



# Decomposing Acute Symptom Severity in Large Vessel Occlusion Stroke: Association With Multiparametric CT Imaging and Clinical Parameters

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**Background and Purpose:** Acute ischemic stroke of the anterior circulation due to large vessel occlusion (LVO) is a multifactorial process, which causes neurologic symptoms of different degree. Our aim was to examine the impact of neuromorphologic and vascular correlates as well as clinical factors on acute symptom severity in LVO stroke.

**Methods:** We selected LVO stroke patients with known onset time from a consecutive cohort which underwent multiparametric CT including non-contrast CT, CT angiography and CT perfusion (CTP) before thrombectomy. Software-based quantification was used to calculate CTP total ischemic and ischemic core volume. Symptom severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) upon admission. Multivariable regression analysis was performed to determine independent associations of admission NIHSS with imaging and clinical parameters. Receiver operating characteristics (ROC) analyses were used to examine performance of imaging parameters to classify symptom severity.

**Results:** We included 142 patients. Linear and ordinal regression analyses for NIHSS and NIHSS severity groups identified significant associations for total ischemic volume [ $\beta = 0.31$ ,  $p = 0.01$ ; Odds ratio (OR) = 1.11, 95%-confidence-interval (CI): 1.02–1.19], clot burden score ( $\beta = -0.28$ ,  $p = 0.01$ ; OR = 0.76, 95%-CI: 0.64–0.90) and age ( $\beta = 0.17$ ,  $p = 0.04$ ). No association was found for ischemic core volume, stroke side, collaterals and time from onset. Stroke topography according to the Alberta Stroke Program CT Score template did not display significant influence after correction for multiple comparisons. AUC for classification of the NIHSS threshold  $\geq 6$  by total ischemic volume was 0.81 ( $p < 0.001$ ).

**Conclusions:** We determined total ischemic volume, clot burden and age as relevant drivers for baseline NIHSS in acute LVO stroke. This suggests that not only mere volume but also degree of occlusion influences symptom severity. Use of imaging parameters as surrogate for baseline NIHSS reached limited performance underlining the need for combined clinical and imaging assessment in acute stroke management.

**Keywords:** large vessel occlusion, multiparametric CT, CT perfusion, cerebral ischemia, stroke

## INTRODUCTION

Multiparametric CT imaging raises the opportunity to comprehensively assess cerebrovascular status in large vessel occlusion (LVO) stroke, including tissue perfusion, topography, collateral flow, thrombus burden or edema formation. These parameters directly translate to morphologic correlates of stroke e.g., penumbra and core volume as well as the temporal course of infarction growth (1–5). For functional assessment of stroke severity the in-person examination using the National Institutes of Health Stroke Scale (NIHSS) comprises the gold standard (6). Taken together imaging and NIHSS are the most crucial factors to guide therapy decision for intravenous thrombolysis (IVT) or endovascular therapy (EVT) (7).

While imaging based parameters and baseline NIHSS were extensively studied regarding their impact on chronic outcome after stroke, the interplay of neuromorphologic and vascular stroke correlates with acute symptom severity remains largely unexplored (8–11). Though a study confirmed the intuitive notion that larger ischemia, causes more severe symptoms, ischemic core and penumbra were not differentiated, leaving their effect on acute neurologic symptoms unclear (10). Other studies on later performed or follow-up MRI found an association between stroke topography and admission symptoms, ignoring LVO status or vascular territory, which complicates translation of these results into the modern thrombectomy era (12, 13).

As clinical application, imaging-based surrogates for acute stroke severity might facilitate and accelerate stroke triage. Due to missing neurologic capacities in hospitals, telestroke networks need to implement video assessment for clinical examination (14, 15). Also, during the COVID-19 pandemic, the in-person examination presents a unique challenge, hence it causes prolonged contact with potentially infected and contagious patients (16). On the other hand, MRI or CT perfusion (CTP) imaging, though crucial for decision making in situations with extended or unclear time window, have been shown to increase pretherapeutic time delays (17).

In this study, we aimed to determine how imaging and clinical factors contribute to acute symptom severity of anterior circulation LVO stroke patients as measured on the NIHSS. Further, we explored the possibility to classify guideline-based NIHSS thresholds by imaging parameters.

## MATERIALS AND METHODS

### Study Design and Cohort

This retrospective study was approved by the local institutional review board according to the Declaration of Helsinki of 2013 and requirement for written informed consent was waived. Patients with acute ischemic stroke due to anterior circulation large vessel occlusion were selected out of a consecutive cohort of 653 patients between 2015 and 2020, who were prospectively enrolled in the German Stroke Registry (clinicaltrials.gov identifier: NCT03356392) and treated with EVT at our institution.

Inclusion criteria were

- Stroke due to anterior circulation large vessel occlusion [internal carotid artery (ICA), middle cerebral artery (MCA)],
- full imaging dataset including non-contrast CT, CT angiography (CTA) and CTP,
- known time from symptom onset.

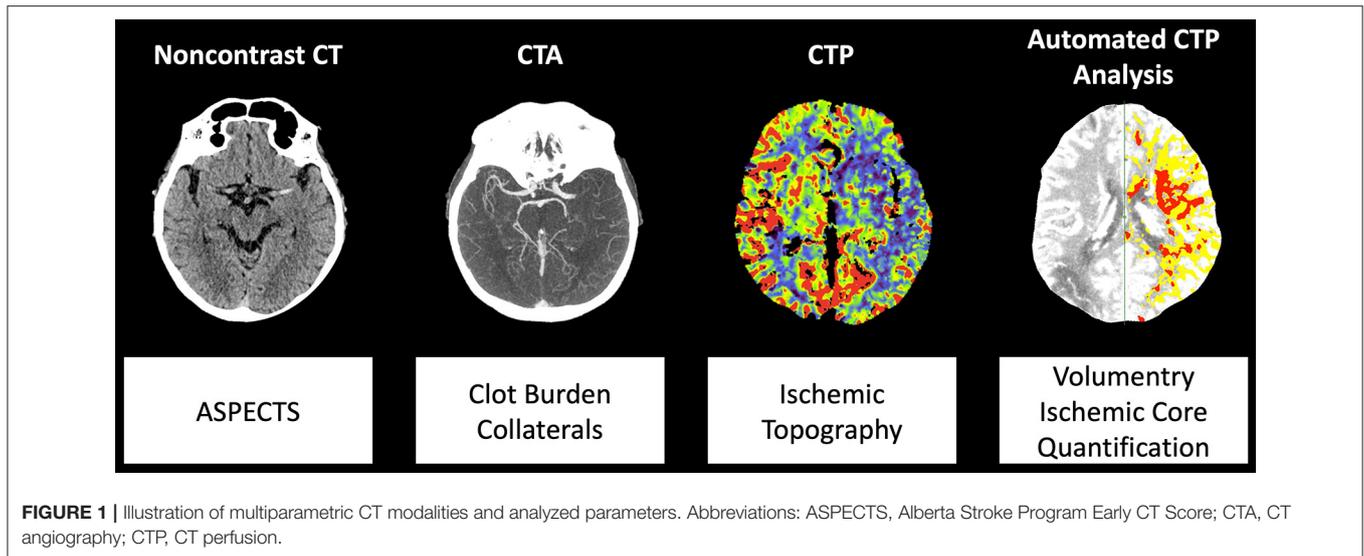
We excluded patients with

- premonitory modified Rankin Scale  $\geq 2$ ,
- bilateral stroke.

A flowchart of patient selection is provided in the Online Data **Supplementary Figure 1**.

### Image Analysis/Measurements

The imaging protocol included non-contrast CT, CTA, and CTP. Examinations were performed on CT scanners of the same vendor (SOMATOM Definition AS+, SOMATOM Definition Flash and SOMATOM Force, Siemens Healthineers, Forchheim, Germany). CTP data were processed using Syngo Neuro Perfusion CT (Siemens Healthineers, Forchheim, Germany) including automated calculation of ischemic core and penumbra volumes according to the manufacturer's thresholds (CBV  $< 1.2/100$  mL and CBF  $< 35.1/100$  mL/min) (18). We defined total ischemic volume as sum of penumbra and core volumes. CTA imaging was obtained in a single sweep from the aortic arch to the vertex with a bolus trigger of 100 HU in the aortic trunk. Expert readers (W.G.K., P.R) blinded to all clinical data including admission NIHSS determined Alberta Stroke Program Early CT Score (ASPECTS) on non-contrast CT as well as regional leptomeningeal (rLM) collateral score according to Menon et al. (20 point ordinal score, higher values indicate better collaterals) and clot burden score according to Tan et al. (10 point ordinal score, smaller values indicate more severe



**FIGURE 1** | Illustration of multiparametric CT modalities and analyzed parameters. Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; CTP, CT perfusion.

vessel occlusion) on CTA (1, 2, 19). In case of disagreement consensus was reached in a separate session. As measure of inter-reader agreement, we calculated the intraclass correlation coefficient. Stroke topography was assessed on cerebral blood flow maps according to the 10 regions of the ASPECTS template by consensus without double reading. An illustration of multiparametric CT modalities and associated parameters is provided in **Figure 1**.

### NIHSS and Clinical Parameters

NIHSS was determined for all 142 patients on admission via in-person examination by on call neurologists. Baseline comorbidities were systematically determined after initial therapy by patient interview or medical records with full datasets available in 138 patients.

### Statistical Analysis

Analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna Austria) and SPSS Statistics 23 (IBM, Armonk NY 2016, commercial software). Categorical variables are reported as number and percentage. All metric and ordinal variables as median (interquartile range, IQR).

Multivariable linear regression analysis was performed to identify associations of NIHSS with clinical and imaging parameters. To avoid overfitting of the regression models, we tested the multicollinearity of independent variables using the variance inflation factor. For ordinal regression we used a 4-point ordinal scale to classify stroke severity according to the NIHSS (1: minor, NIHSS 0–4; 2: moderate, NIHSS 5–15; 3: moderate to severe, NIHSS: 16–20; 4: severe, NIHSS: 21–42) so that the proportional odds assumption was met (20). Independent model parameters included age, sex, time from symptom onset, stroke side, ischemic core volume, total ischemic volume, non-contrast CT ASPECTS, rLM collateral score and clot burden score. For ordinal regression we used an increment of 10 mL for total ischemic volume in order to facilitate interpretation of the resulting OR.

Additional linear and ordinal regression were performed to incorporate the clinical baseline parameters presence of hypertension, dyslipidemia, diabetes mellitus and atrial fibrillation. Incomplete clinical records led to inclusion of 138 patients in this analysis.

For topography, independent association of hypoperfused ASPECTS regions were tested in separate regression models for each region while adjusting for total ischemic volume and stroke side. *P*-values were corrected using Bonferroni's method.

Receiver operating characteristic (ROC) analyses including calculation of the area under the curve (AUC) were used to determine classification performance of imaging parameters for guideline-based NIHSS thresholds (NIHSS  $\geq 6$ ,  $\geq 10$ ,  $\geq 20$ , and  $> 25$ ) (21–23). Optimal cut-off values were determined by maximizing the Youden Index. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

### Patient Characteristics

In this retrospective study 142 patients with LVO stroke were included. Eighty-one of the patients were male and 61 female. Median age was 74 years, [interquartile range (IQR) 63–81 years]. Median time from symptom onset to CT was 124 min (IQR: 70–213 min). Median NIHSS score at admission was 13 (IQR:7–18). Most frequent site of LVO was the M1 segment of the middle cerebral artery (47.9%), followed by the internal carotid artery (25.4%). Median total ischemic volume was 187.5 mL (IQR:152.5–230.7 mL) and median ischemic core volume was 34.8 mL (IQR:21.7–59.1 mL). All patients were treated with EVT according to our inclusion criteria, additionally 102 patients (71.8%) were treated with intravenous thrombolysis. Detailed patient characteristics are displayed in **Table 1**. Frequency of admission NIHSS values are displayed in the Online Data **Supplementary Tables 1, 2**.

**TABLE 1** | Patient characteristics ( $N = 142$ ).

Male sex	81	(57.0%)
Female sex	61	(43.0%)
Median age	74	(63–81)
Male study population	74	(63–80)
Female study population	78	(70–82)
Time from symptom onset to CT (min)	124	(70–213)
NIHSS on admission	13	(7–18)
Hypertension	97	(70.3%)*
Diabetes mellitus	18	(13.0%)*
Hypercholesterolemia	28	(20.3%)*
Atrial Fibrillation	36	(26.1%)*
<b>Treatment</b>		
IV thrombolysis	102	(71.8%)
Endovascular therapy	142	(100%)
<b>Imaging data</b>		
Noncontrast CT-ASPECTS	9	(7–10)
rLM collateral score	16	(12–18)
Clot burden score	7	(4–8)
Total ischemic volume (mL)	187.5	(152.5–230.7)
Ischemic core volume (mL)	34.8	(21.7–59.1)
Mismatch volume (mL)	61.3	(6.1–82.3)
Infarction growth rate (ml/min)	1.5	(0.8–2.9)
Side of stroke		
Right	58	(40.8%)
Left	84	(59.2%)
Occlusion location		
ICA	36	(25.4%)
Carotid T	12	(8.5%)
M1 segment of MCA	68	(47.9%)
M2 segment of MCA	26	(18.3%)

Values presented are count (percentage) for categorical and median (interquartile range) for ordinal or continuous variables. Time is presented in minutes, all volumes are presented in mL. ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; rLM, regional leptomeningeal. \*Available in 138 cases.

## Association of NIHSS With Imaging and Clinical Parameters

Multivariable linear regression analysis in 142 patients presented significant independent association of admission NIHSS with total ischemic volume ( $\beta = 0.31$ ,  $p = 0.01$ ), clot burden score ( $\beta = -0.28$ ,  $p = 0.01$ ), and age ( $\beta = 0.17$ ,  $p = 0.04$ ). Ischemic core volume and rLM collateral score as well as time from symptom onset, non-contrast CT ASPECTS or sex did not show significant associations (all  $p > 0.05$ ). No additional associations were found when including the baseline comorbidities hypertension, diabetes, dyslipidemia or atrial fibrillation (all  $p > 0.05$ ). The variance inflation factor was below the critical value of 3.3 (24).

In ordinal regression analysis with NIHSS values ordered by symptom severity from 1 to 4, significant independent association with total ischemic volume per 10 mL [Odds ratio (OR) = 1.11, 95%-CI: 1.02–1.19,  $p = 0.01$ ] and clot burden score (OR=0.76, 95%-CI: 0.64–0.90,  $p = 0.001$ ) was present.

**TABLE 2** | Linear regression analysis for association of admission NIHSS and imaging parameters ( $N = 142$ ).

Independent variables	$\beta$	$p$ -value	VIF
Age	0.17	<b>0.04</b>	1.14
Sex	0.04	0.63	1.22
Time from symptom onset to CT	0.06	0.43	1.07
Stroke side	-0.12	0.14	1.13
Core volume	-0.10	0.42	2.56
Total ischemic volume	0.31	<b>0.01</b>	2.68
NCCT ASPECTS	-0.11	0.24	1.51
rLM collateral score	0.004	0.97	2.43
Clot burden score	-0.28	<b>0.01</b>	1.77

A multivariate linear regression analysis was performed for the indicated parameters.  $P$ -values  $< 0.05$  indicate statistical significance. Bold numbers indicate  $p < 0.05$ . VIF, variance inflation factor; ASPECTS, Alberta Stroke Program Early CT Score; NCCT, Noncontrast CT; NIHSS, National Institutes of Health Stroke Scale; rLM, regional leptomeningeal.

**TABLE 3** | Ordinal regression analysis for association of symptom severity and imaging parameters ( $N = 142$ ).

Independent variables	OR	$p$ -value	95%-CI
Age	1.03	0.06	1.00-1.05
Sex	0.91	0.79	0.45-1.84
Time from symptom onset to CT	1.00	0.26	1.00-1.00
Stroke side	2.01	0.05	0.99-4.06
Core volume	0.99	0.30	0.98-1.01
Total ischemic volume/10 mL	1.11	<b>0.01</b>	1.02-1.19
NCCT ASPECTS	0.90	0.28	0.74-1.09
rLM collateral score	1.01	0.87	0.91-1.13
Clot burden score	0.76	<b>0.001</b>	0.64-0.90

A multivariate ordinal regression analysis was performed for the indicated parameters. Symptom severity was numerically classified by the NIHSS on admission (1: NIHSS 0-4, 2: NIHSS 5-15, 3: NIHSS: 15-20, 4: NIHSS: 21-42).  $P$ -values  $< 0.05$  indicate statistical significance. Bold numbers indicate  $p < 0.05$ . ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; NCCT, Noncontrast CT; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; rLM, regional leptomeningeal.

Age and stroke side presented a trend toward significance in this analysis (OR=1.03, 95%-CI: 1.00–1.05,  $p = 0.06$  and OR = 2.01, 95%-CI: 0.99–4.06,  $p = 0.05$ ). Detailed results are displayed in **Tables 2, 3**. Analysis including baseline comorbidities are presented in the Online Data **Supplementary Tables 3, 4**. Results using the 4-point scale collateral assessment according to Tan et al. and including occlusion location as independent variable are provided in the Online Data **Supplementary Tables 5–8** (25). Unadjusted bivariate correlation analysis of admission NIHSS and scaled or ordinal parameters is presented in the Online Data **Supplementary Table 9**. ICC presented strong agreement for non-contrast CT ASPECTS, rLM collateral score and clot burden score as displayed in the Online Data **Supplementary Table 10**.

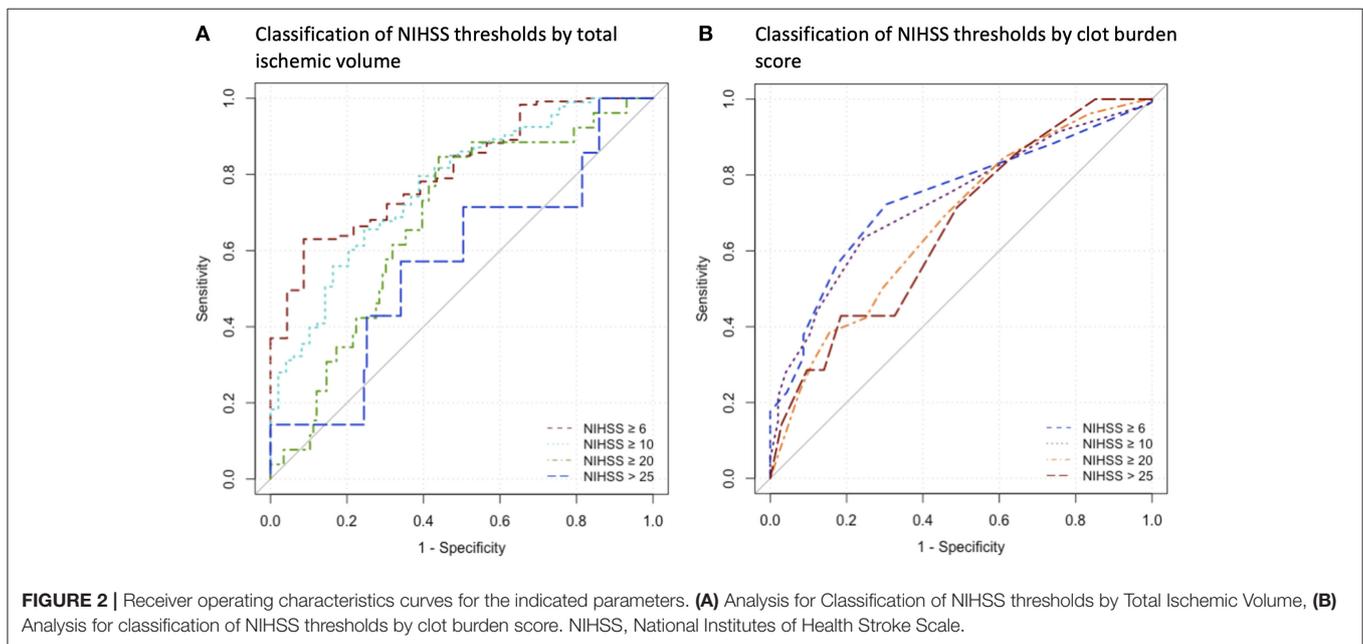
## Association of Admission NIHSS With Stroke Topography

Separate regression models for the 10 ASPECTS regions adjusted for total ischemic volume and stroke side resulted in association

**TABLE 4 |** ROC analysis for classification of NIHSS thresholds by the indicated parameters ( $N = 142$ ).

Threshold parameter	AUC (95% CI)		$p$ -value	Y-Index	Y-Index CP	Sensitivity	Specificity
<b>Classification by total ischemic volume (mL)</b>							
NIHSS $\geq 6$	0.81	(0.72–0.89)	<0.001	0.54	182.6 mL	0.63	0.91
NIHSS $\geq 10$	0.77	(0.69–0.85)	<0.001	0.42	185.9 mL	0.66	0.76
NIHSS $\geq 20$	0.68	(0.57–0.78)	0.001	0.41	185.9 mL	0.85	0.56
NIHSS $> 25$	0.57	(0.33–0.81)	0.569	0.23	208.7 mL	0.57	0.66
<b>Classification by clot burden score</b>							
NIHSS $\geq 6$	0.74	(0.64–0.84)	<0.001	0.42	8	0.72	0.70
NIHSS $\geq 10$	0.73	(0.65–0.81)	<0.001	0.39	7	0.63	0.76
NIHSS $\geq 20$	0.67	(0.56–0.78)	0.003	0.24	7	0.69	0.54
NIHSS $> 25$	0.66	(0.46–0.87)	0.125	0.24	4	0.43	0.81

A receiver operating characteristic analysis was performed for the indicated parameters. Cut points were determined by the Y-Index.  $P$ -values  $< 0.05$  indicate statistical significance. AUC, Area Under the Curve; CI, confidence interval; CP, Cut point; NIHSS, National Institutes of Health Stroke Scale; Y-Index, Youden Index.



of lentiform nucleus ( $\beta = 0.20, p = 0.02$ ) which did not maintain significance after Bonferroni correction for multiple comparisons. Detailed results are presented in the Online Data **Supplementary Table 11**.

### Discriminatory Value of Imaging Parameters for Guideline-Based NIHSS Thresholds

The ROC curve analysis in 142 patients for the discriminatory value of total ischemic volume and clot burden score for the NIHSS threshold  $\geq 6$  resulted in an AUC of 0.810 ( $p < 0.001$ ) and 0.74 ( $p < 0.001$ ) respectively, with lower performance for the other thresholds of NIHSS  $\geq 10, \geq 20,$  and  $> 25$  (AUC  $< 0.8$ ). Detailed results are displayed in **Table 4**. ROC curves are presented in **Figure 2**.

### DISCUSSION

This study presents a comprehensive investigation of multiparametric CT imaging and clinical factors on acute symptom severity in anterior circulation LVO stroke. To our knowledge this is the first study selectively analyzing impact of CTP ischemic core and total ischemic volume while also providing data on the influence of ischemic topography using the routinely applicable ASPECTS template.

Our results indicate that total ischemic volume is a major determinant for acute symptom severity in LVO patients measured by the NIHSS. Notably, there is also an established linear relationship between NIHSS after 24 h and post-treatment infarction volume hinting toward similar mechanisms moderating morphology and symptom severity in the hyperacute and post-therapeutic acute stroke phase (26). We also observed significant association of the clot burden score with NIHSS on

admission similar to other studies (8, 9). Occlusion location did not present independent influence. As possible mechanism we propose that not only ischemic volume but also degree of hypoperfusion, reflected by more severe occlusion, affects acute symptom severity. An interaction that has already been described for initial perfusion deficit and chronic outcome after stroke (27).

Interestingly, neither non-contrast CT ASPECTS nor ischemic core volume exhibited an independent association with symptom severity. As these parameters are closely intertwined, both are particularly useful for predicting morphological and clinical outcomes, yet the effect on acute symptoms seems to be clouded by mere total ischemic volume (28). It is important to note that the inclusion criteria of known time from symptom onset shifted our sample toward an earlier time window. Our study did not reveal correlation of NIHSS and time from symptom onset, though there are observations that NIHSS can worsen during the subacute course of stroke (29). Therefore, our data indicates that the established associations are independent of a defined time window. Later time windows or patients with unknown onset time, however, might still display different dynamics in the translation of ischemic volumes to neurologic symptoms.

Also, collateral status did not impact baseline NIHSS, which is known to affect infarction core growth (5). Accordingly, collateral perfusion would seem to suffice for delaying tissue decline but not for sustaining neurologic function in the acute stroke phase. However, diverging results were found by other studies using less granular collateral scores and disregarding ischemic core volume (9, 30).

Though the NIHSS is known to favor symptoms of the dominant hemisphere, infarction side did not show significant association with symptom severity. These results are in congruence with the findings of Furlanis et al. who found a strong correlation of ischemic volume with baseline NIHSS resulting in similar slopes for right and left hemispheric stroke (10). However, advanced MRI analysis showed left hemispheric stroke led to higher baseline NIHSS (31). Differences in results might partly be explained by the selected study sample containing only LVO patients, requesting dedicated analysis in this important patient group. Also, stroke topography did not significantly impact overall admission NIHSS. Topography seems crucial for chronic stroke symptoms and though there is described location dependency of baseline NIHSS, same locations showed high overlap with lesion volume, which was accounted for in our analysis (13, 15).

Among clinical parameters only age displayed a significant influence on baseline symptom severity with lower NIHSS in younger patients as also found in a prior study (9). Neither sex, nor baseline comorbidities exhibited significant influence.

As potential clinical use, total ischemic volume classified the guideline-based cut-off of admission NIHSS  $\geq 6$  as used in the DEFUSE 3 study with acceptable performance. Other NIHSS

cut-off values of 25 from the WAKE-UP trial or 10 and 20 from the DAWN trial were classified with lower performance (22, 23, 32). Accordingly, only differentiation of minor/moderate stroke by total ischemic volume seems feasible. This underlines the importance of proper clinical and imaging examination for evidence-based therapy decisions.

Limitation of this study include the small sample size and retrospective study design. Second, we used a selected dataset of LVO stroke patients with known time from symptom onset and without premorbid disability ( $\text{pMRS} \leq 1$ ). We chose these criteria as we wanted to examine the temporal effects on stroke symptoms during LVO without bias of existing sequelae. Translatability to patients with unknown onset seems reasonable due to the missing impact of time from symptom onset, however, needs further dedicated validation. Also, subgroups with advanced edema formation indicated by low ASPECTS and presumably larger infarction core were underrepresented in our study, requiring further analysis of this highly discussed subgroup in larger samples (33). In light of the small sample size also the borderline non-significant ordinal regression results for impact of ischemic core volume and stroke side need to be interpreted with caution and require reproduction in larger datasets. Third, imaging was performed using scanners and software of a single vendor (Siemens Healthineers, Forchheim, Germany). While volumetry can differ between different software packages, measurements of the used package presented best agreement with the gold-standard RAPID among other packages (18, 34).

## CONCLUSION

Our data determined total ischemic volume and clot burden as the most relevant neuromorphologic and vascular correlates for baseline NIHSS in acute LVO stroke, suggesting that not only mere volume but also degree of occlusion influences clinical presentation. On the other hand, ischemic core volume and collateral status did not influence acute symptom severity. All associations were independent from time from symptom onset. Our results indicate only limited potential for classification of symptom severity by CT imaging. This highlights the significance and synergy of clinical and imaging assessment in the acute management of stroke patients. Further studies with a larger dataset are needed to clarify the role of collaterals and side of stroke.

## DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article will be made available by the corresponding author upon request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der medizinischen Fakultät, LMU Munich. Written informed consent for participation was not

required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

LS, ST, WK, and PR: conceptualization. LS, ST, FM, WK, and PR: formal analysis and data curation. LS, ST, WK, PR, and MF: writing—original draft. PR, DP-W, SG, SM, LK, MH, JR, and KD: writing—review and editing. PR, WK, JR, and TL:

supervision. All authors: contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2021.651387/full#supplementary-material>

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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