

# Risk stratification for in-hospital mortality in spontaneous intracerebral haemorrhage: A Classification and Regression Tree Analysis

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## Summary

**Background:** Risk stratification for mortality in intracerebral haemorrhage (ICH) helps guide care, but existing clinical prediction rules are too cumbersome for clinical practice because of their complexity.

**Aim:** To develop a simple decision tree model of in-hospital mortality risk stratification for ICH patients.

**Methods:** We collected information on spontaneous ICH patients hospitalized in a teaching hospital in Japan from August, 1998 to December, 2001 ( $n=374$ ). All variables were abstracted from data available at the time of initial evaluation. A prediction rule for in-hospital mortality was developed by the Classification and Regression Tree (CART) methodology. The accuracy of

the model was evaluated using the area under receiver-operator characteristic curve.

**Results:** Overall in-hospital mortality rate was 20.2%. The CART methodology identified four groups for mortality risk, varying from low (2.1%) to high (58.9%). Level of consciousness (coma) was the best single predictor for mortality, followed by high ICH volume (cut-off 10.4 ml), and then age (cut-off 75 years). The accuracy of our CART model (0.86) exceeded that of a multivariate logistic regression model (0.81).

**Discussion:** ICH patients can easily be stratified for mortality risk, based on three predictors available on admission. This simple decision tree model provides clinicians with a reliable and practical tool.

## Introduction

Intracerebral haemorrhage (ICH) accounts for 10% to 15% of all strokes, but is associated with high morbidity and mortality.<sup>1,2</sup> In Japan, the prevalence of ICH is at least twice that in Western countries<sup>3</sup> and the age- and sex-adjusted incidence rate is about 53/100 000 per year.<sup>4</sup> ICH will continue to be an important problem as the population ages, in both Japan and other developed countries.<sup>5</sup> Recombinant Activated Factor VII<sup>6</sup> has been suggested as a potential

treatment for ICH, but optimal management of this condition remains unclear.<sup>7,8</sup>

A first step for reaching a consensus on the management of ICH is the development of prediction rules for risk stratification of ICH patients. Clinical risk prediction tools may be useful in guiding medical decision-making, and provide prognostic information to patients and their family. Moreover, they may help focus attention on potential targets for intervention, and suggest

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which patient groups are most likely to have their outcome influenced by a particular intervention.<sup>2</sup>

Clinical prediction rules were usually developed by multivariate logistic regression models. However, these models may be of limited utility in clinical practice because of their complexity. The number of predictors and mathematical functions often require access to a computer or a calculator to provide risk estimates.

The Classification and Regression Trees (CART) methodology produces a simple decision tree that is relatively easy to apply in clinical practice (at the bedside or in the emergency room), and may provide potential groups to evaluate ICH therapies and management, because it can identify patients at different levels of risk. These algorithms have been used to develop prediction models in various fields.<sup>9–12</sup> For ICH patients, prediction rules of worse outcome (not mortality), have previously been developed using the decision tree method, but with a relatively small sample.<sup>13</sup>

Our objective was to use the CART methodology to develop a practical and user-friendly model of risk stratification for in-hospital mortality of ICH, using the initial evaluation in routine clinical practice.

## Methods

### Data collection

We retrospectively collected information on patients hospitalized with a spontaneous ICH at the Department of Neurology/Neurosurgery in a teaching hospital in Izumo, Japan. We excluded traumatic or subarachnoid haemorrhages. Information from August 1998 to December 2001 was extracted from a computerized database (SHIMANE: Integrated Intelligent Management System). Database elements included demographic information, medical history, initial evaluation (vital signs, laboratory data and radiographic findings), treatments provided, and hospital course. Two investigators independently extracted and recorded the information using a structured data form. A consensus was reached after discussion for any points of disagreement. Institutional Review Board approval was obtained for all aspects of this study. To preserve patient confidentiality, direct patient identifiers were not collected as part of the dataset.

### Potential predictors and outcomes

All variables used for our model were abstracted from data available at the time of initial evaluation of ICH. All potential predictors

were selected from results of previous studies. These included both clinical factors (age,<sup>14–19</sup> level of consciousness,<sup>14,16,18–20</sup> blood pressure,<sup>21</sup> and pulse pressure<sup>22</sup>) and radiographic variables (haematoma volume,<sup>14,16,18,19,22,23</sup> presence of intraventricular haemorrhage,<sup>16,22</sup> and location of haemorrhage<sup>16</sup>). Other extracted variables are summarized in Table 1. The diagnosis of ICH was confirmed by head computed tomography (CT) within 24 h of admission.

Medical history, such as hypertension, diabetes mellitus, heart failure, and ischaemic heart disease, was defined by patient self-report and medical treatment received. Previous stroke was defined as a neurological deficit >24 h prior to the current event. Pulse pressure was defined as the difference between systolic blood pressure and diastolic blood pressure on admission. The level of consciousness was categorized into four levels, based on the Japan Coma Scale:<sup>24</sup> (i) alert; (ii) JCS Grade I (disoriented: awake without stimulation); (iii) JCS Grade II (somnolent: rousable with stimulation, but reverting to previous state if stimulus stops); and (iv) JCS Grade III (comatose: unrousable by any stimulation). ICH haematoma volume was measured on the initial head CT scan using the ABC/2 method, where is the greatest diameter on the largest haemorrhage slice, B is the diameter perpendicular to this, and C is the approximate number of axial slices with haemorrhage multiplied by the slice thickness.<sup>25</sup>

The primary outcome of interest was hospital mortality. Discharge was determined by a neurologist or a neurosurgeon at the time when the medical condition of a patient was recognized to be stable.

### Statistical analysis

For univariate analysis, Student's *t* test was used to test differences in continuous variables and the  $\chi^2$  test was used for differences in proportions among survivors and deaths during hospitalization. In a multivariate logistic regression analysis, we selected predictors using stepwise selection, with entry and removal *p* values both 0.01. To create a multivariate logistic regression model that could be easily interpreted and implemented in practice, all continuous variables were collapsed into binary variables. Possible cut-off points for continuous variables were determined by the results of previous studies and clinical importance. For example, the chosen thresholds for ICH volume were 30, 40, and 60 ml, respectively. SAS for Windows, version 9.1 (SAS Institute Inc.) was used for analyses.

**Table 1** Demographic and clinical characteristics for in-hospital mortality

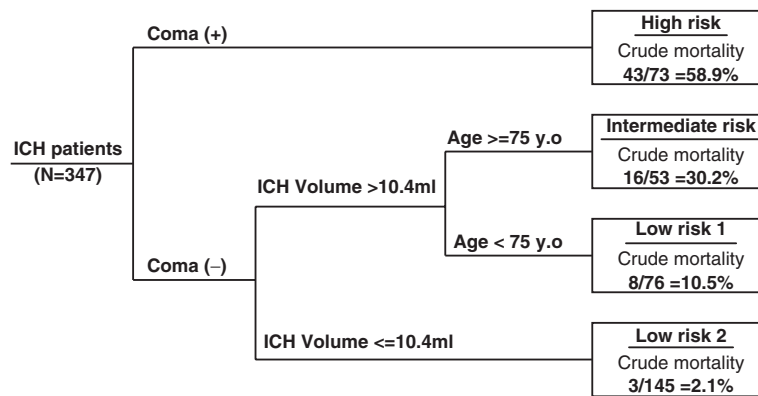
Variable	Death (n=70)	Survival (n=277)	Total (n=347)	p	Missing data (%)
Mean ± SD age (years)	77.2 ± 11.7	70.3 ± 11.7	71.7 ± 12.0	<0.01	0
Males (%)	41 (58.6%)	130 (46.9%)	171 (49.3%)	0.08	0
Operations <sup>a</sup> (%)	8 (11.4%)	48 (17.3%)	56 (16.1%)	0.2	0
Disturbed consciousness <sup>b</sup> (%)	54 (77.1%)	84 (30.3%)	138 (39.8%)	<0.01	0
<i>Initial vital signs, mean ± SD</i>					
Systolic BP (mmHg)	154.0 ± 30.8	152.7 ± 27.4	152.9 ± 28.0	0.7	5 (1.4%)
Diastolic BP (mmHg)	82.5 ± 21.2	82.7 ± 17.8	82.6 ± 18.5	0.9	5 (1.4%)
Pulse pressure (mmHg)	71.5 ± 29.1	70 ± 23.5	70.2 ± 24.7	0.7	5 (1.4%)
Blood temperature ≥ 37.5°C, n (%)	17 (26.2)	21 (7.7)	38 (11.3)	<0.01	10 (2.8)
<i>Medical history</i>					
Hypertension	30 (42.9%)	170 (61.4%)	200 (57.6%)	0.01	0
Diabetes	22 (31.4%)	67 (24.2%)	89 (25.6%)	0.2	0
Ischaemic heart disease	11 (15.7%)	43 (15.5%)	54 (15.6%)	0.9	0
Heart failure	28 (40.0%)	73 (26.4%)	101 (29.1%)	0.03	0
Stroke	22 (31.4%)	57 (20.6%)	79 (22.8%)	0.05	0
<i>CT findings</i>					
Mean ± SD ICH volume (ml)	63.2 ± 49.6	19.6 ± 24.5	28.4 ± 35.7	<0.01	0
IVH (%)	46 (65.7%)	112 (40.4%)	158 (45.5%)	<0.01	0
Location (%)				<0.01	0
Lobar	18 (25.7%)	58 (20.1%)	76 (21.9%)		
Central <sup>c</sup>	39 (55.7%)	190 (68.6%)	229 (66.0%)		
Cerebellum	5 (7.1%)	22 (7.9%)	27 (7.8%)		
Brainstem	8 (11.4%)	7 (2.5%)	15 (4.3%)		
<i>Laboratory values, mean ± SD</i>					
White cell count (10 <sup>9</sup> /l)	100.9 ± 46.2	83.7 ± 33.1	87.0 ± 36.6	<0.01	5 (1.4)
Haemoglobin (g/dl)	12.7 ± 2.2	13.5 ± 1.8	13.3 ± 1.9	<0.01	5 (1.4)
Platelets (10 <sup>10</sup> /l)	18.5 ± 7.3	21.7 ± 5.7	21.0 ± 6.2	<0.01	5 (1.4)
Glucose (mg/dl)	179.5 ± 69.3	154.8 ± 61.6	159.7 ± 63.8	0.01	7 (2.0)
Use of antithrombotic drugs (%)	8 (11.4%)	25 (9.0%)	33 (9.5%)	0.5	0

<sup>a</sup>Haematoma evacuation or external ventricular drain. <sup>b</sup>Somnolent (arousable with stimulation but reverting to previous state if stimulus stops) or comatose (unrousable by any stimulus). <sup>c</sup>Basal ganglia and thalamus. ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; BP, blood pressure.

A prediction rule for in-hospital mortality was developed using the Classification and Regression Tree (CART) methodology.<sup>26,27</sup> Unlike traditional regression methods, a CART analysis is well suited to the generation of clinical decision rules. Moreover, it is a non-parametric statistical technique, and makes no distribution assumptions of any kind, either for dependent or independent variables. CART initially stratifies the data set by the best binary predictor to create a high-risk and a low-risk subgroup that demonstrate the greatest gain in overall subgroup homogeneity with respect to the outcome. A candidate binary predictor for each continuous factor is created based on the optimal threshold value for that factor. The stratification process is then repeated in each of the two subgroups. The process is repeated until the degree of outcome

homogeneity in each subgroup cannot be improved by further stratification, or until the size of a subgroup is smaller than a pre-determined value. Finally, the large tree is pruned based on a cost-complexity index, and the final tree is determined by the methods of cross-validation as the tree with lowest expected misclassification, to avoid overfitting information contained in the data set.

The CART algorithm (CART 5.0, Salford Corp.) was used to analyse 29 potential variables of interest in our cohort. These variables were chosen from 37 variables extracted based on the results of univariate analyses ( $p < 0.25$ ), the number of missing (<10%), and clinical importance. Nodes in the CART tree were constrained to have a minimum size of 100 subjects to consider additional stratification, and each resulting subgroup needed to



**Figure 1.** Predictors of in-hospital mortality and risk stratification. Coma, unrousable by any stimulus; ICH, intracerebral haemorrhage; y.o., years old. Overall, in-hospital mortality was 20.2% (70/347).

have at least 50 subjects. We used the entropy method as a measure of outcome homogeneity within a subgroup. Basing a selection rule on this measure is similar to using the likelihood ratio  $\chi^2$  test to select a predictor with the most statistically significant relationship to the outcome.

We compared the accuracy of our model with that of the ICH score,<sup>16</sup> which is the previous validated prognostic score for prediction of 30-day mortality. To apply the ICH score to our data set, we aggregated the level of consciousness based on Japan coma scale into the three categories of the ICH score which is based on the Glasgow Coma Scale.

The accuracy of the CART and logistic regression models was compared using the area under receiver-operator characteristic curves developed from each method.

## Results

Overall, 347 patients were admitted to our hospital with acute spontaneous ICH between August 1998 and December 2001. Their mean age was 71.7 years (range 35–102) and 49.3% were male. Their other main characteristics are summarized in Table 1. Overall in-hospital mortality rate was 20.2%. Mean length of stay for total hospital was 64.9 days (SD 59.4 days, range 1–368 days). Of those who died, 30% did so within 3 days of admission, about half within 10 days of admission, 67.1% within 30 days, and 84% within 90 days.

Among the 29 variables selected, the CART method identified coma at admission as the best single discriminator between deaths and survivors (Figure 1). Among non-comatose patients, the next best predictor of in-hospital mortality was the ICH volume, dichotomized at a level of 10.4 ml. Among those with an ICH volume >10.4 ml,

age ( $\geq 75$  years old) identified a subgroup with high mortality.

Figure 1 shows the final tree model with the four terminal nodes identified by the CART analysis. The high-risk group (mortality rate 58.9%) includes patients who are comatose at admission. An intermediate group (mortality rate 30.2%) includes non-comatose patients with ICH volume >10.4 ml, and age  $\geq 75$  years. A lower risk group (mortality rate 10.5%) includes non-comatose patients with ICH volume >10.4 ml, and age <75 years old. The lowest risk group (mortality rate 2.1%) include non-comatose patients with ICH volume  $\leq 10.4$  ml. The clinical characteristics of the four risk groups are summarized in Table 2. In Table 2, the modified Rankin Scale (0 indicates full recovery, 6 indicates death) was used for clinical assessment on discharge.<sup>28</sup>

Multivariate logistic regression identified coma, ICH volume ( $\geq 60$  ml), blood temperature ( $\geq 37.5^\circ\text{C}$ ), and infratentorial lesions as the most significant mortality risk predictors (Table 3). Based on the area under the receiver-operator characteristic curves, the accuracy of the CART model was 0.86, while that of the multivariate logistic regression model was 0.81 (Figure 2). In addition, our CART model (0.86) was superior to the ICH score (0.83) based on the multivariate logistic regression model (Figure 3). Therefore, we favoured the CART model as our final prediction rule.

## Discussion

The clinical decision tree produced by the CART methodology provides a simple and reliable model of the risk stratification for in-hospital mortality of ICH patients, based on the combination of three predictors available at admission, including level of consciousness (cut-off point: coma), ICH

**Table 2** Characteristics of risk groups (n=347)

	High risk	Intermediate risk	Low risk	Lowest risk
Total patients	73	53	76	145
Modified Rankin Scale <sup>a</sup> ≥4 at discharge (%)	65 (89.0%)	43 (81.1%)	40 (52.6%)	48 (33.1%)
Alert/disoriented (not somnolent/comatose) at admission (%)	0 (0%)	28 (52.8%)	50 (65.8%)	131 (90.3%)
Mean ICH volume at admission (ml)	66.9 ± 45.0	39.0 ± 37.3	28.9 ± 18.7	4.8 ± 3.3
IVH (%)	55 (75.3%)	30 (56.6%)	33 (43.4%)	40 (27.6%)
<i>Haematoma site</i>				
Lobar (%)	13 (17.8%)	21 (39.6%)	23 (30.3%)	19 (13.1%)
Central <sup>b</sup> (%)	50 (68.5%)	27 (50.9%)	47 (61.8%)	105 (72.4%)
Cerebellar (%)	4 (5.5%)	5 (9.4%)	6 (7.9%)	12 (8.3%)
Brainstem (%)	6 (8.2%)	0 (0.0%)	0 (0.0%)	9 (6.2%)
Operation <sup>c</sup> after hospitalization (%)	18 (24.7%)	5 (9.4%)	29 (38.2%)	4 (2.8%)

<sup>a</sup>Scores of 4–6 indicate death or survival with severe disability (bed-bound and incontinent) or moderate to severe disability (unable to walk without assistance). <sup>b</sup>Basal ganglia and thalamus. <sup>c</sup>Haematoma evacuation or external ventricular drain. ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage.

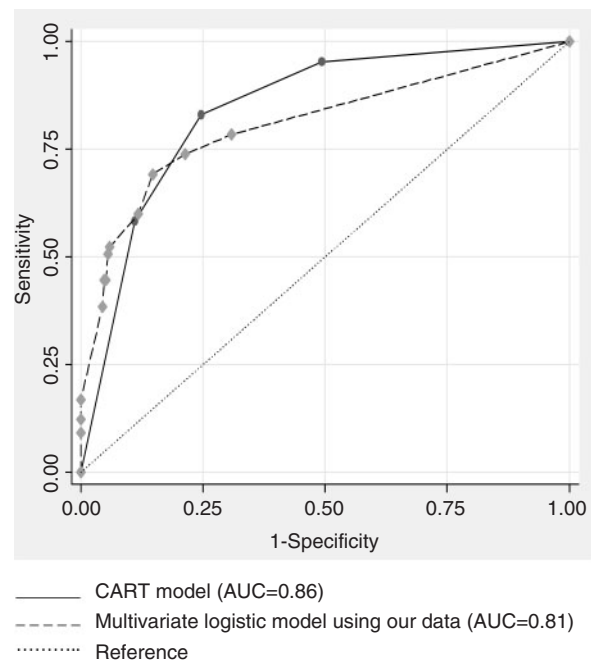
**Table 3** Independent predictors by multivariate logistic analysis

Independent variable	Odds ratio	95%CI	p
Coma	5.7	2.7–11.9	<0.01
ICH volume ≥60 ml	5.0	2.2–11.5	<0.01
Blood temperature ≥37.5°C	4.3	1.8–10.0	<0.01
Infratentorial lesion	3.3	1.4–7.8	<0.01

ICH, intracerebral haemorrhage.

volume (cut-off 10.4 ml), and age (cut-off 75 years). While overall in-hospital mortality was 20.2%, the mortality risk in ICH patients was divided into four groups according to the CART model, varying by about 30-fold from 2.1% to 58.9% (Figure 1).

Level of consciousness on admission has been reported as one of the most important independent predictors of 30-day,<sup>14,16,19</sup> 1-year<sup>18</sup> and all in-hospital mortality<sup>20</sup> in ICH patients. Coma indicates either direct involvement of the brainstem reticular activating system bilaterally in the brainstem tegmentum (usually paramedian pons or thalamus) or increased intracranial pressure with shift in brain contents or frank herniation.<sup>1</sup> Increased damage to the brain also influences the level of consciousness. In the high-risk group (the comatose patients) of our CART model, the mean ICH volume (66.9 ml) and the proportion of intraventricular haemorrhage (75.3%), which are consistent risk factors of mortality for ICH

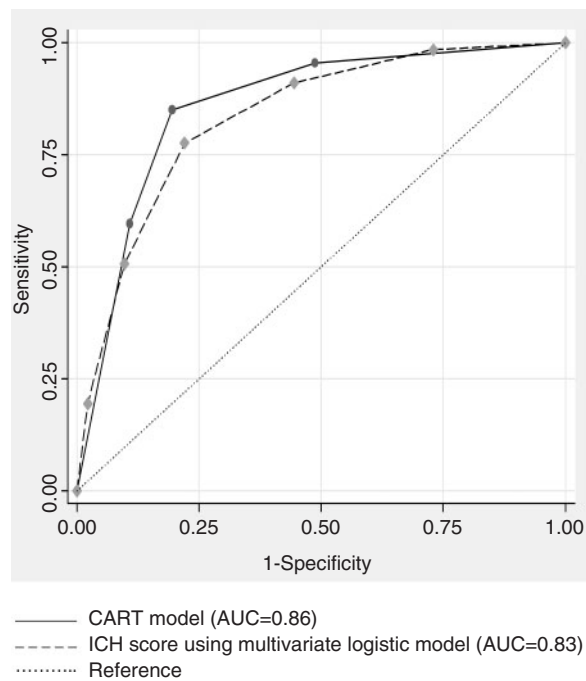


**Figure 2.** ROC curves by Logistic Regression and CART model. Solid line, CART Model (AUC=0.86); dashed line, multivariate logistic model using our data (AUC=0.81); dotted line, reference.

patients, are the largest among the four groups (Table 2).

ICH volume is also one of the important independent predictors of ICH outcome in prior prediction models.<sup>14,16,18,19,23</sup> Increased intracranial pressure and cerebral oedema associated with the initial haemorrhage volume may influence outcome. However, the specific volume cut-off points vary depending on the specific model, such as 30 ml,<sup>16</sup> 40 ml,<sup>23</sup> and 60 ml.<sup>18</sup> The CART algorithm automatically predicts the optimal threshold





**Figure 3.** ROC curves by intracerebral haemorrhage (ICH) score using logistic regression, and CART model. CART Model (AUC=0.86); dashed line, multivariate logistic model using our data (AUC=0.83); dotted line, reference.

value of the continuous variables. It selected the optimal cut-off point as 10.4 ml, and determined that non-comatose patients with volumes  $\leq 10.4$  ml were at lowest risk (2.1%).

This has practical implication for patients' treatment: given the risks of surgery<sup>29</sup> and rFVIIa treatment,<sup>6</sup> this lowest-risk group (non-coma and ICH volume  $\leq 10.4$  ml) might not be best managed in this way. It is an interesting coincidence that the cut-off point of 10.4 ml is almost identical with that of 10 ml as an exclusion criterion for surgery, regardless of the location of ICH, in the American Heart Association Guidelines.<sup>8</sup> Moreover, arterial thromboembolic serious adverse events, such as myocardial infarction and cerebral infarction, occurred in 5% of the rFVIIa-treated patients, compared with none of the placebo-treated patients. Thus, this lowest-risk group of patients might potentially be managed conservatively, without surgery and treatment with rFVIIa, although additional data for rFVIIa in the ongoing phase III are needed to clarify the thromboembolic risk.

Advanced age was an independent predictor of ICH outcome in some previous studies.<sup>14,16,18,19</sup> Elderly people may sustain worse neurological injuries.<sup>16</sup> One randomized controlled trial comparing surgery (endoscopic aspiration) with medical management reported that the benefit of surgery

in terms of quality of life was limited to patients aged  $<60$  years.<sup>30</sup> However, it is also possible that the withdrawal of support in elderly patients may influence prognosis.<sup>17,31</sup> In our CART model, the intermediate-risk group (non-comatose, but  $>75$  years old, with  $>10.4$  ml of ICH volume) was less likely to have an aggressive procedure such as surgery (e.g. craniotomy) during hospitalization (Table 2). In other words, the intermediate risk might reflect the absence of a treatment of proven efficacy for ICH, especially surgery.<sup>32</sup> Thus, this group might be potential targets for an intervention such as treatment with rFVIIa, considering the risk of arterial thromboembolic complication and the patient's and their family's wishes about ICH treatment.

Risk stratification schemes for mortality of ICH patients are typically based on multivariate logistic analysis. The models thus generated are often complex, requiring access to a computer or calculator to provide risk estimates. Even if converted to point scores, the tools developed by the multivariate logistic model still require a nomogram reference to convert a point score to a risk estimate. Risk estimates are useful, but clinicians might prefer to group patients into low risk vs. high risk categories.

Although risk categorization may be based on a point score system, the CART methodology provides a decision tree that is relatively easy to apply in clinical practice. Since the same patient has multiple risk factors, risk factor analysis should consider factors in their combination, rather than isolation. Our CART model stratified ICH patients in a simple three-step process with only three predictors, since it detects interaction among predictors and considers predictors in combination rather than isolation, unlike many constructed multivariable logistic models. Thus, it can provide more simple and accurate prediction tools than the traditional multivariate logistic regression.

There are some potential limitations of our CART model. First, we were limited to the variables that were previously collected from electronic medical record. These variables did not include all of the factors that were previously identified as predictors of mortality following ICH, such as GCS, time of onset, other radiological factors (hydrocephalus<sup>33</sup> and midline shift), patients' or their family's treatment preferences, and withdrawal of treatment by physicians.<sup>31</sup> It is possible that the performance of our model would improve if these other predictors were available. However, our model performed very well<sup>34</sup> (AUC=0.86), using only information routinely available at the time of admission. Second, we choose to

consider only risk groups that contained at least 50 subjects, thereby avoiding small groups with imprecise estimates of mortality risk. One limitation of this constraint is that CART would not identify small groups with at exceptionally high risk, such as brainstem haemorrhage ( $n=15$ , crude mortality 53.3%). More information about small groups at high risk could play an important role in selecting patients for clinical treatment. Finally, since only Japanese ICH patients are included in this study, this model may not apply to patients who are cared for in a different setting. Study results may be influenced by differences in assessment, treatment and management after ICH hospital admission. The CART methodology determined the final tree by the methods of cross-validation, but validation on another, independent data set would be desirable. Despite these potential limitations, the CART model provides a simple tool to predict in-hospital mortality of ICH patients that is easy to use in the clinical practice.

In conclusion, ICH patients can be easily stratified into four levels of risk, based on three predictors available on admission: level of consciousness, ICH volume, and age. This simple decision tree model provides clinicians with a reliably practical tool for in-hospital mortality risk stratification without mathematical calculation.

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