

Differences in Factors Predicting Outcome and Mortality after Mechanical Thrombectomy for Acute Large Vessel Stroke Between Patients over and Under 70 Years of Age: A Five Year Retrospective Study

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Abstract

Aim: To assess the differences in risk factors between different age groups after mechanical thrombectomy (MT) for ischaemic stroke, including recanalization time and functional and radiological scoring.

Methods: Patients treated between December 2009 and January 2014 (n=137) for anterior circulation stroke were divided into age groups. Patient data including National Institutes of Health Stroke Scale (NIHSS) and Alberta Stroke Program Early CT Score (ASPECTS) scoring pre and post procedure and procedural timings were collected. Modified Rankin score was used as functional outcome measure at 90 days.

Results: For the >70 age group, ASPECTS correlated most strongly with outcome (ASPECTS >7 - OR 3.75, 95% CI 1.04-13.5) and mortality (ASPECTS <8 - OR 5.08, CI 1.1-23.3). In the <70 age group, only NIHSS correlated with both outcome (NIHSS <20 - OR 4.17, CI 1.4-12.2) and mortality (NIHSS >20 - OR 6.22, CI 1.4-26.7) (p<0.05). Both NIHSS and ASPECTS done at 24h were strongly associated with outcome at 90 days. Revascularisation >5h after onset in the <70 age group was associated with markedly poorer outcome with increased risk of malignant MCA transformation, while this trend was not seen in the >70 age group.

Conclusions: ASPECT scoring at admission is clinically helpful in patient selection for thrombectomy in the >70 age group as it correlates well with outcome and mortality, but less useful in the <70 age group, possibly due to the increased plasticity of remodelling. Revascularisation time appears to be much more important in the younger age group, and restoration of circulation within 5 hours should be the goal to reduce the risk of reperfusion injury.

Highlights

- ASPECTS predicts outcome with greater sensitivity than NIHSS in the >70 age group
- In the <70 age group, NIHSS was a better predictor and ASPECTS not significant
- Extending times greater than 5 hours in the <70 age group risks reperfusion injury
- Post procedure, both NIHSS and ASPECTS both predict 90 day outcome accurately

Introduction

Mechanical thrombectomy (MT) is an experimental interventional treatment for ischaemic stroke in the UK [1], which has been shown to offer increased rates of recanalisation in cases of large vessel occlusion compared to IV treatment alone or combined IV/IA thrombolysis [2]. Early randomised controlled trials failed to show benefit comparing MT to conventional treatment [3-6], but these trials were criticized for failing to optimise patient selection [7] and used older devices. Recently, four new large randomised controlled trials addressing these issues have proven significant benefit in functional outcome for MT over IV thrombolysis in selected patient groups [8-11].

Alberta Stroke Program Early CT Score (ASPECTS) is a radiological scoring system that places equal weighting on the regions and important structures in the middle cerebral artery territory and can be scored using plain CT, CT-perfusion (CBV-ASPECTS) and diffusion weighted MRI (MRI-ASPECTS)[12]. The different modes have been shown to yield similar scores, though MRI-ASPECTS tends to score lower; however, many patients have contraindications to MRI on an acute admission [13,14]. ASPECTS has been shown in many studies investigating both thrombolysis and endovascular intervention (intra-arterial thrombolysis) to be an independent predictor of outcome, often with a threshold of <8 at admission heralding poorer function at 3 months [15-17]. On the other hand, some studies do not agree on the significance of early ischaemic changes on CT as predictors of long term functional outcome [18].

Age has also been shown to be an important factor in recovery after treatment for ischaemic stroke, with age groups ≥70-80 years associated with a significant reduction in recanalization rates [19]. Even when adjusted for recanalization, this age group displayed poorer clinical outcomes, with a trend of better outcomes with decreasing patient age [20,21].

Time to recanalization has been shown to be important in determining outcome. Younger patients presenting with large

vessel occlusion tend to be treated more aggressively and this may result in guideline breach times being broken. However, it is not currently clear whether this has an effect on patient outcome.

In this study, we evaluate the use of both the clinical National Institutes of Health Stroke Score (NIHSS) and CT ASPECTS in the selection of patients for endovascular thrombectomy and at 24 hours post procedure in evaluating patient prognosis, with further analysis to ascertain whether factors affecting prognosis differ between the <70 and ≥70 year age groups. Recanalisation times between groups are also analysed to determine whether younger patients have increased procedural times and whether this results in differences in 90 day outcome.

Methods

All patients who had received endovascular intervention for anterior circulation stroke at our institution and who were on the thrombectomy register were recruited retrospectively for this study. Intervention was defined as instigating a procedure with intent to progress to mechanical thrombectomy, although this was occasionally not performed if no clot was found or the procedure could not be completed.

Retrospective ASPECT scoring was performed by two neuroradiology trainees on plain CT done at arrival into the Accident and Emergency department and at 24 hours post procedure, as described by Barber et al. [12]. CT examinations were done on a Siemens Somatom Definition AS (Siemens, Erlangen, Germany).

The pathway for neurointervention at our institution has previously been described [22]. Briefly, patients are selected for thrombectomy if they present within 4.5 hours of onset of anterior circulation symptoms and have a treatable carotid bifurcation or proximal middle cerebral artery (M1 or M2) occlusion with no haemorrhagic component or significant established ischaemic change. Age should be ≤80 years, but exceptions are made on a case by case basis dependant on previous function. NIHSS scoring is done by the on-call stroke team on initial examination. Bridging intravenous therapy with alteplase 0.9mg/kg is given if there are no contraindications as a 10% bolus and 90% infusion with 30% dose retained for intra-arterial (IA) use.

Thrombectomy is attempted under general anaesthesia or sedation via femoral arterial access using either a stent-based retrieval device or suction by hand, or by the Penumbra Aspiration Pump® (Penumbra Inc., Alameda, CA, USA) for proximal occlusions. Residual distal thrombus disruption by microwire and IA nimodipine for vasospasm are used if necessary. The procedure is continued until revascularisation is attained, the procedure is abandoned due to technical or patient reasons or the time limit of 6 hours from onset is reached. If transient reperfusion is attained, longer time limits are allowed on a case by case basis.

On completion of the procedure, the femoral arterial catheter is removed and arterial closure device is applied. Blood pressure is maintained at or less than 185/110 and antiplatelet agents and anticoagulants are not routinely used for 24 hours post-procedure

unless a stent is placed, in which case 500 mg aspirin IV is given and dual oral antiplatelet therapy instigated. Otherwise, oral antiplatelet agents are started at 24 hours as per UK guidelines if the CT showed no haemorrhage [23]. If minor haemorrhagic transformation is shown, aspirin is started at reduced dose (75mg OD). At 24 hours NIHSS is repeated by the stroke team. mRS is scored at discharge and at 90 days post procedure. Onset to completion time is defined as the time between symptomatic onset and the timing of the final catheter angiogram.

Differences between groups were investigated by odds ratios and Mann-Whitney U-test (with $p < 0.05$ considered as significant). Independent predictors of outcome were analysed by binary linear regression analysis. SPSS (v.22) was used for all statistical analyses. Cause of death was ascertained for all patients deceased at 90 days.

Results

Outcomes

Of a total of 166 patients in the thrombectomy register at the time of the study, 137 were included in this study with anterior circulation strokes, with the remainder being posterior circulation. Of these, 47% were male and 53% were female, with age ranging from 20 to 90 years (average 63.2). 82 patients fell into the 20-69 age group and 55 patients were over or equal to 70 years of age. 131 patients had a pre-intervention CT and 135 had a post intervention CT. Thrombectomy was not attempted in 13 patients (9.5%) due to it not being required or difficulties during the procedure. Eight patients developed significant post-procedure haemorrhage as determined by SITS-MOST criteria [24] with deterioration of clinical condition (5.8%). Thirty patients had a contra-indication to intravenous thrombolysis meaning that 77.4% of the total patient group received bridging therapy.

Total all-cause mortality at 90 days was 20 of 137 (14.5%) and an outcome of functional independence (mRS 0-2) was achieved in 57/137 patients (41.6%). This is a better result than earlier clinical trials [11,25], but not as was achieved in the most recently published studies (8-10), as our dataset encompasses patients dating back to 2009. There was observed an increase in mortality and decrease in mRS 0-2 with age, with only 30% achieving independence and 30% mortality in the >80 age group.

Mortality cause analysis of the patients deceased at 90 days was undertaken. Twelve deaths in the <70 years age group were found (14.6%), with 2 deaths in the 20-40 years age group. Of these, 9 were due to malignant MCA transformation of stroke (including the 2 in the 20-40 years group) and 3 of other causes (75%). In the ≥70 years group, there were 9 deaths, of which all were due to complications relating to stroke, but only 4 of which had malignant MCA transformation (44.4%). Malignant MCA was observed in 20 of 137 patients in this study with an average age of 56.9 years. Mortality was 100% in the ≥70 years group and 56.3% in the 20-69 years group (Table 1).

NIHSS

Patients were divided into two age groups: 20-69 years and

≥70 years for the remaining analyses. NIHSS was highly predictive of outcome independent of age, with a pre-procedure score of >20 (severe stroke) associated with a significant drop in favourable outcome and increase in mortality compared with the next group (moderate to severe, 16-20, Figure 1). Independent outcome dropped from 51.2% to 23.4%, with mortality rising from 12.2% to 25.5%. NIHSS at 24h post-procedure was predictably more accurate, with a score of <16 associated with 74.2% probability of favourable outcome and 3.0% risk of death, changing to 5% and 40% respectively in the >20 group.

ASPECTS

ASPECT scores were then divided into three groups: 0-4, 5-7 and 8-10, with 10 representing no ischaemic change and 0 complete infarction of the MCA territory. There was an increase

in favourable outcome with increasing ASPECT score group in both age groups to a maximum of 50% in the 8-10 group (Figure 2). Mortality decreased with ASPECT score, but again there was an unexpected excess mortality in the 8-10 group for the 20-69 years age group.

At 24 hours, ASPECTS groupings showed increased correlation with outcome and mortality, especially in the ≥70 years age group with 80% of patients with ASPECTS of 8 or greater achieving independence compared to 50% in the 5-7 group. A score of 0-4 was strongly linked with mortality, with one third (33.3%) mortality in the ≥70 years group compared to 4.5% in the 5-7 group (Figure 3).

Non-parametric analyses

Non-parametric comparison of absolute (non-categorised)

Table 1: Malignant MCA (MMCA) relation with mortality in the 20-69 and ≥70 age groups.

	MMCA Prevalence	MMCA Mortality	MMCA mortality/All cause mortality
Total age groups	20/137 (14.6%)	13/20 (65%)	13/21 (61.9%)
Age 20-69	16/82 (19.5%)	9/16 (56.3%)	9/12 (75%)
Age ≥70	4/55 (7.2%)	4/4 (100%)	4/9 (44.4%)

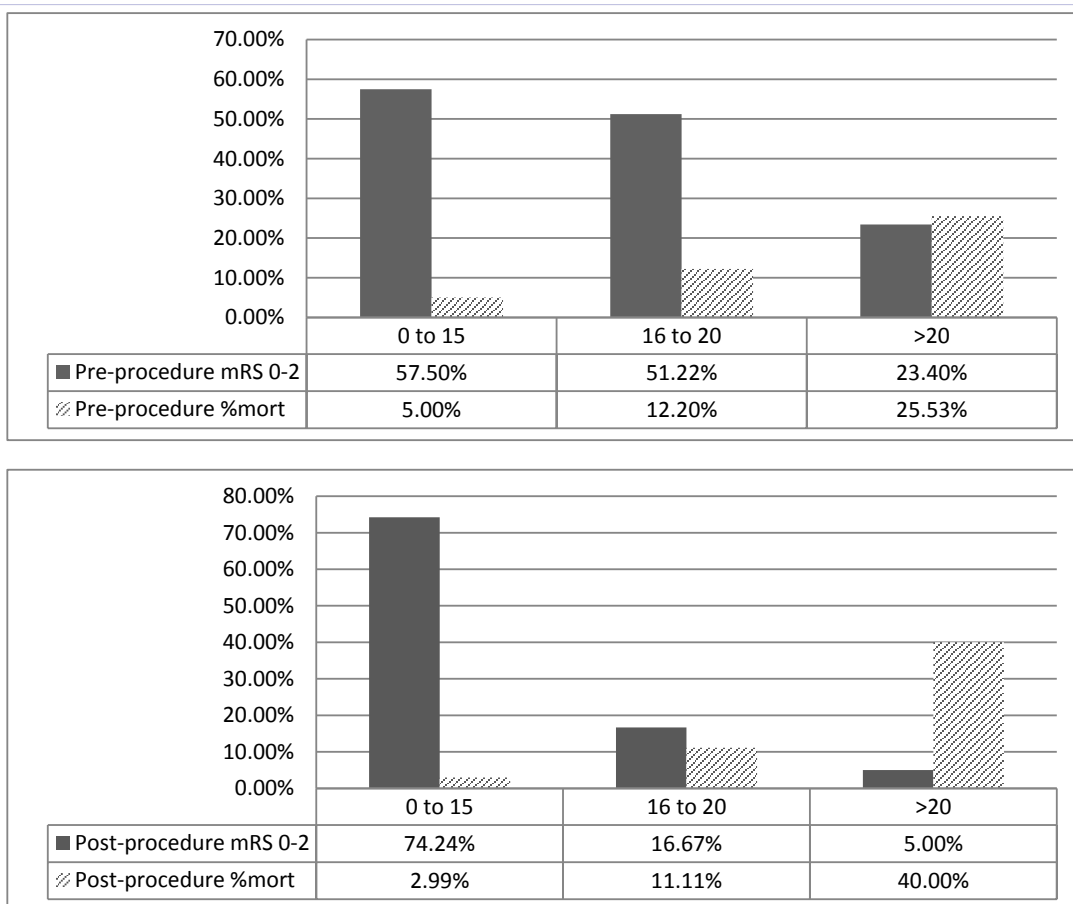


Figure 1: Pre-procedural (top) and post-procedural (bottom) NIHSS related to outcome (expressed as mRS at 90 days) and mortality (mRS 6 at 90 days).

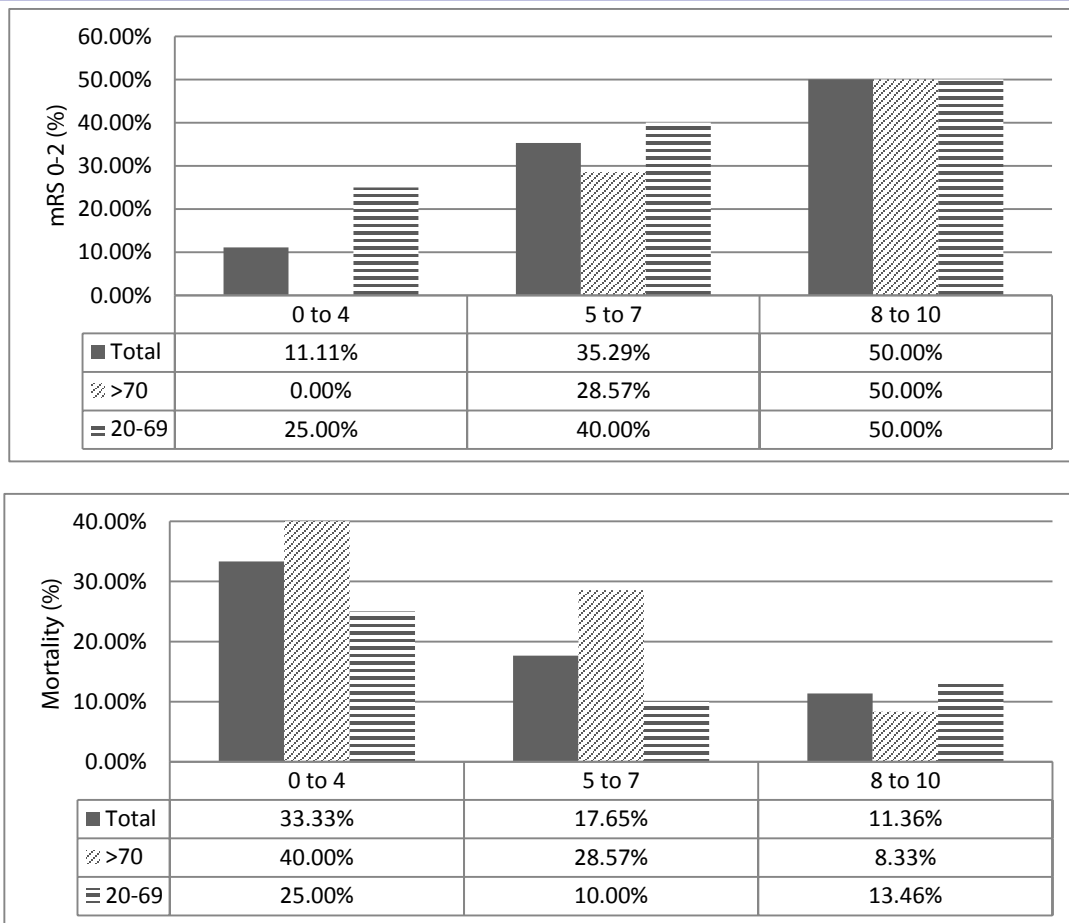


Figure 2: Pre-procedural ASPECTS related to outcome (expressed as mRS at 90 days, top) and mortality (mRS 6 at 90 days, bottom).

pre-intervention scores between outcome groups within the two age ranges showed significant differences in median ASPECT score between good/poor functional outcome groups and for mortality in the ≥ 70 years age group ($p < 0.05$). NIHSS was significant for functional outcome only in this age range. For the 20-69 years age range, both functional outcome and mortality showed significant differences in median NIHSS ($p < 0.05$), with ASPECTS showing no significant difference between groups.

Pre-procedural scoring evaluation

The most important predictive score differed between age groups. In the ≥ 70 years group, the most important pre-procedure score for independent outcome (mRS 0-2) was ASPECTS of > 7 (OR 3.75, 95% CI 1.04-13.5) (Sensitivity 81.8%, specificity 45.4% (sens/spec) for ASPECTS > 7 compared to 77.2% and 56.7% for NIHSS < 20). For mortality in this group, the most important score was ASPECTS of < 8 (OR 5.08, CI 1.1-23.3) and NIHSS was not significant (sens/spec 66.7%/71.7%). However, for the 20-69 years age group, ASPECTS was not significant and the most important score for outcome was NIHSS (sens/spec 56.9%/76.0% for NIHSS < 20 , ASPECTS > 7 not significant). NIHSS < 20 was associated with 4.17 times greater chance of independent outcome (CI 1.4-12.2) and NIHSS of > 20

was associated with 6.22 times greater risk of death (CI 1.4-26.7) (sens/spec 70.0%/72.7%).

Post-procedural scoring evaluation

At 24h post-procedure, NIHSS was the greater predictor of outcome in both groups, with NIHSS < 15 associated with 28.9 times greater probability of independence at 90 days (CI 10.0-83.6). NIHSS cutoff of 15 compared to 20 conferred a slight reduction in sensitivity, but a significant increase in specificity (sens/spec 96.2%/55.0% compared to 90.7%/76.8% for combined age groups). For mortality, ASPECTS was more important in the ≥ 70 years age group, with score of < 5 conferring a 15.5 times greater risk of death (CI 1.74-138) (sens/spec 87.5%/68.9%). Both ASPECTS and NIHSS were important in the 20-69 years age group and combined ASPECTS of < 5 with NIHSS > 20 conferred 40 times greater risk (CI 7.24-221) (sens/spec 83.3%/88.9%).

Linear regression modelling

Further binary linear regression modelling was attempted with age, absolute (non-categorised) ASPECTS and NIHSS scores as variables determining functional outcome. Insufficient data was available to model mortality. Pre-intervention, NIHSS

was the only independent variable when both age groups are considered ($p=0.01$ for 20-69 group and combined groups), but not significant in the ≥ 70 years group when considered separately ($p=0.07$). ASPECTS was not an independent variable for either age group. Post intervention, ASPECTS and NIHSS were both significant independent variables for functional outcome ($p<0.05$).

Onset to completion timing

Analysis of onset to completion time figures showed that there were more breaches of the 6 hour limit in the 20-69 years group compared to the ≥ 70 years group (35/78, 43.7%, compared to 16/52, 30.7%). There was no significant difference between breaching between the youngest patients in the 20-40 group and 41-69 group when considered separately (43.2% and 46.2% respectively), although more patients in the 20-40 years group breached 7 hours (38.6% compared to 13.4% and 9.6% in the 40-69 years group and ≥ 70 years group respectively). Correlating onset to completion time with outcome showed significant increase in mortality and infirmity over 5 hours in both age groups, but there was also a marked increase in mortality above 5 hours in the 20-69 years group. Of the 27 patients in this group revascularised in under 5 hours there was 1 death (3.7%), rising to 22.2% in the 5-6h period (4/18) and >6 h group (7/33). In the ≥ 70 years group, the trend was less marked,

with values of 9.5% (2/20), 12.5% (2/16) and 18.8% (3/16) for the same time periods, respectively. Two patients had no time data available. Looking at the onset to completion times for the patients developing malignant MCA specifically, it was shown that only 1 case occurred before 5h (1/48, 2.1%). Between 5-6 hours there were 7 cases (7/34, 20.6%) and over 6 hours there were 10 cases (10/53, 18.9%). This equated to a sensitivity of 100%/specificity 41.5% for malignant MCA in the 20-69 age group for an onset to completion time of more than 5h.

Discussion

In this study we have shown that the prognostic value of pre-procedural scoring is dependent on patient age, with clinical scoring (NIHSS) having greater value in younger patients and radiological scoring (ASPECTS) having more significance in older patients. We have also shown that younger patients appear more sensitive to recanalization timing, with longer onset to completion time reflected in worse outcomes and higher mortality with increased risk of malignant MCA.

Age is generally considered to be an important factor in determining prognosis after stroke intervention. Several studies show increasing age correlation with unfavourable outcomes [21,26,27] with lower rates of recanalization [19] and higher mortality and haemorrhage [28], especially in the >80 age group. Older patients also demonstrated a higher rate

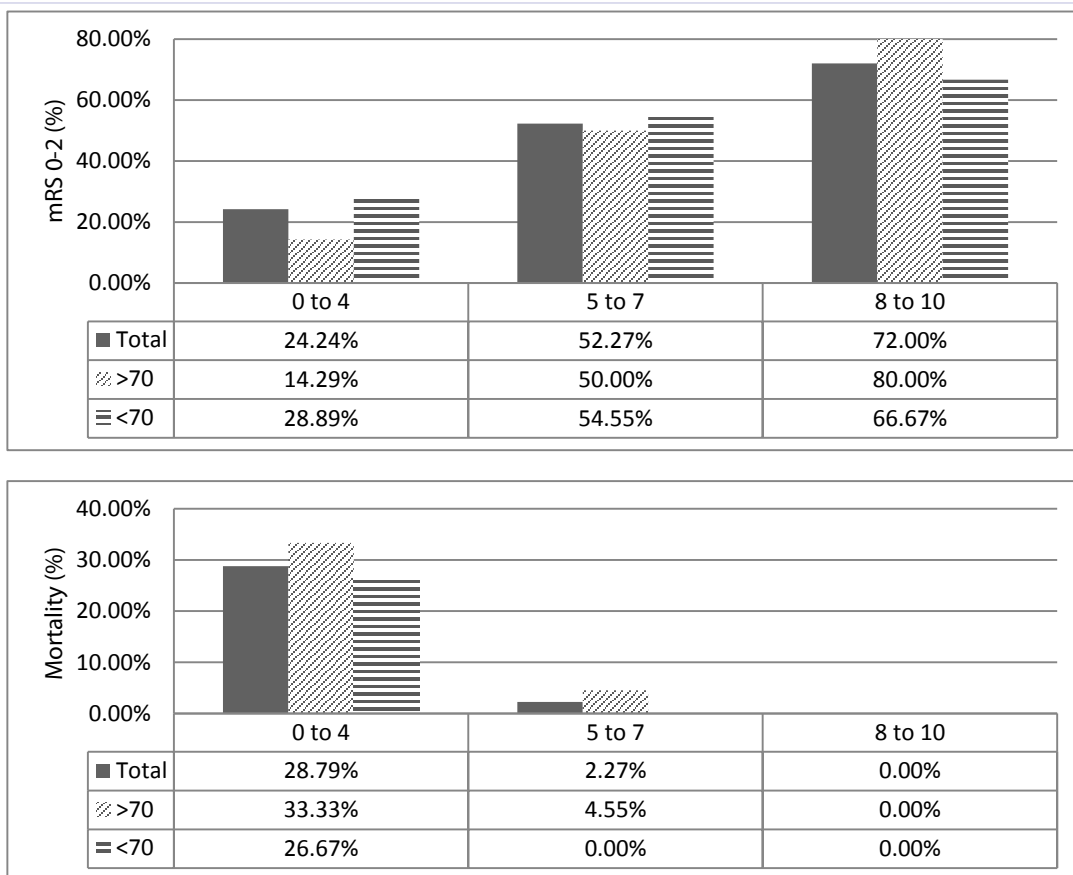


Figure 3: Pre-procedural ASPECTS related to outcome (expressed as mRS at 90 days, top) and mortality (mRS 6 at 90 days, bottom).

of futile recanalization [20,21] (poor outcome despite good flow outcomes).

A variety of studies have shown that NIHSS is an independent predictor of outcome at 90 days for both intra-arterial thrombolysis (IAT) and thrombectomy [29-31]. It has also been shown that higher NIHSS is associated with higher rates of futile recanalization [20] and haemorrhage [32]. However, there is some division over the utility of ASPECTS in the pre-intervention stage in predicting 90 day outcome and mortality. A number of papers show that a higher ASPECTS of >7 is associated with improved outcomes in intra-arterial thrombolysis [15-17,33], with lower scores associated with poorer recanalisation and increased risk of haemorrhage. However, none directly compare younger with older patient age groups, although one study using IAT investigated ASPECTS specifically in the elderly (>80 years age group, [34]).

In studies using mechanical thrombectomy, three studies [26,29,35] also demonstrate an association of ASPECTS with outcome, but two did not demonstrate this association [18,30]. One study comparing the CT ASPECTS and CT perfusion ASPECTS found that only Δ (CBV-CBF) ASPECTS was a significant predictor of successful recanalization [36], with plain CT ASPECTS having a sensitivity of only 77% and specificity 42% for favourable outcome. Again none of the above studies analysed outcome data by age group.

In our study, we showed that ASPECTS was not significantly correlated with outcome in the 20-69 years age group, with NIHSS of 20 the most significant cut-off for favourable outcome or mortality. However, in the ≥ 70 group, ASPECTS scores were significantly different between outcome groups and an ASPECTS cut off of 8 was the most important factor for prognosis, while NIHSS was less important. In linear regression models, NIHSS was the only important independent variable, but was not significant in the ≥ 70 group when considered separately. At 24 hours post-procedure, both ASPECTS and NIHSS are independent predictors of outcome, with ASPECTS more important for predicting mortality in both age groups and NIHSS more important for functional outcome.

Short time from onset to recanalization is generally accepted to be an important prognostic factor, as there is less neuronal damage and associated risk of oedematous changes such as malignant MCA. It has been shown to be associated with improved outcome [37]. In our institution, we currently use a 4.5 hour cutoff from onset for instigation of intervention to complete within 6 hours. However, in our data we can see that there is a dramatic reduction in favourable outcome and increase in mortality above 5 hours from onset, which is especially marked in the younger age group which demonstrated an increase from 3.7% to 22.2% mortality comparing <5h to 5-6h onset to completion times. We also found an increase in incidence of malignant MCA syndrome, with 17 of 18 malignant MCA syndromes occurring with onset to completion times above 5 hours. It was also observed that of the 16 malignant MCAs in the 20-69 years age group, 10 presented with NIHSS >20, indicating a large vessel occlusion (of which 7 of the 9 deaths also had NIHSS >20). It is known that malignant

MCA syndrome is more common in the younger age group [38], likely due to increased inflammatory response and less space in the skull vault for oedematous expansion. We may therefore surmise that increased mortality in the younger age group may have been caused by increased procedural times leading to later revascularisation in patients with large vessel occlusions resulting in reperfusion damage and malignant MCA.

Conclusion

In this study we have shown that both clinical NIHSS and radiological ASPECTS are important in predicting outcome in patients undergoing mechanical thrombectomy. In younger patients under the age of 70, ASPECTS correlates poorly with outcome and mortality and NIHSS is more significant. However, it is of utility in the ≥ 70 years age group, where it correlates well with both functional outcome and mortality together with NIHSS. Post-procedurally, both NIHSS and ASPECTS are helpful in predicting the clinical course of recovery regardless of age group. We also showed increased infirmity and mortality rates in the younger age group, likely due to reperfusion injury when onset to completion times extended above 5 hours (compared to the currently used 6 hour cutoff). In younger patients presenting late or at the borderline, it would be prudent to weigh the benefits and risks of undertaking thrombectomy and risking reperfusion injury compared to letting the infarct take its course with best supportive care with or without thrombolysis. The data in this study supports reducing the recommended onset to completion time to 5 or 5.5 hours from 6 hours for this younger age group, especially if patients present with NIHSS greater than 20.

Competing interests

No grants were obtained for undertaking this study. The authors declare that there are no competing interests.

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