ABSTRACT

Objective The effectiveness of MRI-guided intravenous recombinant tissue-type plasminogen activator (r-tPA) for acute ischaemic stroke (AIS) with an unknown time of onset has been demonstrated by the WAKE-UP Trial. We aim to evaluate its long-term cost-effectiveness from the perspective of Chinese and US healthcare payers.

Methods A combination of decision tree and Markov model was built to project lifetime costs and quality-adjusted life-years (QALYs) associated with intravenous r-tPA or placebo treatment. Model inputs including the transition probabilities, costs and utilities were derived from the WAKE-UP Trial, similar cost-effectiveness studies and other published sources. To compare intravenous r-tPA to placebo, we calculated incremental costs, incremental QALYs and incremental cost-effectiveness ratio (ICER). One-way sensitivity, probabilistic sensitivity and subgroup analyses were performed to evaluate uncertainty in the results.

Results In China, intravenous r-tPA gained an additional lifetime QALY of 0.293 with an additional cost of the Chinese Yuan (¥) of 7871 when compared with placebo, resulting in an ICER of ¥26 870 (US$3894)/QALY. In the USA, intravenous r-tPA yielded a higher QALY (difference: 0.430) and lower cost (difference: ¥−4563) when compared with placebo. In probabilistic sensitivity analyses, intravenous r-tPA had a 97.8% and 99.8% probability of being cost-effective or cost-saving in China and the USA, respectively. These findings remained robust under one-way sensitivity and subgroup analysis except for patients with a National Institute of Health Stroke Scale (NIHSS) Score of less than 4, between 11 and 16, and over 16.

Conclusions MRI-guided intravenous r-tPA for patients with AIS with an unknown time of onset is cost-effective in China and cost-saving in the USA.

INTRODUCTION

Stroke represents a major public health problem around the world, with more than 12 million new cases and 6.5 million deaths every year. In China, an estimated 3.4 million individuals suffered from a new stroke, resulting in 1.5 million deaths in 2019. The total cost of stroke outpatient and inpatient service has reached 20.71 billion Chinese Yuan (¥) ($3.0 billion) with an average annual growth rate of 24.96%. Stroke is a huge burden in the USA as well. Every year, more than 795 000 people have a stroke and about 610 000 of them are first or new strokes. The total cost of stroke in the USA was $103.5 billion in 2016 and 66% of it was indirect cost from underemployment and premature death.

Intravenous thrombolysis with recombinant tissue-type plasminogen activator (r-tPA) is effective in reducing the disability of acute ischaemic stroke (AIS). Economic studies showed that intravenous r-tPA was cost-effective or even cost-saving in China and the USA. However, the efficacy of r-tPA is limited by the time since stroke onset and thrombolytic treatment is only recommended for patients with AIS with an onset time of fewer than 4.5 hours. There are some
categories of strokes, such as wake-up stroke and daytime-unwitnessed stroke, that have an unknown time of onset. These strokes accounted for approximately 14%–27% of all strokes.\cite{13,14} It is uncertain whether these patients would benefit from r-tPA. In a multicentre randomised trial (the WAKE-UP Trial), the researchers sought to determine whether patients with AIS with an unknown time of onset and features suggesting recent cerebral infarction on MRI would benefit from intravenous thrombolysis with r-tPA.\cite{15} The results showed that r-tPA was associated with a significantly better functional outcome and numerically more intracranial haemorrhage (ICH) than placebo at 90 days. Therefore, medical decision analysis is needed to evaluate the advantage or disadvantage of MRI-guided intravenous r-tPA for patients with AIS with an unknown time of onset. Considering that both China and the USA had a large population and heavy burden of stroke, we evaluated the long-term cost-effectiveness of MRI-guided intravenous r-tPA from the perspective of Chinese and US healthcare payers.

METHODS
Model overview
Ethical approval from the institutional review board was not required as no human subjects were involved in the study. We conducted this study according to the Consolidated Health Economic Evaluation Reporting Standards reporting guidelines.\cite{16} A combination of decision tree and Markov model was constructed using decision-analytical software (TreeAge Pro, 2020, Williamstown, Massachusetts, USA) to evaluate the cost-effectiveness of MRI-guided intravenous r-tPA versus placebo for AIS with an unknown time of onset. The schematic structure of the model is provided in figure 1.

A short-run decision-analytical model was created to analyse data on costs and clinical outcomes within the initial 3 months. The target population was analogous to that of the WAKE-UP Trial.\cite{15} Patients were 65 years on average. They were assumed to have AIS with an unknown time of onset and a mismatch between the presence of an abnormal signal on MRI diffusion-weighted imaging and no visible signal change on fluid-attenuated inversion recovery in the region of the acute stroke. These patients could be treated within 4.5 hours after symptom recognition. Patients entered the model to receive either r-tPA or placebo and afterwards transition to one of the seven possible health states according to the degree of disability as assessed by the modified Rankin Scale (mRS) Score. The occurrence of ICH was incorporated into the model with additional costs and disutility.

After the initial 3 months, a long-run Markov state-transition model was used to evaluate the lifetime costs and outcomes. We modelled a lifetime horizon of 30 years and the cycle length was 3 months. During each cycle, patients would either stay in the same state, experience a recurrent stroke or die from other causes. The absorbing state was death (mRS 6) due to stroke or other causes.

Transition probabilities
The input parameters of this model were obtained from the recently published literature (table 1). The mRS health state distribution of the initial 3 months was extracted directly from the WAKE-UP Trial.\cite{15} The annual recurrence rate of stroke after the initial 3 months was 0.118 for the Chinese population\cite{8} and 0.05 for the US population.\cite{17} A constant recurrent rate was assumed in this study.\cite{9,10,18,19} The death rate after recurrent stroke was 0.21 and 0.19 in China\cite{8} and the USA, respectively. According to the previous studies, patients who remained

Figure 1 Schematic structure of the model. Patients with acute ischaemic stroke with an unknown time of onset entered the model to receive either r-tPA or placebo. In the initial 3 months, patients would transition to one of the seven possible mRS health states. After the initial 3 months, patients would either stay in the same state, experience a recurrent stroke or die from other causes during each cycle. mRS, modified Rankin Scale; r-tPA, recombinant tissue-type plasminogen activator.
Table 1  Input parameters

| Model input | Base-case value | Range | Distribution | Source |
|-------------|----------------|-------|--------------|--------|
| Outcomes at initial 3 months with r-tPA | | | | |
| mRS 0 | 0.213 | 0–1 | Dirichlet | Thomalla et al\textsuperscript{15} |
| mRS 1 | 0.323 | | | |
| mRS 2 | 0.213 | | | |
| mRS 3 | 0.122 | | | |
| mRS 4 | 0.071 | | | |
| mRS 5 | 0.020 | | | |
| mRS 6 | 0.039 | | | |
| Outcomes at initial 3 months with placebo | | | | |
| mRS 0 | 0.149 | 0–1 | Dirichlet | Thomalla et al\textsuperscript{15} |
| mRS 1 | 0.269 | | | |
| mRS 2 | 0.229 | | | |
| mRS 3 | 0.169 | | | |
| mRS 4 | 0.133 | | | |
| mRS 5 | 0.040 | | | |
| mRS 6 | 0.012 | | | |
| Probability of ICH with r-tPA | 0.020 | 0.009–0.046 | Beta | Thomalla et al\textsuperscript{15} |
| Probability of ICH with placebo | 0.004 | 0.001–0.023 | Beta | Thomalla et al\textsuperscript{15} |
| Probability of recurrent stroke in China | 0.118 | 0.112–0.124 | Beta | Pan et al\textsuperscript{8} |
| Probability of death after recurrent stroke in China | 0.210 | 0.189–0.232 | Beta | Pan et al\textsuperscript{8} |
| Probability of recurrent stroke in the USA | 0.050 | 0.040–0.060 | Beta | Hong et al\textsuperscript{17} |
| Probability of death after recurrent stroke in the USA | 0.190 | 0.100–0.300 | Beta | Fagan et al\textsuperscript{80} |
| Death HRs | | | | |
| mRS 0 | 1 | 1–1.2 | Lognormal | Samsa et al\textsuperscript{23} |
| mRS 1 | 1 | 1–1.2 | | |
| mRS 2 | 1.11 | 0.89–1.3 | | |
| mRS 3 | 1.27 | 1.02–1.52 | | |
| mRS 4 | 1.71 | 1.37–2.05 | | |
| mRS 5 | 2.37 | 1.90–2.84 | | |
| Cost in the US ($) | | | | |
| MRI | 816 | ± 25% | Gamma | 26 |
| Additional cost of r-tPA treatment | 8619 | 4309–12928 | Gamma | Leppert et al\textsuperscript{9} |
| Acute stroke (mRS 0–3) | 9268 | 4633–13901 | Gamma | Earnshaw et al\textsuperscript{27} |
| Acute stroke (mRS 4–5) | 14115 | 7057–21171 | Gamma | Earnshaw et al\textsuperscript{27} |
| Acute stroke (death) | 16457 | 8228–24685 | Gamma | Earnshaw et al\textsuperscript{27} |
| ICH | 3399 | 2719–4079 | Gamma | Earnshaw et al\textsuperscript{27} |
| Annual posthospitalisation (mRS 0–3) | 8157 | 4078–12235 | Gamma | Earnshaw et al\textsuperscript{27} |
| Annual posthospitalisation (mRS 4–5) | 22139 | 11070–33209 | Gamma | Earnshaw et al\textsuperscript{27} |
| Recurrent stroke | 25143 | 12572–37715 | Gamma | Leppert et al\textsuperscript{9} |
| Cost in China (¥) | | | | |
| MRI | 600 | ±25% | Gamma | Chen et al\textsuperscript{25} |
| Additional cost of r-tPA treatment | 13886 | 10751–16194 | Gamma | Pan et al\textsuperscript{8} |
| Acute stroke (mRS 0–1) | 12214 | 7055–15379 | Gamma | Pan et al\textsuperscript{8} |

Continued
alive after recurrent stroke were assumed to be reallocated equally among health states of equal and greater disability.\textsuperscript{18,19}

The age-specific death rate was drawn from the most recently published census of China\textsuperscript{21} and the US Life Table in the USA.\textsuperscript{22} Disabled patients tend to have increased mortality compared with non-disabled ones and we adjusted the death rate according to the HRs for each mRS health state.\textsuperscript{23} We converted the annual transition probabilities to 3-month probabilities according to the standard formula if necessary.\textsuperscript{24}

Costs
This study was conducted from the perspective of healthcare payers in China and the USA and only direct costs were considered. In China, the additional costs of intravenous thrombolysis, acute stroke treatment cost for different mRS health states, cost of ICH treatment and posthospitalisation cost for different mRS health states were extracted directly from another cost-effectiveness study in which the authors derived these costs from the database of Thrombolysis Implementation and Monitor of Acute Ischaemic Stroke in China and the China National Stroke Registry.\textsuperscript{8} The cost of MRI in China was obtained from previous literature.\textsuperscript{25} The cost of recurrent stroke was assumed to be the same in the two intervention arms because it is unlikely to predict the type and severity of a recurrent stroke. The cost of recurrent stroke in China was not reported in previous literature and we estimated it from our institutional database as the mean expected cost to treat an average stroke without thrombolysis or thrombectomy. In the USA, the cost of MRI was from the Centers for Medicare & Medicaid Services (CPT code 70557).\textsuperscript{36} Acute stroke treatment cost for different mRS health states, cost of ICH treatment and posthospitalisation cost for different mRS health states were derived from a previous study in which these costs were calculated based on multiple resources.\textsuperscript{27} These costs were validated and used by some other similar cost-effectiveness studies.\textsuperscript{9,10,18} The additional cost of intravenous thrombolysis and the cost of recurrent stroke were also reported previously.\textsuperscript{9} To account for the uncertainty, a range of ±25% of the base-case value was used for the costs. All costs were converted to the 2020 price according to the medical care component of the consumer price index if necessary.\textsuperscript{28,29}

Utility
Health-related quality of life values (utility scores) was assigned to all health states. Quality-adjusted life-years (QALYs) was calculated, which was defined as the length of period the patient spent in a particular state multiplied by the corresponding utility score. Currently, the Chinese population-specific utility scores for mRS scores of 0, 1, 2, 3, 4 and 5 were not reported in the previous literature.\textsuperscript{23} The cost of recurrent stroke in China was obtained from previous literature.\textsuperscript{25} The cost of recurrent stroke was assumed to be the same in the two intervention arms because it is unlikely to predict the type and severity of a recurrent stroke. The cost of recurrent stroke in China was not reported in previous literature and we estimated it from our institutional database as the mean expected cost to treat an average stroke without thrombolysis or thrombectomy. In the USA, the cost of MRI was from the Centers for Medicare & Medicaid Services (CPT code 70557).\textsuperscript{36} Acute stroke treatment cost for different mRS health states, cost of ICH treatment and posthospitalisation cost for different mRS health states were derived from a previous study in which these costs were calculated based on multiple resources.\textsuperscript{27} These costs were validated and used by some other similar cost-effectiveness studies.\textsuperscript{9,10,18} The additional cost of intravenous thrombolysis and the cost of recurrent stroke were also reported previously.\textsuperscript{9} To account for the uncertainty, a range of ±25% of the base-case value was used for the costs. All costs were converted to the 2020 price according to the medical care component of the consumer price index if necessary.\textsuperscript{28,29}

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| Model input | Base-case value | Range | Distribution | Source |
|-------------|----------------|-------|--------------|--------|
| Acute stroke (mRS 2–5) | 16149 | 8875–21 177 | Gamma | Pan et al\textsuperscript{8} |
| Acute stroke (death) | 13840 | 6503–18 293 | Gamma | Pan et al\textsuperscript{8} |
| ICH | 2949 | 641–6155 | Gamma | Pan et al\textsuperscript{8} |
| Annual posthospitalisation (mRS 0–1) | 8684 | 2600–11 077 | Gamma | Pan et al\textsuperscript{8} |
| Annual posthospitalisation (mRS 2–5) | 13213 | 3323–16616 | Gamma | Pan et al\textsuperscript{8} |
| Recurrent stroke | 18000 | ± 25% | Gamma | Institutional database |

| Utility | Range | Distribution | Source |
|---------|-------|--------------|--------|
| mRS 0 | 0.80 | 0.64–1 | Beta | Samsa et al\textsuperscript{23} |
| mRS 1 | 0.80 | 0.64–1 | | |
| mRS 2 | 0.65 | 0.52–0.78 | | |
| mRS 3 | 0.50 | 0.4–0.6 | | |
| mRS 4 | 0.35 | 0.28–0.42 | | |
| mRS 5 | 0.20 | 0.16–0.24 | | |
| Death | 0.00 | NA | NA | NA |
| Disutility of ICH | 0.38 | 0.30–0.46 | Normal | Christensen et al\textsuperscript{30} |
| Discount rate | 0.03 | 0.00–0.08 | Beta | Sanders et al\textsuperscript{31} |

NA: not available; mRS: modified Rankin Scale; ICH, intracranial haemorrhage; r-tPA, recombinant tissue-type plasminogen activator.
per additional QALYs gained. One treatment was deemed cost-effective when compared with another if the ICER was below the willingness-to-pay (WTP) threshold. In China, according to the recommendation of the WHO, the WTP threshold was chosen as 3 × gross domestic product per capita. This WTP threshold corresponded to ¥217 341 ($31 499)/QALY in 2020. We used a WTP threshold of $100 000/QALY for the USA.

The base-case analysis was performed with the mean value of all input parameters. One-way sensitivity analyses were performed to identify key parameters related to the robustness of the results by varying one parameter while keeping others fixed. Probabilistic sensitivity analysis was performed with all parameters varying simultaneously in their assigned distributions. A total of 10 000 iterations was carried out to evaluate the impact of uncertainty.

Moreover, subgroup analysis was performed in the prespecified subgroups as defined in the WAKE-UP Trial. In the subgroup analysis, the distribution of mRS health states at the initial 3 months for different subgroups was calculated according to the reported proportion of favourable outcomes (defined as mRS Scores of 0 and 1). During the calculation, the ratio of proportion for different mRS Scores (mRS 0/mRS 1 and mRS 2/mRS 3/mRS 4/mRS 5/mRS 6) in the subgroups was assumed to be as same as that in the overall population. The mRS health states distributions for different subgroups were provided in online supplemental table 1.

**RESULTS**

**Base-case analysis**

The cost, QALY and ICER of r-tPA versus placebo in patients with AIS with an unknown time of onset are summarised in table 2. In China, r-tPA was associated with an additional cost of ¥7871 with an additional QALY of 0.293 over 30 years when compared with placebo, and the ICER was ¥26 870 ($3894)/QALY. In the USA, r-tPA was associated with a higher QALY (0.430) and a lower cost (¥−4563) over 30 years when compared with placebo.

**Sensitivity analysis**

One-way sensitivity analyses were performed to evaluate the impact of the uncertainty of different parameters on the final ICER and the results were presented in the tornado diagram (figure 2). Overall, the results were more sensitive to the posthospitalisation cost for different mRS health states, additional cost of r-tPA treatment and discount rate. However, when these parameters varied

![Figure 2](image-url)
in their ranges, the ICERs remained under the corresponding WTP thresholds both in China and the USA, indicating that the results were robust.

The results of probabilistic sensitivity analyses are presented in figure 3. Among 10,000 iterations, r-tPA had a 97.8% probability of being cost-effective at the WTP threshold of ¥217,341/QALY in China and a 99.8% probability of being cost-effective at the WTP threshold of $100,000/QALY in the USA.

Subgroup analysis

Subgroup analysis was conducted according to the different distributions of mRS health states at the initial 3 months among different subgroups (online supplemental table 1). In China, all the ICERs were below the WTP threshold of ¥217,341/QALY except for the populations with a National Institute of Health Stroke Scale (NIHSS) Score of less than 4, between 11 and 16, and over 16 (figure 4). In the USA, r-tPA is dominant when compared with r-tPA except for the populations with an NIHSS Score of between 11 and 16 and over 16. For the subgroup with an NIHSS Score of less than 4, r-tPA had an ICER of $57,826/QALY when compared with placebo, and it was below the WTP threshold of $100,000/QALY in the USA (figure 5).

DISCUSSION

For patients with AIS with an unknown time of onset, MRI-guided intravenous r-tPA increased life expectancy by 0.293 and 0.430 over a lifetime in China and the USA, near 3.6 months and 5.2 months of perfect health at excellent value. Intravenous r-tPA gained an additional cost of ¥78,711 with an ICER of ¥26,870/QALY and it was cost-effective under the current Chinese WTP threshold.
In the USA, intravenous r-tPA was associated with a lower cost when compared with placebo and was deemed cost-saving in the long run. The robustness of our overall conclusion that intravenous r-tPA was cost-effective or even cost-saving was supported by the sensitivity analyses. In the one-way sensitivity analyses, all the ICERs were below the WTP threshold when the parameters varied in their ranges. In the probabilistic sensitivity analyses, intravenous r-tPA had a 97.8% and 99.8% probability of being cost-effective or cost-saving in China and the USA, respectively. Moreover, in the subgroup analysis, intravenous r-tPA was cost-effective or cost-saving in all subgroups except for patients with an NIHSS Score of less than 4, between 11 and 16, and over 16, which was due to the similar treatment effects for r-tPA and placebo or a small number of participants in these subgroups.

The cost-effectiveness of intravenous r-tPA for treating AIS has been extensively studied before. However, all these studies are limited to the time window of 0–3 hours, 3–4.5 hours or 0–6 hours. In all, the literature generally indicated that intravenous r-tPA was a cost-effective or dominant strategy compared with the traditional treatment for patients with AIS. Our results and conclusions were comparable to the studies from the Chinese and US perspective. For example, Pan et al investigated the cost-effectiveness of thrombolysis with r-tPA within 4.5 hours of AIS in China. In this study, r-tPA yielded an ICER of ¥15 500/QALY in 30 years when compared with placebo, and its cost and effectiveness were ¥120 880 and 4.993 QALYs, respectively.8 In the USA, Boudreau et al studied the cost-effectiveness of intravenous r-tPA within 3 hours of AIS and found that r-tPA resulted in an additional gain of 0.39 QALY and a lifetime cost saving of $25 000. In probabilistic sensitivity analysis, intravenous r-tPA was dominant compared with no r-tPA in nearly 100% of probability.10

We noticed a study that modelled the cost-effectiveness of MRI-guided treatment of acute wake-up stroke.37 The authors created a microsimulation model to simulate the wake-up stroke patient population with an average age of 65 years and 60% of them being male. According to the results, the MRI-based treatment strategy for this population was cost-effective. However, the conclusion was sensitive to several factors such as sleep duration, hospital travel and door-to-needle times. The stroke onset time was decided by the MRI and the mRS health state distributions, which we believe were the major limitations of this study. Our study has the advantage of using the latest effectiveness data from the multicentre randomised WAKE-UP Trial.15 This study focused on outcomes based on the mismatch between diffusion-weighted imaging and fluid-attenuated inversion recovery findings on MRI rather than on a time-dependent effect of intravenous r-tPA. Therefore, the sensitivity and specificity of MRI to determine stroke onset time were not incorporated into our model as they were unnecessary. Our study also has the advantage of analysing from the perspective of China and the USA, both of which are inflicted by the heavy burden of stroke. Even though MRI-guided intravenous r-tPA for stroke with an unknown time of onset has not been suggested in China,12 the 2019 Guideline from the American Heart Association/American Stroke Association for the early management of AIS suggests that in patients with AIS with unknown time of onset, MRI can be useful to select those who can benefit from intravenous r-tPA within 4.5 hours of stroke symptom recognition (Class of recommendation IIa, level of evidence B).11

The limitations of our study should be noted. First, our model was based on required assumptions such as the average age and time window of treatment. Therefore, the results and conclusions are specific to those assumptions. Generalising the conclusions to other situations should be done with caution. Second, the data on input parameters were from numerous published studies including clinical trials. We were not able to estimate the costs and effectiveness after AIS with one data source. The inconsistency among these published studies might...
cause some bias towards our study. Third, our results were based on the efficacy findings of the WAKE-UP Trial that was conducted in Europe. It is unknown whether similar treatment effects would occur if the participants were restricted to Chinese or US patients. What’s more, the utility scores were not Chinese-population specific. However, the sensitivity analyses have accounted for these uncertainties and this is not unprecedented in other cost-effectiveness studies.

CONCLUSIONS

In summary, MRI-guided intravenous r-PA for patients with AIS with an unknown time of onset is cost-effective in China and cost-saving in the USA. However, further studies are needed to evaluate the benefit of intravenous r-PA for treating specific subgroups of patients.

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Contributors

Songfeng Zhao and Yuhong Cheng were responsible for the study design. Songfeng Zhao and Yuhong Cheng prepared the manuscript. Xin Tong, Mingyang Han, Linjin Ji and Yuxiong Che collected the data. Weiwu Hu and Aihua Liu built the model and conducted the statistical analysis. Weiwu Hu and Aihua Liu were responsible for the overall content as guarantors. All the authors reviewed the model structure, data source, formula and results.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

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Data are available upon reasonable request.

Supplemental material

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