

Cost–Utility Analysis of Magnetic Resonance Imaging Management of Patients with Acute Ischemic Stroke in a Spanish Hospital

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ABSTRACT

Introduction: Stroke has a high rate of long-term disability and mortality and therefore has a significant economic impact. The objective of this study was to determine from a social perspective, the cost–utility of magnetic resonance imaging (MRI) compared to computed tomography (CT) as the first imaging test in acute ischemic stroke (AIS).

Methods: A cost–utility analysis of MRI compared to CT as the first imaging test in AIS was performed. Economic evaluation data were obtained from a prospective study of patients

with AIS ≤ 12 h from onset in one Spanish hospital. The measure of effectiveness was quality-adjusted life-years (QALYs) calculated from utilities of the modified Rankin Scale. Both hospital and post-discharge expenses were included in the costs. The incremental cost-effectiveness ratio (ICER) was calculated and sensitivity analysis was carried out. The costs were expressed in Euros at the 2004 exchange rate.

Results: A total of 130 patients were analyzed. The first imaging test was CT in 87 patients and MRI in 43 patients. Baseline variables were similar in the two groups. The mean direct cost was €5830.63 for the CT group and €5692.95 for the MRI group ($P =$ not significant). The ICER was €11,868.97/QALY.

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The results were sensitive when the indirect costs were included in the analysis.

Conclusion: Total direct costs and QALYs were lower in the MRI group; however, this difference was not statistically significant. MRI was shown to be a cost-effective strategy for the first imaging test in AIS in 22% of the iterations according to the efficiency threshold in Spain.

Keywords: Acute ischemic stroke; Computed tomography; Cost–utility analysis; Magnetic resonance; Spain; Stroke

INTRODUCTION

According with Global Burden of Diseases, Injuries, and Risk Factors Study [1], stroke was the second most common cause of death and the third most common cause of disability-adjusted life-years worldwide in 2010 [2]. Patients who survive a stroke have a higher risk of another stroke, ischemic heart disease, or dementia [3]. Stroke has a considerable economic impact during hospitalization and following discharge [4–11]. Major advances in acute stroke care include the creation of dedicated stroke units [12], thrombolytic therapy [13, 14], and new diagnostic techniques, especially imaging techniques. Recent research into drugs for treating stroke is based on the identification of the diffusion–perfusion mismatch in magnetic resonance imaging (MRI).

Despite technological advances in neuroimaging, computed tomography (CT) remains the examination of choice in patients with acute stroke [15]. MRI is more sensitive and more specific than CT in early detection of acute ischemic stroke (AIS) [16–18]; moreover, the variability in the interpretation of results is lower in MRI [16]. MRI in patients with acute stroke allows for a rapid diagnostic evaluation

and provides necessary and relevant information [19]. Furthermore, MRI techniques are as effective as CT for ruling out or defining the magnitude of hemorrhage [20–22]. Thrombolysis based on MRI ≥ 3 h after stroke onset is safer and potentially more effective than thrombolysis based on CT within 3 h in patients with acute stroke [23, 24]. However, MRI is more expensive and less widely available than CT.

The current study aimed to determine, from a societal perspective, the cost–utility of MRI compared with CT as the first imaging test in patients with AIS.

METHODS

A cost–utility analysis from societal perspective was developed. The study was conducted in patients with AIS at a referral hospital for stroke in Girona, Spain. The Hospital Doctor Josep Trueta's (Girona, Spain) ethics committee approved the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data for the economic evaluation were obtained from an ad hoc prospective observational study that included patients with AIS who presented or were referred to the hospital between December 1, 2003 and March 9, 2005. The inclusion criteria were: age ≥ 18 years, stroke less than 12 h from onset, admission to the hospital's stroke unit, and informed consent of the patient or relative. A 90-day time horizon was considered for outcomes according to the hospital's stroke

management protocol. Because the time horizon was less than a year, future discounting was not required.

Alternatives Evaluated

The alternatives evaluated were cranial CT and cranial MRI (diffusion, perfusion MRI, and angiography). These alternatives were selected because CT was the most used in the study period and MRI was the technology that was to be evaluated, for the advantages in sensitivity, specificity [16], vascular occlusion, and mismatch area.

Patients were assigned to undergo CT or MRI as the initial imaging technique in function of the availability of scanners at the time of emergency room admittance: patients admitted between 8 a.m. and 8 p.m. on weekdays (except holidays) underwent MRI as the initial imaging test, whereas patients admitted between 8 p.m. and 8 a.m. on weekdays or at any time on weekends and holidays underwent CT.

Hospital and Post-Discharge Costs

According to the perspective of the study, both direct health costs and other patient's costs were included. The expenditure for the following resources used in the hospital was quantified for each patient: Cranial CT, cranial MRI, others diagnostic tests, physiotherapy, pharmacological treatment, and hospital stay. In addition, a questionnaire was used to obtain information from patients about the post-discharge resources used in the first 90 days after onset, for example, institutionalization, rehabilitation, home adaptations, caregivers, and pharmacological treatment. All expenditures were expressed in Euros (2004). The information source for the costs is shown in the results.

Effectiveness

The measure of effectiveness was quality-adjusted life-years (QALYs). QALYs were estimated from utility values obtained from the modified Rankin Scale (mRS) and the time (in years) that the patient remained in that health state (mRS). The mRS is a tool widely used to assess primary or secondary outcomes in multicenter studies of stroke. The scale is validated in several languages, including Spanish [25]. This scale has been used in other studies, including a clinical trial for a neuroprotective stroke agent, and reflects changes in the health status of patients [26]. The mRS was determined by a structured interview [27] before stroke, at hospital discharge, and 90 days after stroke. The investigator who assessed the mRS was trained and certified in the use of the mRS and was blinded to the diagnostic imaging test performed. A favorable clinical outcome was defined as an mRS score ≥ 2 .

For each value of the mRS, a utility value obtained from previous studies [28, 29] was assigned. These utilities were used because they were obtained from the Spanish general population through different methods of measurement preferences. Each health state (mRS) was associated with a utility value [28]. As in that study [28], no utility value was assigned to patients with an mRS score of zero, it was decided to give a utility value of 0.90 that was obtained from a cost-utility analysis of recombinant tissue plasminogen activator (rt-PA) in patients with stroke [29]. Table 1 shows the utility value used in the current study for each mRS value.

The times considered for the calculation of QALYs were: Time 1 (in years) = length of hospital stay (LOS)/365 stay (from the stroke to discharge); and time 2 (in years) = (90 days–

Table 1 Modified Rankin Scale and utilities

Health status (mRS)/measurement method	DG	VAS
1	0.78	0.68
2	0.48	0.47
3	0.26	0.20
4	−0.04	0.07
5	−0.72	−0.02
6	0.00	0.00

The DG and VAS are methods of estimating utilities. Source: Pinto-Prades and Abellán-Perpiñán [28]

DG double gamble, mRS modified Rankin Scale, VAS visual analog scale

LOS)/365 (from discharge until 90 days after stroke).

Incremental Cost-Effectiveness Ratio

The total costs (hospital and post-discharge costs) for each study group were calculated. The incremental cost-effectiveness ratio (ICER) was calculated as follows: (Cost MRI−Cost CT)/(QALY MRI−QALY CT).

Clinical Data Collection

In addition to the data for economic evaluation, the following variables were recorded: Sex, age, cardiovascular risk factors, prior treatment, date and hour of symptoms onset, and prior functional dependence. Stroke severity was determined daily by the National Institutes of Health Stroke Scale (NIHSS).

Analysis

Data were analyzed for associations between categorical variables with the Chi-square test. The comparison of medians was done with the

non-parametric Mann–Whitney *U* test. The comparison of means was done with Student's *t* test. Statistical significance was set at 0.05.

One-way and multi-way sensitivity analyses were performed. In the one-way analysis, utility parameters (obtained by visual analog scale [VAS]), indirect costs, including lost productivity from days off work (obtained in the interview with the patient or caregiver), and adjusted QALY (assuming the patient's initial mRS remained unchanged) were considered. The multi-way sensitivity analysis was performed using non-parametric bootstrapping [30]; a total of 1000 bootstrap samples were obtained.

Data were analyzed with SPSS® (version 15.0., SPSS Inc., Chicago, IL, USA).

RESULTS

Of 472 consecutive patients with stroke, 130 fulfilled the inclusion criteria. Of these, 87 patients underwent CT as the first imaging test and 43 patients underwent MRI. A total of 117 patients were alive 90 days after stroke and 3 patients were lost to follow-up. Baseline values did not differ between the two groups: 60% were male, most were retired, and 85% had an mRS score of 0 before stroke (Table 2).

In both groups, hospital stay accounted for approximately 80% of hospital costs, and institutionalization accounted for nearly 45% of the post-discharge costs until 90 days after stroke (Table 3). On the other hand, no significant differences between the two groups were found in mRS (Table 4).

Table 5 shows the results of the ICER analysis. The use of MRI was observed to be a less expensive alternative, but resulted in less QALY than CT for the diagnosis of AIS. In the one-way sensitivity analyses, the ICER increased with all

Table 2 Characteristics of included patients

Variable	CT (<i>n</i> = 87)	MRI (<i>n</i> = 43)	<i>P</i> value
Age, years			
Mean (SD)	69 (11)	68 (13)	0.685
30–45 years	3.4%	7.0%	
46–60 years	19.5%	16.3%	
61–75 years	43.7%	51.2%	
76–90 years	33.3%	25.6%	
Sex, male	55.2%	69.8%	0.110
Employment prior to stroke ^a			0.951
Employed	24.4%	25.0%	
Retired	48.7%	52.8%	
Housewife	23.1%	19.4%	
Unemployed	1.3%	0.0%	
Receiving compensation	2.6%	2.8%	
Risk factors			
Hypertension	67.8%	60.5%	0.407
Atrial fibrillation	20.7%	18.6%	0.780
AMI	8.0%	11.6%	0.507
Diabetes mellitus	23.0%	16.3%	0.375
Smoking	14.9%	18.6%	0.593
Prior stroke	17.2%	14.0%	0.632
mRS score prior to stroke			
0	90.8%	88.4%	0.906
1	5.7%	7.0%	
2	3.5%	4.6%	
NIHSS at admission, median (IQR)	8 (4–16)	7 (3–18)	0.825
Time from stroke onset to imaging, minutes, mean (SD)	262.15 (173.56)	256.36 (175.45)	0.860

AMI acute myocardial infarction, CT computed tomography, MRI magnetic resonance imaging, mRS modified Rankin Scale, NIHSS National Institutes of Health Stroke Scale, SD standard deviation

^a Information available only for patients, whose discharge destination was home, 72.4% and 74.4% for CT and MRI, respectively

variables included, except with the adjusted QALY (Table 6). In the ICER analysis performed with the bootstrap, the simulated cases mainly

fall in quadrants III and IV (Fig. 1). This result is confirmed in the acceptability curve of cost-effectiveness, where it can be appreciated that

Table 3 CT, MRI and P value (each one of them has two columns: resource use and costs)

Resource	CT		MRI		P value		Information source
	Resource use, median (IQR)	Costs (Euros), mean (SD)	Resource use, median (IQR)	Costs (Euros), mean (SD)	Resource use	Costs	
Hospital resources							
Diagnostic tests							
Cranial CT	2 (1–2)	111.61 (39.60)	1 (0–1)	45.48 (43.45)	<0.001	<0.001	ICS
Cranial MRI	0 (0–1)	115.42 (134.64)	1 (1–1)	281.42 (75.67)	<0.001	<0.001	ICS
Chest X-ray	1 (1–1)	5.92 (1.97)	1 (1–1)	5.85 (1.31)	0.841	0.825	DOGC
Transcranial Doppler/Duplex	1 (1–1)	35.41 (19.46)	1 (1–1)	39.56 (16.12)	0.227	0.229	DOGC
Carotid Duplex	1 (0–1)	29.07 (22.30)	1 (0–1)	27.80 (22.75)	0.761	0.763	DOGC
Continuous carotid Doppler	1 (0–1)	26.95 (22.78)	1 (0–1)	34.21 (20.30)	0.079	0.079	DOGC
Echocardiogram	1 (0–1)	33.47 (33.97)	1 (0–1)	33.86 (34.18)	0.949	0.951	DOGC
Physiotherapy	2 (0–5)	9.79 (11.96)	2 (0–4)	7.26 (9.15)	0.361	0.223	DOGC
Pharmacological treatment ^a	6 (4–9)	304.71 (427.44)	5 (3–6)	241.11 (387.59)	0.025	0.412	Hospital Josep Trueta
Hospital stay (days)							
Stroke unit	5 (3–6)	2092.57 (1298.19)	4 (4–6)	1945.26 (830.21)	0.821	0.499	
Conventional bed	0 (0–4)	771.93 (1286.58)	0 (0–2)	503.44(973.63)	0.372	0.230	
Total stay (mean)	6 (4–11)	2864.50 (1938.44)	6 (4–7)	2448.70 (1289.84)	0.619	0.205	
Total hospital costs	–	3536.85 (2196.29)	–	3165.25 (1446.63)	–	0.316	

Table 3 continued

Resource	CT		MRI		P value		Information source
	Resource use, median (IQR)	Costs (Euros), mean (SD)	Resource use, median (IQR)	Costs (Euros), mean (SD)	Resource use	Costs	
Post-discharge resources							
Institutionalization (median, days) ^b	76.0 (67–95)	1106.83 (2385.44)	79.0 (42.25–89.0)	1386.12 (2564.83)	0.471	0.571	DOGC
Rehabilitation sessions ^c	41.2%	46.82 (82.95)	60.0%	54.77 (78.85)	0.085	0.627	DOGC
Additional resources ^c	38.2%	89.30 (253.90)	40.0%	148.06 (335.18)	0.869	0.299	Catalog orthotic and prosthetic devices covered by the ICS
Home adaptations ^c	14.7%	130.65 (724.69)	31.0%	202.57 (660.61)	0.064	0.617	Patients or relatives
Caregiver ^d	56.4%	966.77 (1965.73)	54.0%	894.22 (1986.77)		0.855	Home care services
Ambulance use ^c	35.3%	111.06 (322.93)	41.4%	171.52 (371.64)	0.570	0.374	DOGC
Pharmacological treatment	2 (0–3)	92.82 (123.15)	1 (0–3)	129.17 (127.33)	0.696	0.146	Catalog of the Official College of Pharmacists 2004
Carotid endarterectomy	0	0	2.8%	878.56	0.139	<0.001	Hospital Josep Trueta
Total costs post-discharge	–	2558.44 (2891.03)	–	3019.20 (3379.26)	–	0.455	
Total direct costs (mean)	–	5830.63 (4255.54)	–	5692.95 (4268.11)	–	0.863	

CT computed tomography, DOGC Official Gazette of the Government of Catalonia 2004, ICS Catalan Institute of Health, IQR interquartile range, MRI magnetic resonance imaging, SD standard deviation

^a Included treatment with recombinant tissue plasminogen activator(CT: 28.7%, MRI: 23.3%)

^b Patients whose discharge destination was a nursing home, rehabilitation center, or another hospital

^c Percentage of patients who needed to use the resource

^d Percentage of patients who needed to pay a caregiver or whose relatives left their jobs to care for them

Table 4 Modified Ranking Scale at discharge and 90 days after stroke

Variable	CT	MRI	P value
mRS at discharge	<i>n</i> = 87	<i>n</i> = 43	
Mean (SD)	3.4 (1.5)	3.4 (1.6)	0.980
Categorized mRS score			
≤2	26.4%	34.9%	0.891
3–5	71.3%	60.5%	0.424
Death	2.3%	4.7%	
mRS at 90 days after stroke	<i>n</i> = 85	<i>n</i> = 42	0.276
Mean (SD)	2.6 (1.8)	3.0 (2.0)	
Categorized mRS score			
≤2	50.6%	42.9%	0.503
3–5	41.2%	42.9%	
Death	8.2%	14.2%	

CT computed tomography, *MRI* magnetic resonance imaging, *mRS* modified Rankin Scale, *SD* standard deviation

22% of the iterations of the MRI result in a cost per QALY of €30,000, regarded as the limit of efficiency in Spain (Fig. 2).

DISCUSSION

The findings of the current study show that clinical outcomes at discharge and 90 days after stroke, as well as the total direct costs, were similar for patients in the two groups. Interestingly, although MRI examination

was nearly four times more expensive than CT examination to assess AIS, the overall direct hospital costs were not higher in the group examined with MRI. These results are in line with those reported by Beinfeld and Gazelle [31], who found no increase in hospital costs between 1996 and 2002 despite a substantial increase in the use of CT and MRI.

The median LOS in the stroke unit was lower in the MRI group which may be due to earlier diagnosis and initiation of treatment, and possibly attributable to greater confidence in the information provided by MRI. In both groups, the mean LOS was lower than previously reported values (9.2–26 days) [6, 32, 33]; however, these studies included patients with cerebral hemorrhage.

Total direct hospital costs did not differ between groups, although the mean cost in the MRI group was slightly lower due to the shorter hospital stay in that group. As reported in other studies [6, 7, 11, 34–36], hospital stay was the largest single expenditure in the acute phase, particularly when the patient was in the stroke unit.

In line with another study in stroke patients [10], only 24% of patients in the current study were employed when the stroke occurred. Most patients returned home after hospital discharge, also in agreement with the results of other studies [9, 10]. This data was reflected in sensitivity analysis where when costs due to

Table 5 Cost-effectiveness of MRI versus CT in patients with acute ischemic stroke

Alternative	Cost (Euros)	Incremental cost	Effectiveness (QALY)	Incremental effectiveness	ICER (cost/QALY)
CT	5830.63		0.05230		
MRI	5692.95	−137.68	0.04070	−0.1160	11,868.97

CT computed tomography, *ICER* incremental cost-effectiveness ratio, *MRI* magnetic resonance imaging, *QALY* quality-adjusted life-year

Table 6 One-way sensitivity analysis

Parameter	Variation in costs (Euros)	Variation in QALY	ICER
Utility:VAS ^a	–	–0.00758	18,163.59
Adjusted QALY	–	0.01479	–9308.99
Indirect costs	–235.07	–	19,870.67

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-year, VAS visual analog scale

^a VAS was used as utility to calculate QALY

lost productivity were included (days off work) the ICER was higher.

More than half of the patients in the current study needed a caregiver; 71% of the caregivers were not paid, a proportion in line with the results of a previous study [9], in which 74% of the patients who required assistance were attended by family members or friends. Thus, informal care plays an important role in stroke. Approximately, 26% of the caregivers in the current study were family members who had to leave their jobs to care for the patient.

In this study, the use of MRI rather than CT as the initial diagnostic tool for assessing stroke patients did not result in better outcome at discharge or 90 days after stroke. However, no changes were made in the treatment protocol for patients undergoing MRI for the initial assessment. Because rt-PA treatment in the first 3 h is based on the absence of hemorrhage or extensive infarct, this information can be reliably obtained with a simple CT study. There were no significant differences between the two groups in the distribution of patients treated with rt-PA. However, a recent study [37] found that using MRI-based penumbra to select patients for intravenous rt-PA after routine CT in patients with AIS increased costs, but was more cost-effective.

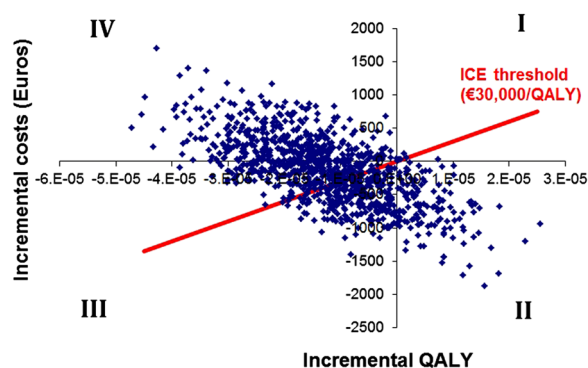


Fig. 1 Incremental cost-effectiveness (ICE) plane of MRI versus CT in patients with acute ischemic stroke. Results of probabilistic sensitivity analysis. Simulation cases of patients in the CT and MRI group. CT computed tomography, MRI magnetic resonance imaging, QALY quality-adjusted life-year

No significant differences between the groups in mRS was found. Likewise, no significant differences in the parameters that were calculated from mRS, such as utilities and QALYs, were found. ICER in the simulations varied widely due to the lack of significant differences in the effectiveness of the two techniques.

When a sensitivity analysis using utility values obtained with the VAS was performed, the variation in effectiveness between the two groups remained minimal (it was even lower than in the analyses of the baseline data), so the ICER was higher. As is shown in the graph of the cost-effectiveness plane (Fig. 1), a considerable proportion of the results of this study were located in the third quadrant, indicating that MRI is less expensive, but also less effective in terms of QALYs. Thus, MRI is not considered a dominant alternative or a dominated alternative. However, in a proportion of the bootstrap results MRI would be located in quadrant IV, meaning that it was less effective and more costly than CT. Thus, MRI would be a dominated alternative.

Discussing two systematic reviews of cost-effectiveness of CT and MRI for some clinical

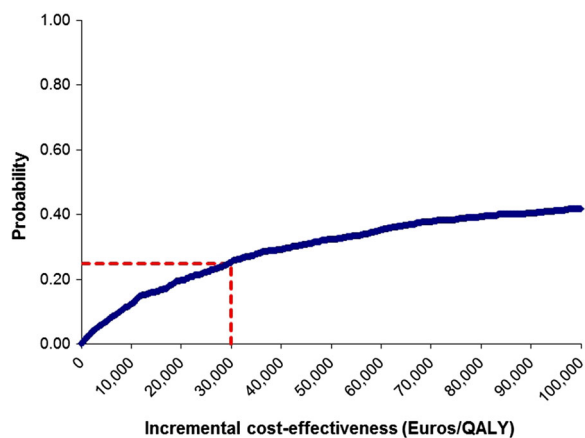


Fig. 2 Acceptability curve of magnetic resonance imaging versus computed tomography in patients with acute ischemic stroke. *QALY* quality-adjusted life-year

disorders (including stroke), Murtagh et al. [38] highlight that diagnostic imaging technologies can improve or expedite diagnosis of disease, but do not necessarily change outcomes. Indeed, many factors can affect a patient's outcome after imaging.

The current study has some limitations. The small sample size may have made it difficult to detect some significant differences; however, a bootstrap analysis was performed to increase the power of the study. The method for assigning patients to the study groups depended on the time of onset of stroke, and it cannot be ruled out that this did not introduce a selection bias. Nonetheless, at admission, the groups were similar in neurological deficit, cardiovascular risk factors, and prior disability.

The time horizon is important in economic evaluations. Here 90 days was used; this follow-up period is similar to other studies of the costs and of managing stroke [8, 39, 40]. In this sense, one study of the cost-effectiveness of thrombolytic therapy with alteplase [41] concluded that thrombolytic therapy based on MRI is not cost-effective in the short term; however, in the long term (at 3 years and

30 years) thrombolytic therapy based on MRI was the dominant alternative compared to conventional treatment.

Another important limitation is the cost. In the current study, costs are presented in Euros at the 2004 exchange rate. It was not considered appropriate to update the costs to 2014 because there were different aspects to consider other than the consumer price index, such as the structure of the market (supply, demand, innovation, and economic crisis among others). Nonetheless, the decision making of those technologies is supported by the sensitivity analysis.

The current results indicate that it is economically and clinically feasible to perform emergency MRI to diagnose AIS. These results could be extrapolated to other settings where diffusion-weighted imaging, perfusion MRI, and/or MRI angiography are available, because if those conditions are not fulfilled the investment needed to purchase this technology would have to be included in the analysis. In addition to a suitable infrastructure, coordinated teamwork among the neurology, emergency, and radiology departments is extremely important. Without the interdisciplinary teamwork in stroke management at the authors' hospital, it would have been impossible to carry out this study.

These results may help guide hospital financial managers and clinicians. However, it is important to emphasize that the decision of which neuroimaging technique to apply must always be made on an individual basis in function of the patient's age, symptoms, time since onset of the event, and availability of the imaging techniques, among other factors. More studies on the cost-effectiveness of new imaging studies will be needed when radiological findings, such as brain hemodynamics, volume of the penumbra, size of the infarction, and

presence of vascular occlusion, are included in the treatment protocols of AIS.

CONCLUSION

The three main findings obtained from this study that can be considered when deciding which imaging technique to use for the initial assessment in AIS are: (1) Health outcomes are equivalent whether CT or MRI is used, since therapeutic decision making is not based on neuroimaging results; (2) the direct costs related to the use of CT or MRI are equivalent because the higher post-discharge costs in the MRI group is compensated by the lower direct cost of hospitalization and the need for MRI in some patients initially examined with CT; and (3) the cost-effectiveness analysis performed with the bootstrap method indicates that MRI was cost-effective in a proportion of cases. Caution is warranted in interpreting these results.

Although the cost information used was from 2004, and considering the modifications over time that this implies, it is important to bear in mind that the conclusions described will stay the same. Additionally, this study will allow the authors to verify their conclusions with a new prospective multicenter study on the management of MRI on patients with AIS in the future.

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Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. Elizabeth Parody, Salvador Pedraza, María del Mar García, Carlos Crespo, Joaquín Serena, and Antoni Dávalos declare no conflict of interest.

Compliance with ethics statement. The Hospital Doctor Josep Trueta's (Girona, Spain) ethics committee approved the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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