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Perfusion computed tomography in patients with stroke thrombolysis

Hiroyuki Kawano,[1] Andrew Bivard,[1] Longting Lin,[1] Henry Ma,[2] Xin Cheng,[3] Richard Aviv,[4] Billy O'Brien,[5] Kenneth Butcher,[6] Min Lou,[7] Jingfen Zhang,[8] Jim Jannes,[9] Qiang Dong,[3] Christopher R. Levi[1] and Mark W. Parsons[1]

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Stroke shortens an individual's disability-free life. We aimed to assess the relative prognostic influence of pre- and post-treatment perfusion computed tomography imaging variables (e.g. ischaemic core and penumbral volumes) compared to standard clinical predictors (such as onset-to-treatment time) on long-term stroke disability in patients undergoing thrombolysis. We used data from a prospectively collected international, multicentre, observational registry of acute ischaemic stroke patients who had perfusion computed tomography and computed tomography angiography before treatment with intravenous alteplase. Baseline perfusion computed tomography and follow-up magnetic resonance imaging were analysed to derive the baseline penumbra volume, baseline ischaemic core volume, and penumbra salvaged from infarction. The primary outcome measure was the effect of imaging and clinical variables on Disability-Adjusted Life Year. Clinical variables were age, sex, National Institutes of Health Stroke Scale score, and onset-to-treatment time. Age, sex, country, and 3-month modified Rankin Scale were extracted from the registry to calculate disability-adjusted life-year due to stroke, such that 1 year of disability-adjusted life-year equates to 1 year of healthy life lost due to stroke. There were 772 patients receiving alteplase therapy. The number of disability-adjusted life-year days lost per 1 ml of baseline ischaemic core volume was 17.5 (95% confidence interval, 13.2–21.9 days, $P < 0.001$). For every millilitre of penumbra salvaged, 7.2 days of disability-adjusted life-year days were saved ($\beta = -7.2$, 95% confidence interval, −10.4 to −4.1 days, $P < 0.001$). Each minute of earlier onset-to-treatment time resulted in a saving of 4.4 disability-free days after stroke (1.3–7.5 days, $P = 0.006$). However, after adjustment for imaging variables, onset-to-treatment time was not significantly associated with savings in disability-adjusted life-year days. Pretreatment perfusion computed tomography can (independently of clinical variables) predict significant gains, or loss, of disability-free life in patients undergoing reperfusion therapy for stroke. The effect of earlier treatment on disability-free life appears explained by salvage of penumbra, particularly when the ischaemic core is not too large.

1 Departments of Neurology, John Hunter Hospital, University of Newcastle, Lookout Road, New Lambton Heights, NSW 2305, Australia
2 Department of Neurology, Monash Medical Centre, Monash University, 246 Clayton Road Clayton, VIC, 3168, Australia
3 Department of Neurology, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China
4 Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada
5 Department of Neurology, Gosford Hospital, Holden Street, Gosford, NSW, 2250, Australia
6 Division of Neurology, Department of Medicine, University of Alberta, 13-103 Clinical Sciences Building, 11350-83 Avenue, Edmonton, Alberta, T6G 2R3, Canada
7 Department of Neurology, the Second Affiliated Hospital of Zhejiang University, No.88 Jiefang Road, Hangzhou, 310009, China
8 Department of Neurology, Baotou Central Hospital, Inner Mongolia, Baotou, 014040, China
9 Department of Neurology, The Queen Elizabeth Hospital, 28 Woodville Road Woodville South, SA, 5011, Australia

Correspondence to: Mark Parsons,
Department of Neurology, John Hunter Hospital, Lookout Road, New Lambton Heights, NSW 2305, Australia
E-mail: mark.parsons@hnehealth.nsw.gov.au

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Abbreviations: DALY = disability-adjusted life-year; NIHSS = National Institutes of Health Stroke Scale; INSPIRE = International Stroke Perfusion Imaging Registry; TIMI = thrombolysis in myocardial infarction

Introduction

Stroke significantly shortens life expectancy and is the leading cause of adult disability in the developed world. Previous studies have identified that an individual's life expectancy after stroke was reduced by 12 years for males and 14 years for females (Peeters *et al.*, 2002). Early treatment with thrombolysis increases the chance of a good outcome with minimal disability at 3–6 months (Emberson *et al.*, 2014). Whilst measurement of disability on the modified Rankin scale at 3–6 months is the standard for acute stroke trials, this fails to take into account the longer term effects of stroke. The disability-adjusted life-year (DALY) can more accurately quantify the true long-term burden of stroke (World Health Organization, 2015*a*). The DALY is a time-based measure which combines information from premature death and from disability, with one DALY indicating 1 year of healthy life lost due to stroke. Hong *et al.* (2010*a*) showed that thrombolysis for stroke may have greater benefit of DALY saved in younger patients (<70-years-old) than elderly patients (≥70-years-old). Recently, Meretoja *et al.* (2014) reported that earlier treatment with stroke thrombolysis may save disability-free life. However, this analysis did not take into account acute stroke pathophysiology, or treatment effectiveness as assessed by subsequent measures of reperfusion or recanalization. The relative prognostic influence of pre- and post-treatment modern imaging variables (e.g. ischaemic core and penumbral volumes) compared to standard clinical predictors (such as onset-to-treatment time) on long-term stroke disability in patients undergoing thrombolysis is unknown (Bivard *et al.*, 2011).

In the present study, we used the DALY metric to assess, and compare, the effect of both modern imaging and clinical variables on long-term disability after stroke thrombolysis. We hypothesized that a large volume of pretreatment ischaemic core would predict greater loss of disability-free life, and that large volumes of salvaged penumbra would predict longer healthy lifetime after stroke.

Materials and methods

Acute ischaemic stroke patients presenting to hospital within 12 h of symptom onset at nine centres between 2011–13 were prospectively recruited in the International Stroke Perfusion Imaging Registry (INSPIRE). As part of this study, patients underwent baseline multimodal CT imaging with non-contrast CT, perfusion CT, and follow-up imaging with MRI at 24 h post-stroke. Clinical stroke severity was assessed at the two imaging time points using National Institutes of Health Stroke Scale (NIHSS) score. Early neurological improvement was defined as acute NIHSS score minus 24-h NIHSS score. Eligible patients were treated with intravenous thrombolysis according to local guidelines and the clinical judgement of the treating physician. Three-month disability was assessed 90 days after stroke by the modified Rankin Scale. Written informed consent was obtained from all participants, and the INSPIRE study was approved by the local ethics committees in accordance with Australian NHMRC guidelines.

Multimodal CT protocol

Pretreatment CT imaging included brain non-contrast CT, perfusion CT and CT angiography using either 64-, 128-, or 320-detector scanners (GE Lightspeed, Siemens Somatom Definition Flash dual source, Philips Brilliance iCT, and Toshiba Aquilion One). Axial slice coverage ranged from 40 mm to 160 mm. CT angiography was performed after perfusion CT with acquisition from the aortic arch to vertex. Scanner details are summarized in Supplementary Table 1.

Twenty-four-hour imaging protocol

As close as possible to 24 h after acute imaging, all patients underwent a stroke MRI protocol on a 1.5 T or 3 T scanner. The magnetic resonance protocol included: diffusion-weighted image, perfusion-weighted imaging, magnetic resonance time of flight angiography and fluid attenuated inversion recovery imaging. For those with a contraindication to MRI, repeat non-contrast CT and CT angiography was performed using the above protocols.

Imaging data

All perfusion imaging was postprocessed on commercial software MIStar (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia). Acute perfusion imaging was processed using single value deconvolution with delay and dispersion correction (Bivard *et al.*, 2013). Previously validated thresholds were applied to measure the volume of the acute perfusion lesion (relative delay time > 3 s) and acute ischaemic core (relative cerebral blood flow < 30%) (Bivard *et al.*, 2014). Penumbral volume was calculated from the volume of the perfusion lesion (relative delay time threshold > 3 s) minus the volume of the ischaemic core (relative cerebral blood flow threshold < 30% within the relative delay time > 3 s lesion). All acute CT angiography and follow-up magnetic resonance angiography were assessed for occlusion severity by a central reading group with each case being read by two experienced readers. Salvaged penumbra volume was calculated from (baseline perfusion volume − baseline ischaemic core volume) − (follow-up infarct volume − baseline ischaemic core volume). Follow-up infarct volume was measured on 24-h diffusion-weighted imaging.

Vascular recanalization was based on the thrombolysis in myocardial infarction (TIMI) grade, with assignments of 3 (complete recanalization), 2 (partial recanalization), 1 (minimal

recanalization) and 0 (no recanalization). For the purposes of this study recanalization was defined as TIMI grade 2–3, and no recanalization TIMI grade 0–1. Symptomatic intracerebral haemorrhage after alteplase was defined as clinical deterioration causing an increase in NIHSS score of $\geqslant$ 4 points, if the intracerebral haemorrhage was likely to be the cause of the clinical deterioration (Larrue *et al.*, 2001).

Disability-adjusted life-year

To translate 3-month clinical outcome data into a long-term measure of stroke disability, we used the DALY metric (World Health Organization, 2015*a*). DALY is a measure consisting of two components: years of life lost due to premature death, and years of life lost due to disability. In other words, the fewer DALYs, the greater the disability-free life after stroke, and 1 year of DALY indicates 1 year of disability-free life lost. Years of life lost due to premature death is calculated as the difference between life expectancy of a person in the general population at a given age, sex, and country, and age-, sex-, and country-matched life expectancy of a stroke patient in a certain modified Rankin Scale category. The long-term annual risk of death after stroke was taken from published literature (1.53, 1.52, 2.17, 3.18, 4.55, and 6.55 times that of the general population for modified Rankin Scale categories 0–5, respectively) (Hong *et al.*, 2010*a*). Years of life lost due to disability is calculated by multiplying the life expectancy of a stroke patient by a disability weight. The disability weights were taken from published literature (0.000, 0.053, 0.228, 0.353, 0.691, and 0.998 for modified Rankin Scale categories 0–5, respectively) (Hong *et al.*, 2009). We used life table data of the general population in each country in INSPIRE (Australia, Canada, and China) (World Health Organization, 2015*b*). The detailed mathematical derivation is provided in the Supplementary material. Although DALYs traditionally have been reported with discounting and age-weighting rate (Hong *et al.* 2010*a*), in 2012, the World Health Organization made a major policy change and stopped using age-weighting and discounting rate for DALY calculations (Murray *et al.*, 2012). In this study, we calculated our data according to this new policy, DALY in which neither future discounting nor age weighting were used. We calculated DALYs for each patient, and also converted into 'DALY-days' by multiplying 'years of DALY' by 365 days.

Statistical analysis

We used Wilcoxon rank sum test or chi-square test to the relationship between patients with reperfusion therapy within 6 h of onset and those who arrived at hospital within 6 h of stroke onset but did not receive reperfusion therapy. Modified Rankin Scale category-specific life expectancies and DALYs were calculated for each patient. Univariate linear regression analysis was used to test the effect on DALY of clinical variables (age, sex, NIHSS score, and onset-to-treatment time), and imaging variables (baseline penumbra volume, baseline ischaemic core volume, and penumbra salvaged from infarction). We then used multivariate linear regression to adjust for the effect on DALY of clinical and imaging variables that were univariate predictors. We also analysed the relationship between DALY and salvaged penumbra volume separately for patients $<$70 and $\geqslant$70 years old. Finally, we assessed between early neurological improvement, salvaged penumbra and DALY. These statistical analyses were performed on JMP 10 package (SAS Institute Inc, Cary, NC, USA). Values of $P < 0.05$ were considered significant.

Results

During the study period, 1518 patients were enrolled in INSPIRE. Of these patients, 690 patients were excluded due to no reperfusion therapy, which included nine patients with incomplete data (seven with poor quality CT perfusion data, two with lack of age and sex information). Of these 681 patients without reperfusion therapy, 599 patients arrived at hospital within 6 h of stroke onset. We also excluded 22 patients due to reperfusion therapy after 6 h of stroke onset, and 34 patients treated with reperfusion therapy but with incomplete data (23 with poor quality of CT perfusion data, eight with lack of sex information, three with lack of treatment time). Thus, 772 patients who received alteplase and who underwent perfusion CT before treatment within 6 h of stroke onset were analysed (Table 1). Of 701 patients who underwent follow-up CT angiography or magnetic resonance angiography, 40% of patients ($n = 283$) achieved recanalization. There was no patient treated with mechanical thrombectomy during the study period at the INSPIRE centres as this was prior to the positive thrombectomy trial results. Comparing patients with those 722 patients with reperfusion therapy within 6 h of onset, 599 patients who arrived at hospital within 6 h of stroke onset but did not receive reperfusion therapy had significantly mild symptoms, smaller CT perfusion lesions, and better clinical outcomes.

Disability-adjusted life-days and imaging variables

In 772 patients who underwent alteplase treatment within 6 h of stroke onset, 17.5 DALY-days were lost per 1 ml of baseline ischaemic core volume [95% confidence interval (CI), 13.2–21.9, $P < 0.001$, Table 2].

In patients with recanalization, baseline penumbra volume did not affect the DALY-days lost due to stroke (non-significant loss of 0.7 DALY-days, 95% CI, –4.8–13.5 days, $P = 0.808$, Fig. 1A). However, patients without recanalization lost 7.5 DALY-days per 1 ml of baseline penumbra (95% CI, 2.8–12.3, $P = 0.002$, Fig. 1A). Thus, lack of recanalization markedly affected the extent of baseline penumbra progressing to infarction, and hence led to substantially more DALY-days lost.

Disability-adjusted life-days and salvaged penumbra volume

Salvaged penumbra volume was significantly higher in patients with recanalization [median 56.7 ml, interquartile range (IQR) 21.6–102.0] than in patients without

Table 1 Patient characteristics

	Patients with reperfusion therapy ⩽ 6 h (*n* = 772)	Patients who arrived at hospital ⩽ 6 h, without reperfusion therapy (*n* = 599)	Patients with reperfusion therapy > 6 h (*n* = 22)	*P*-value
Age, years, median (IQR)	73 (64–80)	73 (62–81)	62 (46–73)	0.666
Male sex	414 (53.6%)	312 (52.1%)	15 (68.2%)	0.571
Baseline NIHSS score, median (IQR)	14 (9–17)	10 (6–14)	14 (6–18)	<0.001
Onset-to-treatment time, minutes	152.0 (115.9–189.8)	NA	523.1 (415.2–679.4)	NA
Penumbra volume, ml	47.7 (11.0–96.5)	13.5 (2.7–44.5)	9.4 (2.9–39.7)	<0.001
Ischaemic core volume, ml	13.9 (3.4–42.4)	8.3 (0.8–21.9)	37.7 (3.1–75.0)	<0.001
Recanalization (TIMI 2–3)	283 (36.7%)	110 (18.4%)	0	<0.001
Symptomatic intracerebral haemorrhage	26 (3.4%)	5 (0.8%)	1 (4.6%)	0.002
Modified Rankin Scale at 3 months, median (IQR)	2 (1–4)	1 (0–3)	3 (1–4)	0.002
Modified Rankin Scale 0–1 at 3 months	356 (46.1%)	311 (51.9%)	7 (31.8%)	0.033
Modified Rankin Scale 0–2 at 3 months	458 (59.3%)	387 (64.6%)	10 (45.5%)	0.046
Case fatality at 3 months	84 (10.9%)	44 (7.4%)	0	0.031

Characteristics of the patients treated with reperfusion therapy within 6 h of stroke onset, those who arrived at hospital within 6 h but did not received reperfusion therapy, and those with reperfusion therapy over 6 h.

NA = not applicable. *P*-values were derived from Wilcoxon rank sum test and chi-square test between patients with reperfusion therapy ⩽6 h of onset and those who arrived at hospital within 6 h of stroke onset but did not receive reperfusion therapy.

recanalization (median 8.1 ml, IQR −0.9–49.6, $P < 0.001$). As a result, in patients with recanalization, each 1 ml of salvaged penumbra resulted in a saving of 11.8 DALY-days (β = −11.8, 95% CI, −16.6 to −7.1, $P < 0.001$, Fig. 1B). For the median amount of penumbra salvaged in patients with recanalization, this translated to 660 DALY-days saved. However, in patients without recanalization, the small volumes of salvaged penumbra volume did not save DALY-days (non-significant saving of 4.1 DALY-days, β = −4.1, 95% CI, −9.4 to −1.2, $P = 0.128$, Fig. 1B). Therefore, salvage of the penumbra by recanalization resulted in substantially reduced long-term disability.

The effect of penumbral salvage on saving DALY-days lost was also much greater in younger patients. In patients ⩾70 years-old, each 1 ml of salvaged penumbra resulted in a saving of 3.0 DALY-days (β = −3.0, 95% CI, −5.2 to −0.7 days, $P = 0.009$). However, in patients <70 years old, each 1 ml of salvaged penumbra resulted in a much greater saving of 10.5 DALY-days (95% CI, 3.5–17.6 days, $P = 0.003$).

Disability adjusted life-days and onset-to-treatment time

Each minute reduction in onset-to-treatment time resulted in a saving of 4.4 DALY-days after stroke (95% CI, 1.3–7.5 days, $P = 0.006$; Fig. 1C and Table 3). In patients with recanalization, each 1-min decrease in onset-to-treatment time saved 10.9 DALY-days (95% CI, 5.1–16.7 days, $P < 0.001$, Fig. 1C). However, in those without recanalization, reduction in onset-to-treatment time did not save DALY-days (Fig. 1C). This was opposite to the effect of baseline penumbral volume (Fig. 1A), where DALY-days were lost in patients without recanalization, but earlier treatment time in patients with recanalization paralleled the effect of penumbral salvage on DALY-days saved (Fig. 1B). In other words, earlier treatment time resulted in more savings of DALY-days due to greater penumbral salvage.

After adjustment for the clinical variables (age, sex, and baseline NIHSS score), each minute reduction of onset-to-treatment time still resulted in a saving of 3.2 DALY-days (95% CI, 0.6–5.8, $P = 0.015$, Table 3). However, after adjusting for clinical variables and for baseline ischaemic core volume, penumbra volume and/or penumbra salvaged, reduction in onset-to-treatment time did not lead to a significant saving in DALY-days (Tables 2 and 3). In contrast to onset-to-treatment time, penumbral salvage remained a significant predictor of DALY-days saved after adjustment for other variables.

Disability adjusted life-days and baseline NIHSS score

Each point increase of baseline NIHSS score resulted in an increase of 98.9 days of DALY lost (95% CI, 67.2–130.7 days, $P < 0.001$). The effect was even stronger in patients without recanalization, with 128.2 days of DALY lost (95% CI, 85.4–171.0 days, $P < 0.001$) (Fig. 1D). This was similar to the effect seen where baseline penumbral volume was a stronger predictor of DALY-days lost in patients without recanalization (Fig. 1A). Indeed, each point increase of baseline NIHSS score was significantly associated with baseline penumbral volume (β = 4.6 ml, 95% CI, 4.0–5.2, $P < 0.001$), and also baseline ischaemic core volume (β = 2.3 ml, 95% CI, 1.5–2.5, $P < 0.001$). There was also a significant association between early

Table 2 Comparison of DALY-days, patients' characteristics, and perfusion CT variables

	β (95% CI)	*P*-value	R2	*P*-value
Univariate linear regression analyses				
Age, per 1 year increase	−95.4 (−107.4 to −83.4)	<0.001	0.240	
Female	55.4 (−126.9–237.8)	0.551	0.001	
Baseline NIHSS score, per 1-point increase	98.9 (67.2–130.7)	<0.001	0.046	
Onset-to-treatment time, per 1-min increase	4.4 (1.3–7.5)	0.006	0.010	
Baseline ischaemic core volume, per 1-ml increase	17.5 (13.2–21.9)	<0.001	0.075	
Baseline penumbra volume, per 1-ml increase	4.1 (1.0–7.5)	0.015	0.008	
Salvaged penumbra volume, per 1-ml increase	−7.2 (−10.4 to −4.1)	<0.001	0.032	
Multivariate linear regression analyses				
Age, sex, baseline NIHSS score, onset-to-treatment time			0.333	<0.001
Age, per 1-year increase	−104.2 (−115.7 to −92.8)	<0.001		
Female	151.9 (1.5–302.3)	0.048		
Baseline NIHSS, per 1-point increase	132.4 (105.5–159.3)	<0.001		
Onset-to-treatment time, per 1-min increase	3.2 (0.6–5.8)	0.015		
Age, sex, baseline NIHSS score, onset-to- treatment time, baseline ischaemic core volume			0.387	<0.001
Age, per 1-year increase	−106.3 (−117.3 to −95.3)	<0.001		
Female	146.7 (2.4–291.0)	0.046		
Baseline NIHSS, per 1-point increase	101.3 (74.5–128.2)	<0.001		
Onset-to-treatment time, per 1-min increase	1.5 (−1.0–4.0)	0.246		
Baseline ischaemic core volume, per 1-ml increase	15.8 (12.0–19.6)	<0.001		
Age, sex, baseline NIHSS score, onset-to-treatment time, baseline penumbra volume			0.334	<0.001
Age, per 1-year increase	−104.9 (−116.4 to −93.4)	<0.001		
Female	155.5 (4.9–306.0)	0.043		
Baseline NIHSS, per 1-point increase	124.2 (93.8–154.6)	<0.001		
Onset-to-treatment time, per 1-min increase	3.1 (0.6–5.7)	0.017		
Baseline penumbra volume, per 1-ml increase	1.8 (−1.3–5.0)	0.249		
Age, sex, baseline NIHSS score, onset-to-treatment time, salvaged penumbra volume			0.333	<0.001
Age, per 1-year increase	−88.1 (−100.4 to −75.7)	<0.001		
Female	15.6 (−143.6–174.8)	0.848		
Baseline NIHSS, per 1-point increase	145.7 (114.5–176.8)	<0.001		
Onset-to-treatment time, per 1-min increase	2.7 (−0.1–5.4)	0.052		
Salvaged penumbra volume, per 1-ml increase	−7.9 (−10.7 to −5.1)	<0.001		
Age, sex, baseline NIHSS score, onset-to-treatment time, baseline ischaemic core volume, penumbra volume			0.388	<0.001
Age, per 1-year increase	−106.0 (−117.1 to −95.0)	<0.001		
Female	145.2 (0.7–289.7)	0.049		
Baseline NIHSS, per 1-point increase	104.4 (74.8–133.9)	<0.001		
Onset-to-treatment time, per 1-min increase	1.5 (−1.0–4.0)	0.243		
Baseline ischaemic core volume, per 1-ml increase	16.0 (12.1–19.8)	<0.001		
baseline penumbra volume, per 1-ml increase	−0.8 (−3.8–2.3)	0.628		
Age, sex, baseline NIHSS score, onset-to-treatment time, baseline ischaemic core volume, salvaged penumbra volume			0.417	<0.001
Age, per 1-year increase	−90.8 (−102.4 to −79.3)	<0.001		
Female	7.4 (−141.7–156.5)	0.922		
Baseline NIHSS, per 1-point increase	111.3 (81.2–141.3)	<0.001		
Onset-to-treatment time, per 1-min increase	−0.1 (−2.7–2.5)	0.938		
Baseline ischaemic core volume, per 1-ml increase	19.5 (15.4–23.7)	<0.001		
Salvaged penumbra volume, per 1-ml increase	−8.5 (−11.1 to −5.9)	<0.001		

neurological improvement (= acute NIHSS score −follow-up NIHSS score) and salvaged penumbra volume. Each point of neurological improvement translated to 4.0 ml of salvaged penumbra (95% CI, 3.3–4.7, $P < 0.001$), i.e. the more penumbra was saved, the greater the clinical improvement. Thus, the strong effect of baseline NIHSS on DALY-days lost was, at least partly, explained by the association between baseline NIHSS and

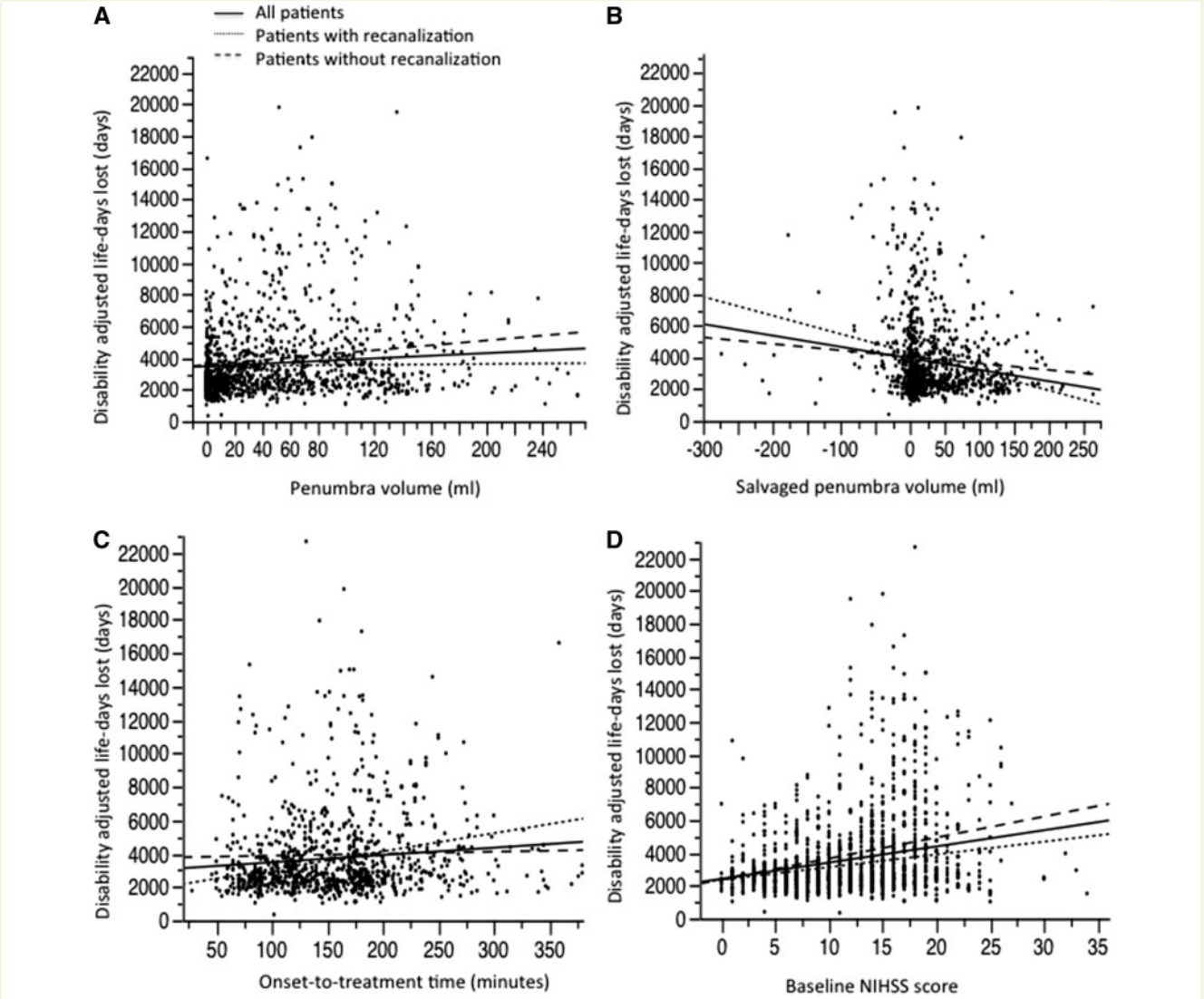

Figure 1 Relationship between disability adjusted life-days, baseline penumbra volume (A), salvaged penumbra volume (B), onset-to-treatment time (C) and baseline NIHSS score (D) in all patients, patients with recanalization, and patients with poor recanalization. (**A**) Patients lost 4.1 DALY-days per 1 ml baseline penumbra (β = 4.1, 95% CI, 0.8–7.5 days, $P = 0.015$). In patients with recanalization, baseline penumbra volume did not affect the DALY-days lost due to stroke (β = 0.7, 95% CI, −4.8–13.5 days, $P = 0.808$). However, patients without recanalization lost 7.5 DALY-days per 1 ml of baseline penumbra (β = 7.5, 95% CI, 2.8–12.3, $P = 0.002$). (**B**) Each 1 ml of salvaged penumbra resulted in a saving of 7.2 DALY-days (β = −7.2, 95% CI, −10.4 to −4.1, $P < 0.001$). In patients with recanalization, each 1 ml of salvaged penumbra resulted in a saving of 11.8 DALY-days (β = −11.8, 95% CI, −16.6 to −7.1, $P < 0.001$). In patients without recanalization, the small volumes of salvaged penumbra volume did not save DALY-days (β = −4.1, 95% CI, −9.4−1.2, $P = 0.128$). (**C**) Each minute reduction in onset-to-treatment time resulted in a saving of 4.4 DALY-days after stroke (β = 4.4, 95% CI, 1.3–7.5, $P = 0.006$). In patients with recanalization, each 1 min decrease in onset-to-treatment time saved 10.9 DALY-days (β = 10.9, 95% CI, 5.1–16.7 days, $P < 0.001$). In those without recanalization, reduction in onset-to-treatment time did not save DALY-days (β = 1.2, 95% CI, −3.1– 5.4, $P = 0.589$). (**D**) Each point increase of baseline NIHSS score resulted in an increase of 98.9 days of DALY lost (β = 98.9, 95% CI, 67.2–130.7 days, $P < 0.001$). In patients with recanalization, each point increase of baseline NIHSS score resulted in an increase of 77.7 DALY-days (β = 77.7, 95% CI, 11.4–144.0, $P = 0.022$). The effect was even stronger in patients without recanalization, with 128.2 days of DALY lost (β = 128.2, 95% CI, 85.4–171.0 days, $P < 0.001$).

extent of baseline penumbra, and then the subsequent lack of penumbral salvage in those without recanalization (Fig. 1).

We also performed the same statistical analysis for patients with reperfusion therapy both within and over 6 h of stroke onset (Supplementary Tables 2 and 3).

Discussion

The current study has demonstrated significant relationships between modern imaging variables before and after reperfusion therapy and the length of disability-free life after stroke. Saving a millilitre of penumbra translated to

Table 3 DALY-days per 1-min increase of onset-to-treatment time

	Days of DALY		
	Unadjusted	Adjusted[a] (clinical)	Adjusted[b] (clinical + perfusion CT)
DALY-days (95% CI)	4.4 (1.3–7.5)	3.2 (0.6–5.8)	1.5 (–1.0–4.0)
P-value	0.006	0.015	0.2424

[a]Adjusted for age, sex, and baseline NIHSS score.
[b]Adjusted for age, sex, baseline NIHSS score, core volume, and penumbra volume.

significant benefits equivalent to more than a week of disability-free life. The benefit gained in disability-free survival by salvaging penumbra was even greater in younger patients. We also found that each minute saved in onset-to-treatment time translated to benefits equivalent to several days of disability-free life. However, this association was not observed after adjustment for imaging variables. Notably, after adjustment for clinical variables, baseline ischaemic core volume remained a strong predictor of loss of disability-free life, and extent of penumbra salvaged remained a strong predictor of longer disability-free life.

The gains seen in disability-free life with penumbral salvage are an order of magnitude greater than those observed with onset-to-treatment time. This is partly because, after adjustment, salvaging 1 ml of penumbra saved more than a week of disability-free life whereas earlier treatment only saved (a statistically non-significant) 1.5 days (Tables 2 and 3). Furthermore, as the median amount of penumbra salvaged was >50 ml in patients with recanalization, this translated into more than 1 year of disability-free life saved in many patients. To gain the same savings from earlier treatment is clearly not possible. After adjustment for baseline perfusion CT variables, even treating 1 h earlier could range from no effect at all on disability-free life to, at best, 240 days saved (upper 95% CI, Tables 2 and 3). It is particularly important to note that in the regressions where baseline ischaemic core volume was added, onset-to-treatment had no effect on disability-free life, yet even 1 ml increase in ischaemic core volume resulted in 20 days less of disability-free life (Tables 2 and 3). The clinical importance of this finding is that earlier (or later) treatment is of minimal consequence if there is a large ischaemic core on perfusion CT. This knowledge is also crucial to inform patients (and families) about the low probability of a good outcome in response to reperfusion therapy.

Interestingly, in the INSPIRE cohort, we demonstrated a larger benefit to a patient's long-term healthy life per 1 min earlier treatment time than previously reported (4.4 days compared to 1.8 days; Meretoja *et al.*, 2014). It is possible that the patients offered reperfusion therapy with alteplase in INSPIRE were a more therapy responsive population given the use of modern CT profiling before treatment. This is supported by the fact that adjusting for imaging variables led to a marked reduction in disability-free days saved by earlier treatment time. While many others have observed individually that earlier treatment or greater penumbral salvage, respectively improve stroke outcome, we have shown for the first time in humans that earlier treatment results in less disability because it saves penumbra. Indeed, the entire benefit of earlier onset-to-treatment on saving DALYs appears to be fully explained by greater penumbral salvage. When adjusting for both baseline ischaemic core and penumbra, onset-to-treatment time had no effect on disability-free life, meaning that time of treatment will not affect clinical outcome if the ischaemic core is too large and/or there is minimal penumbra to save.

The effect of baseline stroke severity on disability-free life was also very interesting. Baseline NIHSS score appeared to reflect extent of both baseline ischaemic core and penumbra, and its effect on DALY-days lost paralleled that of baseline penumbra, having a stronger effect on days lost in patients without recanalization (Fig. 1). The association between acute to 24 h NIHSS improvement and penumbral salvage also strongly suggests that the effect of baseline NIHSS on disability-free life relates to the extent of subsequent penumbral salvage, which in turn is dependent upon successful recanalization (Fig. 1).

The DALY metric for clinical outcome measures has some advantages over the conventional modified Rankin Scale. In acute stroke trials, the modified Rankin Scale has been the most used clinical outcome scale, and the modified Rankin Scale is usually dichotomized into 0–1 (good, excellent) or 0–2 (favourable) versus not. While the dichotomization of modified Rankin Scale can make clinical interpretation simple, it discards the detailed modified Rankin Scale information, such as the degree of severity of disability in modified Rankin Scale 3, 4, or 5. An ordinal analysis can address this problem, but the modified Rankin Scale is still only evaluated at a specific time point, and does not always reflect patient's remaining life. In contrast, the DALY metric indicates the burden of stroke by measuring the premature of death and disability for patient's remaining life. Nonetheless, at the present moment, we still need modified Rankin Scale data to calculate DALY.

Our study has some limitations; firstly a patient's lifetime will be influenced by subsequent neurological or other medical complications and comorbidities occurring beyond the 3 month outcome time point. Numbers of complications were reported to be associated with loss of healthy lifetime

(Hong *et al.*, 2010*b*). In our study, we did not collect information on comorbidities or subsequent other diseases. Second, we used disability weights and the long-term annual risk of death after stroke for each modified Rankin Scale category using published literature (Hong *et al.*, 2009, 2010*a*). However, the World Health Organization recently provided disability weights as valued by the general public for mild (0.021), moderate (0.076–0.312), and severe stroke (0.539–0.567) (Salomon *et al.*, 2012), but these cannot be directly translated to modified Rankin Scale categories. Third, we used CT perfusion imaging analysis from different scanners, which might slightly influence the results of imaging analysis. Fourth, we showed that rescue of penumbral tissue could result in the increase of disability free life; however, this study does not identify that CT perfusion volumetric cut-points that identify patients more likely to benefit from reperfusion therapy. Finally, our results were based on the data from developed countries, therefore may not be applicable to developing countries.

Conclusions

The effects of baseline perfusion CT ischaemic core and of penumbra salvaged on disability-free life after stroke were greater than those seen with onset-to-treatment time. In fact, greater penumbral salvage appears to be the sole mechanism as to why earlier treatment increases disability-free life. Furthermore, earlier treatment had no effect on disability-free life after adjustment for baseline core volume. These novel scientific findings also have important clinical and health economic implications, in that perfusion CT can independently predict significant gains, or loss, of disability-free life in patients undergoing reperfusion therapy for stroke.

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Supplementary material

Supplementary material is available at *Brain* online.

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