfusion	752 (49.9)	182 (50.6)	305 (45.8)	265 (55.2)
CT Perfusion	754 (50.1)	178 (49.4)	361 (54.2)	215 (44.8)
Time to Imaging, median (IQR)	220.0 (104.4–381.3)	380.0 (248.8–536.0) ^{3,4}	172.0 (88.5–293.0) ^{3,5}	190.0 (93.3–345.8) ^{4,5}
Tmax 6, median (IQR)	92.0 (48.8–145.3)	93.0 (47.0–144.0)	93.0 (48.0–149.1)	91.7 (52.0–141.8)
Tmax 10, median (IQR)	34.0 (12.0–71.3)	30.0 (9.0–72.5)	33.0 (12.0–70.0)	36.0 (14.6–74.5)
Core, median (IQR)	13.0 (0.0–42.0)	14.2 (0.0–45.5)	10.0 (0.0–35.0) ⁶	16.8 (0.0–50.9) ⁶
Mismatch, median (IQR)	61.0 (28.0–107.0)	59.0 (26.6–103.0)	66.0 (30.9–114.0) ⁷	57.0 (24.0–101.0) ⁷
Mismatch Ratio, median (IQR)	3.2 (1.6–7.1)	3.1 (1.7–6.8)	3.9 (1.8–8.5) ⁸	2.8 (1.4–6.3) ⁸
HIR, median (IQR)	0.4 (0.2–0.6)	0.4 (0.2–0.5) ⁹	0.4 (0.2–0.6)	0.4 (0.3–0.6) ⁹

^{1,3,4} p < 0.001 in pair-wise comparison.

^{2,5} p < 0.05 in pair-wise comparison.

^{6,7,8,9} p < 0.01 in pair-wise comparison.

* Data missing for 21 cases.