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Large vessel occlusive stroke with milder baseline severity shows better collaterals and reduced harm from thrombectomy transfer delays

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Abstract

Background: Patients with large vessel occlusion (LVO) stroke presenting with milder baseline clinical severity are common and require endovascular thrombectomy. However, such patients are difficult to recognize using pre-hospital severity-based triage tools and therefore are likely to require a secondary inter-hospital transfer if transported to a non-thrombectomy center. Given the potential for milder severity to represent better underlying cerebrovascular collateral circulation, it is unknown whether transfer delays are still associated with poorer post-stroke outcomes in this patient group.

Aims: We primarily aimed to examine whether the harmful effect of inter-hospital transfer delay for thrombectomy was different for LVO patients with mild or severe deficits. Secondarily, we also investigated whether imaging markers of collateral circulation were different between severity groups.

Methods: Registry data from two large Australian thrombectomy centers were used to identify all directly presenting and secondarily transferred LVO patients undergoing thrombectomy, divided into those with lower (NIHSS <10) and higher (NIHSS ≥ 10) baseline deficits. The primary outcome was the functional independence or return to baseline defined as modified Rankin Scale 0–2 or baseline at 90 days. Patients with complete baseline CT-perfusion data were analyzed for imaging markers of collateral circulation by baseline severity group.

Results: A total of 1210 LVO patients undergoing thrombectomy were included, of which 273 (22.6%) had lower baseline severity. Despite similar thrombolysis and recanalization rates, transferred patients had lower odds of achieving the primary outcome compared to the primary presentation to a thrombectomy center, where baseline severity was higher (adjusted odds ratio (aOR) 0.759 (95% CI 0.576–0.999)), but not when severity was lower (aOR 1.357 (95% CI 0.764–2.409), p-interaction = 0.122). In the imaging analysis of 436 patients, those with milder severity showed smaller median ischemic core volumes (12.6 (IQR 0.0–17.9) vs 27.5 (IQR 6.5–37.1) mL, $p<0.001$)), higher median perfusion mismatch ratio (10.8 (IQR 4.8–54.5) vs 6.6 (IQR 3.5–16.5), $p<0.001$), and lower median hypoperfusion intensity ratio (0.25 (IQR 0.18–0.38) vs 0.40 (IQR 0.22–0.57), $p<0.001$).

Discussion: Patients receiving secondary inter-hospital transfer for thrombectomy had poorer outcomes compared to those presenting directly to a thrombectomy center if baseline deficits were severe, but this difference was not observed when baseline deficits were milder. This result may potentially be due to our secondary findings of significantly improved collateral circulation markers in lower-severity LVO patients. As such, failure of pre-hospital screening tools to detect lower-severity LVO patients for pre-hospital bypass to a thrombectomy center may not necessarily deleteriously affect outcome.

Data access statement: Anonymized data not published within this article will be made available on request from any qualified investigator.

Keywords
Stroke, thrombectomy, outcomes, treatment

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Introduction

For patients with large vessel occlusion (LVO), endovascular thrombectomy (EVT) with or without intravenous thrombolytics dramatically improves functional post-stroke outcome.[1] As EVT efficacy sharply diminishes with time,[2] delays from secondary inter-hospital transfers for EVT (as opposed to direct EVT-center presentation) are associated with harm.[3,4]

Pre-hospital triage tools for selecting likely EVT candidates reduce the need for secondary transfers, but there is considerable uncertainty in balancing tool sensitivity and specificity[5] based on the accepted threshold of clinical severity that triggers a positive tool assessment.

Approximately 30% of patients with LVO have milder baseline severity.[6] Although previous literature has established a link with collateral circulation adequacy and improved outcomes following the transfer for EVT,[7] it is not currently known whether this is disproportionately represented by patients with lower baseline severity. Such patients may experience milder symptoms due to better collaterals that maintain blood flow above the symptomatic threshold. Consequently, they may have slower infarct growth kinetics and potentially experience less harm from secondary transfer delays, yet no literature currently exists for clinical outcomes of this patient cohort when transfer status is considered.

Aims

This observational study aimed to primarily investigate the association of baseline severity with clinical outcome differences in LVO patients presenting directly to a thrombectomy center versus receiving inter-hospital transfer for EVT. As a second exploratory aim, we explored imaging markers of collateral adequacy in LVO patients with mild or severe deficits and their association with functional outcomes.

Methods

Patient inclusion

We performed a multicenter, retrospective cohort study using a descriptive epidemiological design. Data were sourced from open-label stroke registries from two major Australian metropolitan EVT centers (Royal Melbourne Hospital and Royal Adelaide Hospital) including consecutive patients who directly presented or underwent secondary transfer for EVT from 2016 to 2021, with complete 90-day follow-up data. EVT was mostly offered for internal carotid artery (ICA), first- or proximal second-segment middle cerebral artery (MCA) and basilar artery LVOs. We stratified patients by transfer status and by dichotomized baseline severity using the National Institutes of Health Stroke Scale on presentation to the first hospital, defined as lower (NIHSS < 10) or higher (NIHSS ≥ 10) severity based on the likely threshold of LVO detection of commonly used triage tools using an earlier dataset.[6] Data collection was approved by the Melbourne Health Human Research Ethics Committee with waiver of consent (QA2013072 and QA2016123).

Outcomes

The primary outcome was the functional independence or return to baseline functioning assessed at 90 days with the modified Rankin Scale (mRS), defined as mRS 0–2 or return to premorbid mRS. We explored further outcomes including mRS 0–1/baseline, mRS 5–6, and mortality as secondary endpoints. Sensitivity analyses were also conducted for patients achieving good reperfusion post-EVT and those with only anterior circulation LVO. Finally, the association of baseline severity when NIHSS is treated as a continuous variable with functional outcomes stratified by transfer status was tested as a secondary analysis.

Our secondary exploratory imaging outcomes aimed to compare the adequacy of collateral circulation between patients with lower versus higher baseline severity and its association with 90-day outcomes. This was performed in a smaller subsample of the primary analysis cohort where patients had complete baseline CT-perfusion data and was not stratified by transfer status. We used previously validated baseline CT-perfusion parameters[8] obtained through RAPID processing software (iSchemaView, Inc.): (1) estimated ischemic core volume (cerebral blood flow $< 30\%$), (2) critically hypoperfused tissue (time-to-maximum > 6 s), (3) perfusion mismatch ratio (ratio of time-to-maximum > 6 s volume/cerebral blood flow $< 30\%$ volume), and (4) hypoperfusion intensity ratio (ratio of time-to-maximum $>$ 10-s volume/$>$ 6-s volume). Imaging markers

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Table 1. Baseline characteristics of lower and higher severity groups.

	NIHSS < 10	NIHSS ⩾ 10	p
No. of patients	273	937	
Age, mean (SD)	69.97 (13.8)	69.72 (14.0)	0.908
Female sex	118 (43.2%)	419 (44.7%)	0.678
NIHSS, median (IQR)	6 (4–8)	18 (14–22)	<0.001
Premorbid mRS			0.117
0–1	256 (93.8%)	857 (91.5%)	
2	7 (2.6%)	31 (3.3%)	
3	9 (3.3%)	47 (5.0%)	
4	1 (0.4%)	2 (0.2%)	
Inter-hospital transfer	135 (49.5%)	524 (55.9%)	0.062
Intravenous thrombolysis	249 (91.2%)	879 (93.8%)	0.134
Occlusion location			<0.001
ICA	34 (12.5%)	181 (19.2%)	
M1	136 (49.8%)	587 (62.6%)	
M2	61 (22.3%)	118 (12.6%)	
Basilar	17 (6.2%)	29 (3.1%)	
Others	25 (9.2%)	22 (2.3%)	
Successful reperfusion (TICI 2b/3)	228 (83.5%)	799 (85.3%)	0.502
Onset-to-thrombolysis, median (IQR), min	192.2 (117–218)	171.0 (106–190)	0.008
Onset-to-thrombectomy arterial access, median (IQR), min	334.0 (201–354)	309.6 (183–350)	<0.001

NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation; IQR: interquartile range; ICA: internal carotid artery; TICI: thrombolysis in cerebral infarction.

were then compared to our primary clinical outcome of mRS 0–2 or return to baseline.

Statistical analysis

Mann–Whitney U test was used for continuous variables and Fisher's exact test for categorical variables. The association of 90-day mRS in patients with lower versus higher deficits, and the association of imaging markers and outcomes, was investigated using logistic regression modeling adjusted for age, occlusion site, and premorbid mRS. We used a second model with the addition of adjustment for time from onset to thrombolysis and onset to EVT commencement as a secondary analysis. Transfer status by degree of deficit interactions was assessed by including respective multiplicative interaction terms in regression models. Sensitivity analyses were also conducted for those achieving good reperfusion (Thrombolysis In Cerebral Infarction grade 2b/3) and to only include internal carotid and first/second middle cerebral artery occlusions. Statistical analysis was performed using SPSS v27 (IBM Corp.) and Stata v17SE (StataCorp, TX, USA).

Results

Patient characteristics

Table 1 shows baseline patient characteristics. A total of 1210 LVO patients with complete 90-day mRS data were included, of which 273/1210 (22.6%) had lower baseline severity. Milder severity patients had lower rates of secondary transfer and longer onset-to-arterial access, while those with higher deficits showed increased proportion of ICA/M1 occlusions at baseline. Median onset-to-groin puncture

time was 282 (IQR 219–381) for secondarily transferred patients and 210 (IQR 162–289) min for patients presenting directly to an EVT-center ($p < 0.001$). The vast majority (>90%) received intravenous thrombolysis, with median onset-to-needle times of 150 (IQR 115–199) for transfer and 148 (IQR 105–195) min for direct-presenting patients ($p = 0.058$).

Primary clinical outcome analysis

The primary outcome (mRS 0–2 or baseline) was achieved in 203 (74.4%) patients with lower baseline deficits and 430 (45.9%) in patients with higher baseline deficits ($p < 0.001$). Figure 1 and Table 2 show 90-day mRS scores for lower and higher deficit LVO patients depending on transfer status. Secondary transfer was associated with lower odds of the primary outcome for patients with higher baseline deficit (aOR 0.76 (95% CI 0.58–1.00)) but not with lower baseline deficit (aOR 1.36 (95% CI 0.76–2.41), p-interaction = 0.12).

Additional secondary analysis outcomes (Table 2) and sensitivity analyses (Supplemental Tables S1 and S2) show the need for transfer associated with trends toward poorer outcomes in the higher severity group. Further adjustment for time from onset to thrombolysis and EVT commencement (Supplemental Table S3) generally negated the effect of transfer status across both milder (aOR 1.21 (95% CI 0.64–2.32)) and severe groups (aOR 0.87 (95% 0.63–1.20), p-interaction = 0.94).

When analyzing baseline NIHSS as a continuous variable (Supplemental Table S4), higher baseline severity was associated with lower rates of good functional outcomes in both direct (aOR 0.91 (95% CI 0.88–0.93)) and transfer groups (aOR 0.88 (0.85–0.91) p-interaction = 0.10), and higher rates of very poor outcomes (mRS 5–6) in direct (aOR 1.10 (95% CI 1.06–1.14)) and transfer groups (aOR 1.14 (95% CI 1.10–1.16), p-interaction = 0.16).

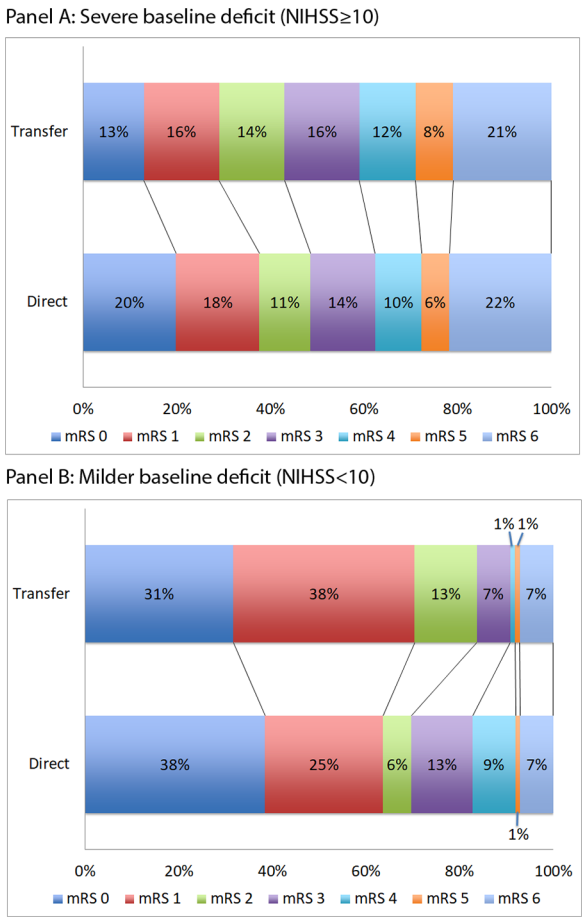
Secondary imaging analysis

The secondary analyses for collateral circulation were performed with baseline CT-perfusion data processed for 436 of the original 1210 patients, of which 107 (24.5%) were lower severity. Table 3 shows the differences in CT-perfusion markers between lower and higher deficits.

Patients with milder severity LVO showed lower median estimated ischemic core volume (12.6 (IQR 0.0–17.9) vs 27.5 (IQR 6.5–37.1) mL, $p < 0.001$) and lower median critically hypoperfused tissue volume (107.6 (IQR 66.2–138.3) vs 130 (IQR 91.7–166.0) mL, $p < 0.001$). In addition, those with milder severity had greater median perfusion mismatch ratio (10.8 (IQR 4.8–54.5) vs 6.6 (IQR 3.5–16.5), $p < 0.001$) and lower median hypoperfusion intensity ratio (0.25 (IQR 0.18–0.38) vs 0.40 (IQR 0.22–0.57), $p < 0.001$). When baseline NIHSS was treated as a continuous variable, correlation with imaging markers was weak overall (Supplemental Figure S1).

When correlated to 90-day outcome, each incremental increase in ischemic core volume, critically hypoperfused tissue volume, and hypoperfusion intensity ratio was significantly associated with lower rates of functional independence and increased mortality, while there were no significant associations with perfusion mismatch ratio (Supplemental Table S5).

Figure 1. Association of transfer status with outcome in patients with differing baseline severities.



Discussion

In our observational study, secondary inter-hospital transfer for EVT was associated with poorer outcomes for LVO patients with higher baseline deficits. We observed no difference in outcomes for LVO patients with milder baseline deficits, although did not demonstrate statistical heterogeneity, possibly due to the smaller numbers in this group.

In additional analyses, further adjustment for time to reperfusion generally negated the negative effects of

Table 2. Clinical outcomes at 90 days by baseline severity and transfer group.

	NIHSS < 10 (n = 273)			NIHSS ⩾ 10 (n = 937)			
	Direct (n = 138)	Transfer (n = 135)	OR (95% CI)	Direct (n = 413)	Transfer (n = 524)	OR (95% CI)	p-interaction
Functional independence or return to baseline (mRS 0–2 or baseline)	n = 97 (70.29%)	n = 105 (77.78%)	1.357 (0.764, 2.409)	n = 200 (48.43%)	n = 230 (43.89%)	0.759 (0.576, 0.999)	0.122
Freedom from disability or return to baseline (mRS 0–1 or return to baseline)	n = 84 (60.90%)	n = 88 (65.19%)	1.012 (0.601, 1.705)	n = 144 (34.87%)	n = 159 (30.34%)	0.799 (0.600, 1.063)	0.320
Death or severe disability (mRS 5–6)	n = 15 (10.87%)	n = 7 (5.19%)	0.555 (0.221, 1.392)	n = 93 (22.52%)	n = 128 (24.43%)	1.247 (0.901, 1.727)	0.105
Death (mRS 6)	n = 12 (8.70%)	n = 6 (4.44%)	0.636 (0.2326, 1.737)	n = 65 (15.74%)	n = 87 (16.60%)	1.186 (0.817, 1.720)	0.227
Ordinal mRS analysis			0.890 (0.573, 1.382)			0.818 (0.649, 1.030)	0.588

NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; CI: confidence interval.
Analyses adjusted for age at admission, site of occlusion and premorbid mRS.

Table 3. Collateral circulation imaging markers.

	NIHSS < 10	NIHSS ⩾ 10	p
No. of patients	329	107	
Estimated ischemic core volume (CBF < 30%), median (IQR)	12.6 (0.0–17.9)	27.5 (6.5–37.1)	<0.001
Critically hypoperfused tissue volume (Tmax > 6 s), median (IQR)	107.6 (66.2–138.3)	130.0 (91.7–166.0)	<0.001
Perfusion mismatch ratio (Tmax > 6 s/CBF < 30%)*, median (IQR)	10.8 (4.8–54.5)	6.6 (3.5–16.5)	<0.001
Hypoperfusion intensity ratio (Tmax > 10s/6s), median (IQR)	0.25 (0.18–0.38)	0.40 (0.22–0.57)	<0.001

NIHSS: National Institutes of Health Stroke Scale; CBF: cerebral blood flow; IQR: Interquartile range; Tmax: time-to-maximum.
*CBF < 30% defaulted to minimum of 1 mL for calculation.

transfer in the higher severity group, consistent with a previous US-based analysis of EVT transfer,[3] whereas it did not appreciably change the result for milder severity patients. When baseline NIHSS was analyzed as a continuous variable, higher severity was incrementally associated with worsened outcomes in both direct and transfer groups with no statistical heterogeneity.

We performed a secondary exploratory analysis of collateral circulation adequacy according to baseline severity in a smaller group of patients with available CT-perfusion data. This showed that all imaging collateral circulation markers were significantly better in milder severity LVO patients. Furthermore, this dataset showed that each incremental increase in ischemic core volume, critically hypoperfused volume, and hypoperfusion intensity ratio (indicating worsened collateral status) was significantly associated with poorer outcomes. Interestingly, there was no association between perfusion mismatch ratio and outcomes, which contrasts with some small observational studies[9] but is broadly in line with the findings of a meta-analysis of early window EVT trials where mismatch volume did not predict outcomes once ischemic core was included in the model.[10]

The implications of our findings are that, although LVO patients with milder baseline severity are less likely to be identified by severity-based triage tools, the time delay incurred by secondary transfer was not observed to be deleterious on outcomes. This may potentially be due to our secondary findings that milder severity LVO patients showed fewer ICA/M1 occlusions and significantly better markers of collateral circulation adequacy. Collateral circulation was strongly associated with improved outcomes in our imaging analysis subsample, although this was not stratified by transfer status. Given the known association of

collateral parameters with slower infarct growth kinetics during secondary transfer for EVT,[7] this is likely to represent one reason for the disparity in clinical outcomes between different baseline severity groups in our study, although we have not conducted a formal causal analysis given the observational nature of our study.

Therefore, our results would suggest that pre-hospital triage tools for EVT should primarily focus on patients with higher clinical severity who demonstrate significantly worsened outcomes from transfer delay. Lowering specificity to increase milder LVO stroke detection triage tool sensitivity may not be beneficial and the trade-off in specificity may give rise to potential concerns of delay in intravenous thrombolysis and EVT-center overburdening. Up to 20% of patients with a visible vessel occlusion and initially mild symptoms subsequently deteriorate,[11] possibly due to eventual collateral failure. As such, LVO patients with milder severity may still require secondary transfer for monitoring at an EVT-center. However, this could be completed with less urgency and better patient selection than immediate pre-hospital bypass. Alternatively, if pre-hospital detection and triage of milder LVO patients are desired, imaging with mobile stroke units could be used.[12]

The limitations of this study include its retrospective nature and relatively small sample of patients with milder severity, which may have limited interpretation of functional outcome data. Larger studies with greater precision are needed to confirm these findings. There may also have been selective referral of patients to EVT-centers, creating potential bias in the cohort of secondarily transferred patients. We were only able to collect baseline CT-perfusion data on a limited proportion of our sample due to numerous transfer sites not using RAPID software and manual collection feasibility. Therefore, we have made the decision not to perform imaging analyses stratified by transfer status given the likelihood of biased data. Finally, the vast majority of our included patients received intravenous thrombolysis, such that caution should be advised in extrapolation of results to thrombolysis-ineligible patients.

Conclusion

In our observational study, patients with LVO and higher baseline severity (NIHSS $\geq$ 10) showed poorer outcomes if secondary inter-hospital transfer for thrombectomy was required. In contrast, this deleterious effect was not observed in milder baseline severity (NIHSS $<$ 10) patients. This difference may be potentially explained by our exploratory secondary analyses showing milder severity patients with fewer ICA/M1 occlusions and better baseline CT-perfusion markers of collateral adequacy. This therefore suggests potential mitigation of the harmful effects of time delays incurred by secondary inter-hospital transfer in milder severity patients. Consequently, pre-hospital triage tools used to bypass suspected LVO patients to thrombectomy centers should prioritize detection of patients with more severe deficits.

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Data availability

Anonymized data not published within this article will be made available on request from any qualified investigator.

Supplemental material

Supplemental material for this article is available online.

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