Crossed cerebellar tracer uptake on acute-stage ^{123}I-iomazenil SPECT imaging predicts 3-month functional outcome in patients with non-fatal hypertensive putaminal or thalamic hemorrhage

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Abbreviated title: Crossed cerebellar diaschisis on iomazenil SPECT

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Abstract

Purpose: Whereas single-photon emission computed tomography (SPECT) images obtained 180 min after administration of ^{123}I-iomazenil (late images) are proportional to the distribution of central benzodiazepine receptor binding potential, SPECT images obtained within 30 min after ^{123}I-iomazenil administration (early images) correlate with regional brain perfusion. The aim of the present study was to determine whether crossed cerebellar tracer uptake on acute-stage ^{123}I-iomazenil SPECT imaging predicts 3-month functional outcome in patients with non-fatal hypertensive putaminal or thalamic hemorrhage.

Methods: Forty-six patients underwent early and late SPECT imaging with ^{123}I-iomazenil within 7 days after the onset of hemorrhage. A region of interest (ROI) was automatically placed in the bilateral cerebellar hemispheres using a three-dimensional stereotaxic ROI template, and the ratio of the value in the cerebellar hemisphere contralateral to the affected side to that in the ipsilateral cerebellar hemisphere (AR_{cbl}) were calculated in each patient. Each patient's physical function was measured using the modified Rankin scale score (mRS) 3 months after onset.

Results: AR_{cbl} on early ($\rho = -0.511$; $P = 0.0003$) and late ($\rho = -0.714$; $P < 0.0001$) images correlated with the mRS 3 months after the onset of hemorrhage. Multivariate analysis showed that only a low AR_{cbl} in late images was significantly associated with a poor functional outcome (mRS ≥3 at 3 months after onset) (95% confidence intervals, 0.001 to 0.003; $P = 0.0212$). **Conclusion:** Crossed cerebellar tracer uptake on acute-stage ^{123}I-iomazenil SPECT imaging predicts 3-month functional outcome in patients with non-fatal hypertensive putaminal or thalamic

hemorrhage.

Keywords: putaminal hemorrhage • thalamic hemorrhage • ^{123}I-iomazenil • crossed cerebellar diaschisis • functional outcome

Introduction

Hypertensive intracerebral hemorrhage accounts for ≤15% of all strokes and is associated with a poor prognosis.[1] For patients who develop putaminal or thalamic hemorrhage, several features including advanced age, severe clinical presentation, hyperglycemia, larger hemorrhage volume, and presence of intraventricular hemorrhage are associated with mortality.[2-5] However, factors related to long-term functional outcomes in patients with non-fatal putaminal or thalamic hemorrhage that is characterized as a combination of no or slight disturbance of consciousness and moderate or severe hemiparesis in the acute stage have been rarely reported.

The distribution of central benzodiazepine receptors in the human brain has been widely studied with single-photon emission computed tomography (SPECT) and ^{123}I-iomazenil (IMZ).[6-10] Whereas images obtained 180 min after administration of ^{123}I-IMZ (late images) are proportional to the distribution of central benzodiazepine receptor binding potential,[6-8] images obtained within 30 min after tracer administration (early images) correlate with regional brain perfusion.[11] Central benzodiazepine receptor binding potential on late images of ^{123}I-IMZ SPECT may be associated with neural density in the brain cortex, and a reduction in central benzodiazepine receptor binding potential may indicate cortical neural damage or loss.[6-10] According to these hypotheses, reductions in central benzodiazepine receptor binding potential are irreversible. However, several investigators have demonstrated that recovery of ^{123}I-IMZ uptake in the ipsilateral cerebral cortex after revascularization surgery for carotid stenosis[12] or surgical removal of intracranial meningioma[13] is associated with postoperative improvement in cognitive function,

suggesting central benzodiazepine receptor downregulation in viable neural tissue along with a decline in brain function.[12,14-16]

Crossed cerebellar diaschisis is defined as a reduction in neural activity in the cerebellar hemisphere contralateral to a supratentorial lesion.[17] This phenomenon can be demonstrated as crossed cerebellar hypometabolism with positron emission tomography or as crossed cerebellar hypoperfusion with brain perfusion SPECT.[17-20] The mechanism underlying crossed cerebellar diaschisis reportedly consists of interruption of the cerebropontocerebellar pathway that causes deafferentation disruption of the corticopontocerebellar pathway, which then causes functional deafferentation and transneural metabolic depression of the contralateral cerebellar hemisphere.[19,20] With a thalamic hemorrhage, interruption of the efferent pathway to the thalamus from the contralateral cerebellar dentate nucleus can also be associated with crossed cerebellar diaschisis.[21]

In patients with an ischemic stroke of the middle cerebral artery territory, crossed cerebellar hypoperfusion 10 days after the onset of stroke[18] or crossed cerebellar hypometabolism 1 month after the onset of stroke[22] reportedly indicates a worse clinical outcome. Although crossed cerebellar hypoperfusion is also frequently observed in patients with hypertensive putaminal or thalamic hemorrhage,[9,23-25] the clinical significance of this phenomenon in such patients remains undetermined. Further, a study investigated the presence or absence of asymmetry of tracer uptake in the cerebellar hemispheres on late images of ^{123}I-IMZ SPECT in patients with hypertensive putaminal or thalamic hemorrhage.[9] However, the sample size of this study was small (five patients), and its results were not

prospectively compared with clinical outcomes.[9]

The aim of the present prospective study was to determine whether crossed cerebellar tracer uptake on acute-stage (within 7 days after the onset) ^{123}I-IMZ SPECT imaging predicts 3-month functional outcome in patients with non-fatal hypertensive putaminal or thalamic hemorrhage.

Methods

Study Design

The present study was a prospective observational study. The protocol of this study was reviewed and approved by the institutional ethics committee, and written, informed consent was obtained from all subjects or their next of kin prior to the patients' participation.

Patient Selection

Patients with the following conditions were prospectively included in the present study: (1) 80 years of age or younger; (2) no past history of ischemic or hemorrhagic stroke; (3) past history of hypertension or detection of hypertension on hospitalization; (4) premorbid modified Rankin scale score, 0; (5) hospitalization within 48 hours after onset; (6) level of consciousness on the National Institutes of Health Stroke Scale at hospitalization, 0 or 1; (7) putaminal or thalamic hemorrhage on computed tomography (CT) performed at the time of hospitalization; and (8) modified Rankin scale score ≥2 immediately before the ^{123}I-IMZ SPECT study.

Patients with the following conditions were excluded from the present study: (1) presence of vascular anomaly, arterial-venous fistula, moyamoya disease, or venous thrombosis on CT or magnetic resonance (MR) angiography performed at the time of hospitalization; (2) presence of steno-occlusive diseases in the carotid and vertebro-basilar arteries on CT or MR angiography; (3) presence of ischemic or hemorrhagic lesions in the contralateral thalamus or internal capsule and/or brainstem and/or cerebellum on CT or MR imaging performed at the time of hospitalization; (4) requirement for surgical evacuation, ventricular drainage, and/or ventricular- or lumbar-peritoneal shunting within 3 months after onset; (5) enlargement of the hemorrhage or development of other new hemorrhagic or ischemic strokes after performing the ^{123}I-IMZ SPECT study; and (6) not obtaining informed consent.

^{123}I-IMZ SPECT

Brain SPECT studies were performed using a triple-head gamma camera (GCA-9300R, Toshiba Medical Systems Corp., Tochigi, Japan). The spatial resolution of the gamma camera with a high-resolution fan-beam collimator was 8.5 mm full width at half maximum. The SPECT acquisition protocol consisted of a matrix size of 128 × 128 and 30-min continuous acquisition (5 min/rotation) over 360° in 4° steps. Post-acquisition, the data were corrected for scatter with the triple energy window method, and then reconstructed by filtered backprojection. A Butterworth preprocessing filter was applied, with a cut-off frequency of 0.08 cycles per pixel (1 pixel = 1.72 mm). For attenuation correction, the iterative Chang

method was used, and the attenuation map was generated by extracting the skin contour and assuming the inner region side as a uniform attenuation body. The attenuation coefficient was 0.146 cm^{-1}.

^{123}I-IMZ SPECT was performed from 2 days to 7 days after onset in the same manner described previously.[11] Briefly, an intravenous injection of approximately 167 Mbq ^{123}I-IMZ was administered following a 1-min infusion of physiologic saline at a rate of 20 mL/min. Immediately after administration of the ^{123}I-IMZ, scans were initiated with a scanning duration of 26 min (early images), and 180 min later, scans were also initiated with a scanning duration of 26 min (late images).

All SPECT images were transformed into the standard brain size and shape by linear and nonlinear transformation using SPM2 for anatomic standardization.[26] Thus, brain images from all subjects had the same anatomic format. Three hundred eighteen constant regions of interest (ROIs) were automatically placed in both the cerebral and cerebellar hemispheres using a three-dimensional stereotaxic ROI template.[27] The ROIs were grouped into 10 segments (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, hippocampus, and cerebellar) in each hemisphere according to the arterial supply. Eight (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior) of these 10 segments were combined and defined as a cerebral hemispheric ROI (**Fig. 1**). The mean value of radioactive counts on early and late ^{123}I-IMZ SPECT images was measured in the bilateral cerebral and cerebellar hemispheric ROIs. Then, for early and late images of each patient, the asymmetry

ratio in the cerebral hemispheric ROI (AR_{crb}) was calculated as the value in the cerebral hemisphere ipsilateral to the side of the hemorrhage divided by the value in the contralateral cerebral hemisphere; the asymmetry ratio in the cerebellar hemispheric ROI (AR_{cbl}) was calculated as the value in the cerebellar hemisphere contralateral to the side of the hemorrhage divided by the value in the ipsilateral cerebellar hemisphere.

Management of Patients

The hematoma volume was calculated from measurements of the maximum width × maximum length × thickness × 1/2 of the high-density area on the CT scans performed at the time of hospitalization.[28] The medical treatment depended on the clinical condition of each individual patient. Patients essentially received physical rehabilitation from the day after hospitalization to 3 months after onset. When a patient had a modified Rankin scale score of 1 within 3 months after onset, physical rehabilitation ceased at that time. Speech therapy was also given when aphasia was present. A neurologist blinded to patient data measured the patient's physical function using the modified Rankin scale score immediately before the ^{123}I-IMZ SPECT study and 3 months after onset. Patients with modified Rankin scale scores ≤2 and ≥3 at 3 months after onset were defined as having good and poor functional outcomes, respectively. CT or MRI was also performed at 3 months after onset and at the time when neurological deficits worsened or when new deficits developed. According these CT or MRI findings, whether the hemorrhage was enlarged or new hemorrhagic or ischemic lesions developed for 3 months was determined.

Statistical Analysis

Data are expressed as the mean ± SD. Correlations among ^{123}I-IMZ SPECT data were determined using the Spearman's rank correlation coefficient, and when 95% confidence intervals (CI) of the correlation coefficients did not overlap each other, these correlation coefficients were defined as statistically different. Correlations between ^{123}I-IMZ SPECT data and the modified Rankin scale score 3 months after onset were determined using the Spearman's rank correlation coefficient. The relationship between each variable and the 3-month functional outcome was evaluated with univariate analysis using the Mann-Whitney's U test or χ^2 test. A multivariate statistical analysis of factors related to 3-month functional outcome was also performed using a logistic regression model. Variables with $P < 0.2$ in the univariate analyses were selected for analysis in the final model. Statistical significance for all analyses was set at the $P < 0.05$ level. The accuracy of ^{123}I-IMZ SPECT data in predicting the 3-month functional outcome was assessed using receiver operating characteristic (ROC) curves when the relationship between the two parameters was statically significant. Exact 95% CIs of the sensitivity, specificity, and positive- and negative-predictive values were computed using binomial distributions.

Results

During the 48-month period of the study, a total of 56 patients met the

inclusion criteria. Of these 56 patients, three had ischemic or hemorrhagic lesions in the contralateral thalamus or internal capsule and/or brainstem and/or cerebellum on CT or MR imaging performed at the time of hospitalization. Two other patients underwent surgical evacuation or ventricular drainage before undergoing ^{123}I-IMZ SPECT. Informed consent was not obtained from two other patients. These seven patients were excluded from the present study, and the remaining 49 patients underwent ^{123}I-IMZ SPECT. Of the 49 patients, one patient each developed enlargement of the hemorrhage with neurological deterioration or new brainstem infarctions after undergoing ^{123}I-IMZ SPECT within 3 months after onset. Another did not undergo measurement of physical function 3 months after onset. Finally, the remaining 46 patients were analyzed.

The mean age of the 46 patients (31 men, 15 women) was 64 ± 10 years (range, 31–80 years). Nineteen and 27 patients had a hemorrhage in the left and right cerebral hemispheres, respectively. Twenty and 26 patients had a putaminal and thalamic hemorrhage, respectively. Hematoma volume ranged from 1 ml to 38 ml. Eight patients exhibited intraventricular hemorrhage.

Of the 46 patients studied, ^{123}I-IMZ SPECT was performed 4.5 ± 1.6 days (range, 2–7 days) after onset. **Fig. 2** shows correlations among ^{123}I-IMZ SPECT data in patients. AR_{crb} (ρ =0.706 [95% CI, 0.523 to 0.827]; P <0.0001) or AR_{cbl} (ρ =0.487 [95% CI, 0.229 to 0.681]; P =0.0006) correlated between early and late images. Although the correlation coefficient for AR_{cbl} was lower than that of AR_{crb}, no significant difference was observed between the two correlation coefficients.

The modified Rankin scale score 3 months after onset was 1 in seven

patients, 2 in 17 patients, 3 in three patients, 4 in 11 patients, and 5 in eight patients; 24 and 22 patients were defined as having good and poor functional outcomes, respectively.

Fig. 3 shows correlations between ^{123}I-IMZ SPECT data and the modified Rankin scale score 3 months after onset. For early and late images, although AR_{crb} did not correlate with the modified Rankin scale score 3 months after onset, AR_{cbl} was significantly correlated with the score (ρ = −0.511 [95% CI, −0.698 to −0.259]; P = 0.0003 for early images, ρ = −0.714 [95% CI, −0.832 to −0.534]; P < 0.0001 for late images).

Table 1 shows results of the univariate analyses of factors related to the functional outcomes. Patients with poor functional outcomes were older than those with good functional outcomes. Hematoma volume, the incidence of intraventricular hemorrhage, and the modified Rankin scale score immediately before the ^{123}I-IMZ SPECT study were greater in patients with poor functional outcomes than in those with good functional outcomes. AR_{cbl} in early and late images was lower in patients with poor functional outcomes than in those with good functional outcomes. After closely related variables were eliminated in the univariate analyses, the following confounders (P < 0.2) were included in the logistic regression model for the multivariate analysis: age, hematoma volume, intraventricular hemorrhage, modified Rankin scale score immediately before the ^{123}I-IMZ SPECT study, AR_{crb} in late images, and AR_{cbl} in early and late images. On multivariate analysis, only a low AR_{cbl} in late images was significantly associated with a poor functional outcome (95% CI, 0.001 to 0.003; P = 0.0212).

Fig. 4 shows the ROC curve of AR_{cbl} in late images, which can be used to assess its ability to predict a poor functional outcome. The area under the ROC curve was 0.922 (95% CI, 0.804 to 0.981). Sensitivity, specificity, and positive- and negative-predictive values for AR_{cbl} in late images at the cut-off point (0.981) lying closest to the upper left corner of the ROC curve for the prediction of a poor functional outcome were 77% (95% CI, 60 to 95), 100% (95% CI, 100 to 100), 100% (95% CI, 100 to 100), and 83% (95% CI, 69 to 97), respectively.

Representative images of CT and early and late ^{123}I-IMZ SPECT images from a patient with a good and a patient with a poor functional outcome are shown in **Fig. 5** and **6**, respectively.

Discussion

The present study demonstrated that crossed cerebellar tracer uptake on acute-stage ^{123}I-IMZ SPECT imaging predicts 3-month functional outcome in patients with non-fatal hypertensive putaminal or thalamic hemorrhage.

In the present study, cerebral asymmetry on tracer uptake strongly correlated between early and late images of ^{123}I-IMZ SPECT. As early images of ^{123}I-IMZ SPECT show the distribution of brain perfusion,[11] these findings indicated close consistency of affected-to-contralateral cerebral asymmetry between blood flow and central benzodiazepine receptor binding potential in putaminal or thalamic hemorrhages. Hatazawa et al. [9] suggested that compression of cortical gray matter due to hematoma and surrounding edema and subsequent ischemic injury is a

possible mechanism of the pathogenesis of the reduction in central benzodiazepine receptor binding potential on ^{123}I-IMZ SPECT. In such a situation, cerebral perfusion may be matched with cerebral metabolism, resulting in a reduction in cerebral perfusion that is in proportion to the reduction in central benzodiazepine receptor binding potential. The present study also showed a correlation of the cerebellar asymmetry on tracer uptake between early and late images of ^{123}I-IMZ SPECT, although this correlation was weaker than that of cerebral asymmetry. These data did not correspond with a previous finding by Hatazawa et al. who reported that crossed cerebellar hypoperfusion on brain perfusion SPECT was not accompanied by crossed cerebellar hypoactivity of central benzodiazepine receptor binding potential on ^{123}I-IMZ SPECT.[9] Although differences in the sample size (5 versus 46 patients) and the timing of performing ^{123}I-IMZ SPECT (more than 7 days versus 7 days or less after onset) between the two studies may cause discrepancies in the results, our data suggested that crossed cerebellar hypoactivity of central benzodiazepine receptor binding potential sometimes develops along with crossed cerebellar hypoperfusion in the acute stage of putaminal or thalamic hemorrhage.

Results of the univariate analyses showed that older age, larger hematoma volume, presence of intraventricular hemorrhage, and poor physical function in the acute stage were related to a poor functional outcome. These data corresponded with previous findings obtained from patient populations including those with fatal and non-fatal intracerebral hemorrhages.[2-5] Thus, clinical features of our patient population, although consisting of only patients with non-fatal putaminal or thalamic hemorrhage, may be comparable with those of the previous studies. In such a patient

population, the degree of cerebellar asymmetry on early images of ^{123}I-IMZ SPECT, indicating the degree of crossed cerebellar hypoperfusion, was correlated with the modified Rankin scale score 3 months after onset. These data were consistent with a previous finding in which crossed cerebellar hypoperfusion 10 days after onset indicates a worse clinical outcome in patients with an ischemic stroke in the middle cerebral artery territory.[18] Further, in the present study, the degree of cerebellar asymmetry on late images as well as that on early images were correlated with the modified Rankin scale score 3 months after onset, and multivariate analysis demonstrated that only the latter was significantly associated with a poor functional outcome. As these functional outcomes essentially may depend on the degree of damage to the pyramidal tract ipsilateral to the hemorrhage, our data suggested that crossed cerebellar hypoactivity indicating central benzodiazepine receptor binding potential may reflect irreversible damage to the pyramidal tract more strongly than crossed cerebellar hypoperfusion. Crossed cerebellar diaschisis reflects damage to the cerebropontocerebellar pathway or the efferent pathway to the thalamus from the contralateral cerebellar dentate nucleus rather than damage to the pyramidal tract.[19-21] As all these tracts pass through the internal capsule, they may be affected in the same way by putaminal or thalamic hemorrhage, explaining the present results.

The cerebellar asymmetry on late images of ^{123}I-IMZ SPECT provided specificity of 100% and a positive-predictive value of 100% for predicting a poor functional outcome. This specificity and positive-predictive value suggest that cerebellar asymmetry on late images is suitable as a screening test for acute-stage prediction of functional outcome, and may lead to effective strategies for neuro-

rehabilitation.

The present study possesses several limitations that require discussion. The present study included only patients who met strict inclusion criteria, and our results may not be applicable to patients older than 80 years or those with a history of stroke or severe disturbance of consciousness. Ischemic or hemorrhagic lesions in the thalamus or internal capsule contralateral to the present putaminal or thalamic hemorrhage, even if they are old, may cause contralateral crossed cerebellar diaschisis, resulting in underestimation of crossed cerebellar diaschisis caused by the present hemorrhage. Brainstem lesions also may affect neural activity, blood flow, and metabolism in the unilateral or bilateral cerebellar hemispheres. The present findings may also not be applicable to patients with these lesions.

Conclusions

The present study demonstrated that crossed cerebellar tracer uptake on acute-stage ^{123}I-IMZ SPECT imaging predicts 3-month functional outcome in patients with non-fatal hypertensive putaminal or thalamic hemorrhage.

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Figure legends

Figure 1. Diagrams showing the regions of interest (ROIs) of a three-dimensional stereotaxic ROI template. The white and yellow ROIs indicate cerebral and cerebellar hemispheres, respectively.

Figure 2. Correlations among ^{123}I-iomazenil single-photon emission tomography (SPECT) data in patients. **Left** and **right** graphs indicate a correlation between early and late images on cerebral asymmetry ratio (AR_{crb}) and cerebellar asymmetry ratio (AR_{cbl}), respectively.

Figure 3. Correlations between ^{123}I-iomazenil SPECT data and modified Rankin scale score 3 months after onset. **Upper left**, **lower left**, **upper right**, and **lower right** graphs indicate AR_{crb} on early images, AR_{cbl} on early images, AR_{crb} on late images, and AR_{cbl} on late images, respectively. The horizontal line on the lower right graph denotes the cut-off point lying closest to the upper left corner of the receiver operating characteristic curve for predicting a poor functional outcome.

Figure 4. Receiver operating characteristics curve of AR_{cbl} on late images to assess its ability to predict a poor functional outcome. AUC, area under the receiver operating characteristics curve; CI, confidence interval.

Figure 5. ^{123}I-iomazenil SPECT images of a 54-year-old man with a right putaminal hemorrhage of 35 ml exhibiting a modified Rankin scale score of 5 at 6

days after onset. Three months later, the score improved to 2. Tracer uptake is lower in the right cerebral hemisphere than in the left cerebral hemisphere on early (**left**) and late (**right**) images. Whereas the uptake is lower in the left cerebellar hemisphere than in the right cerebellar hemisphere on the early image, this cerebellar asymmetry disappears on late images.

Figure 6. ^{123}I-iomazenil SPECT images of a 74-year-old man with a left putaminal hemorrhage of 38 ml exhibiting a modified Rankin scale score of 5 at 6 days after onset. Three months later, the score remained 5. Tracer uptake is lower in the left cerebral hemisphere than in the right cerebral hemisphere on early (**left**) and late (**right**) images. The uptake is also lower in the right cerebellar hemisphere than in the left cerebellar hemisphere on early and late images.

Figure 1

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Figure 2

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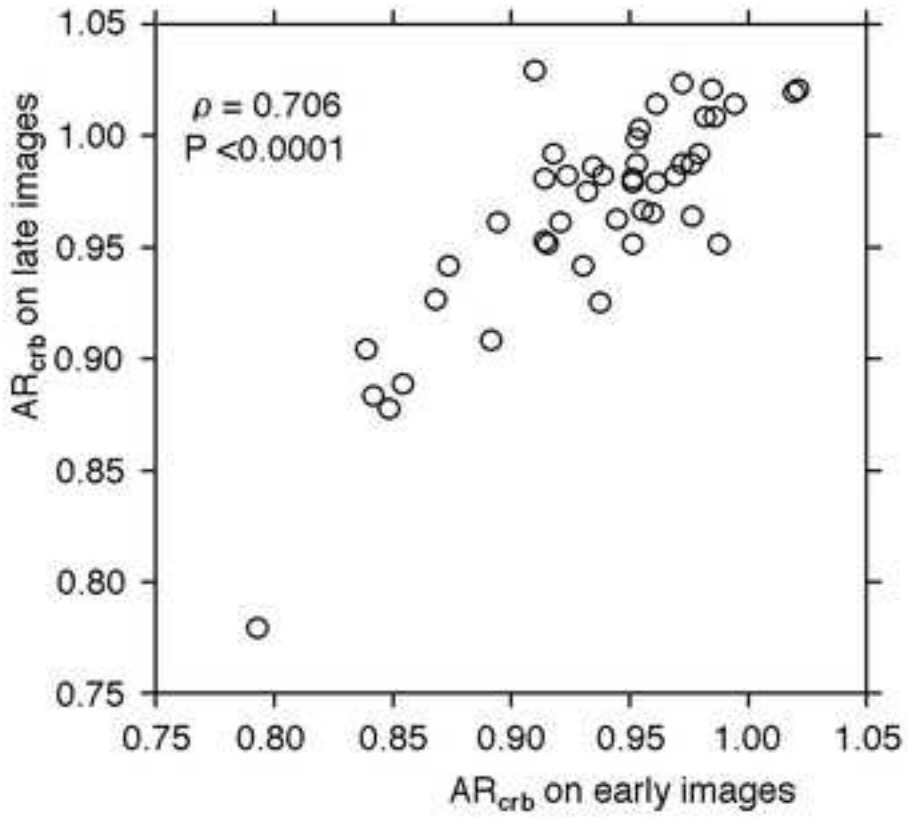

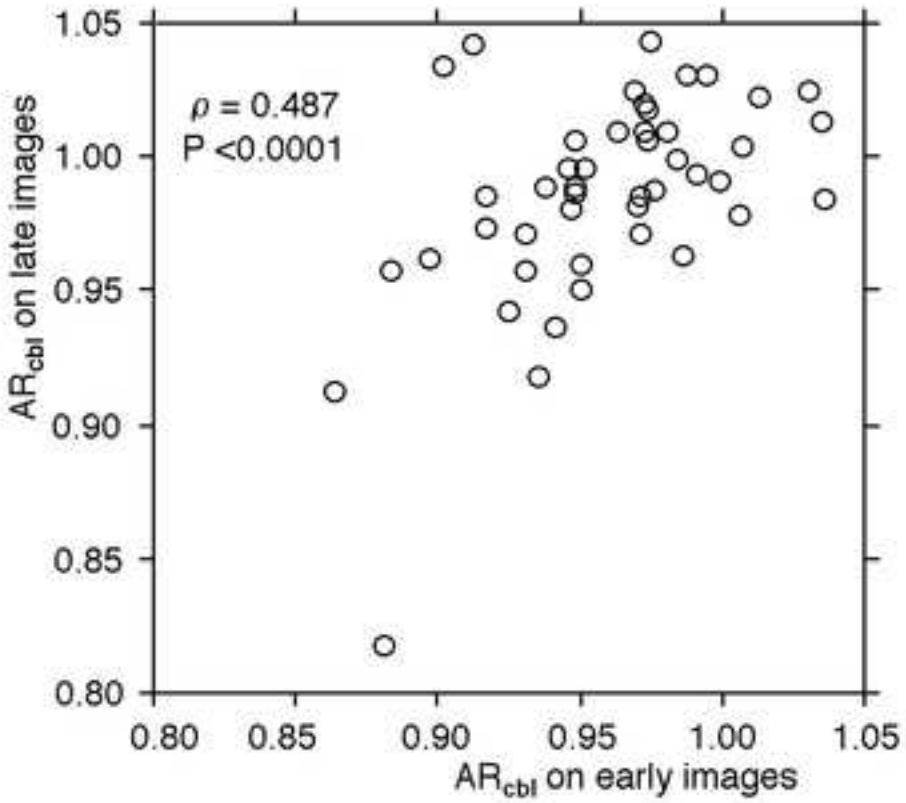

Figure 3

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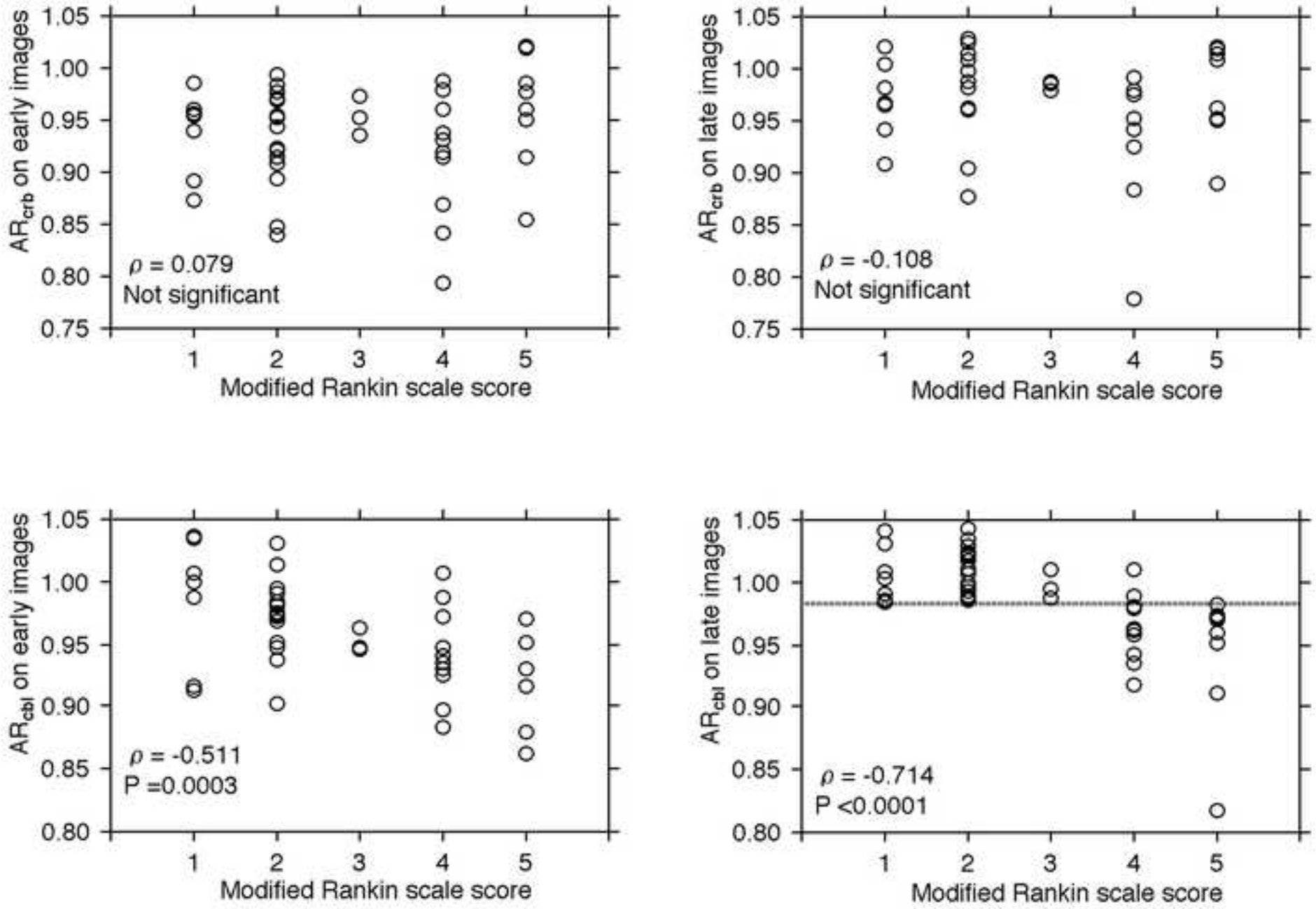

Figure 4

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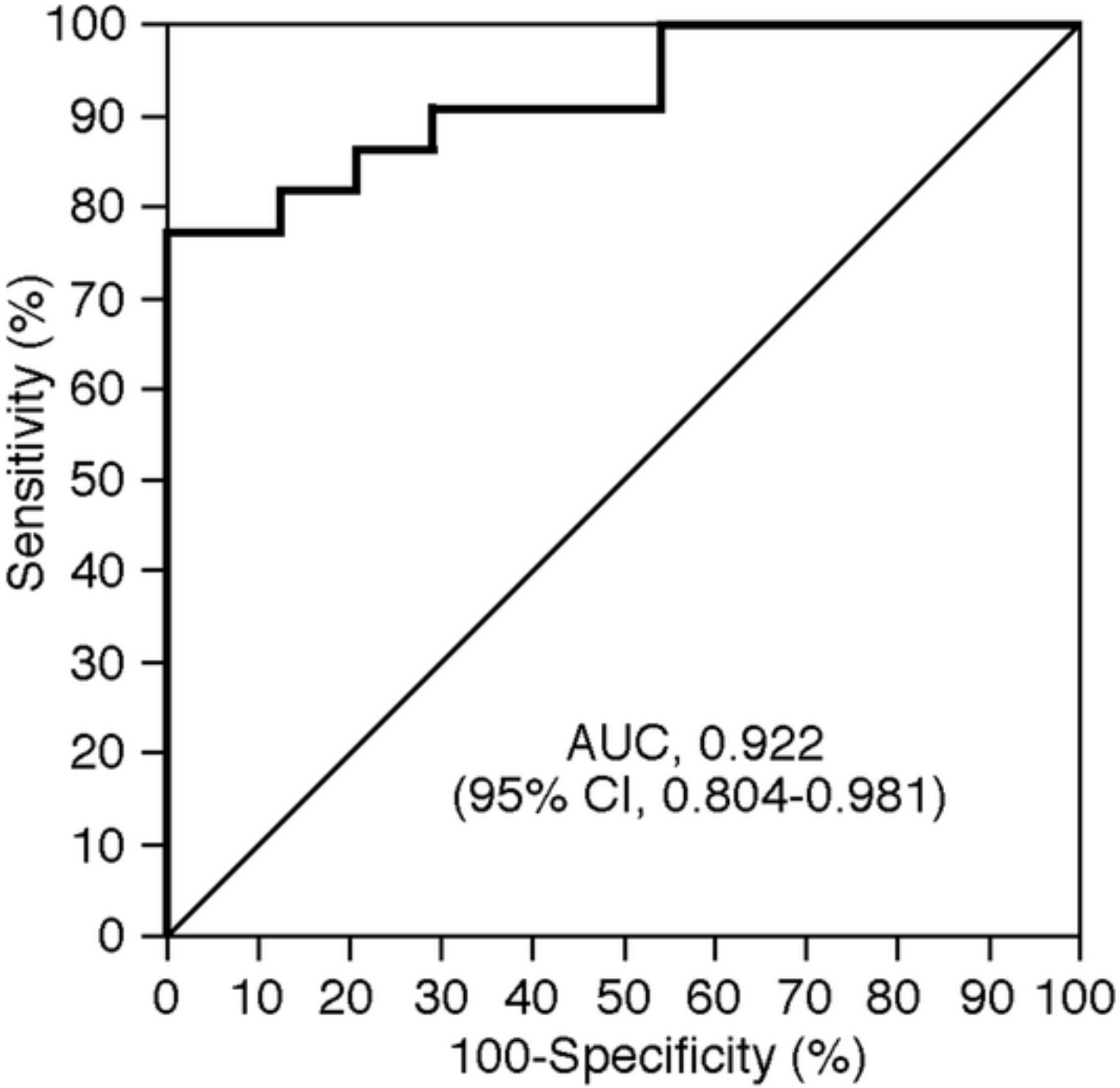

Figure 5

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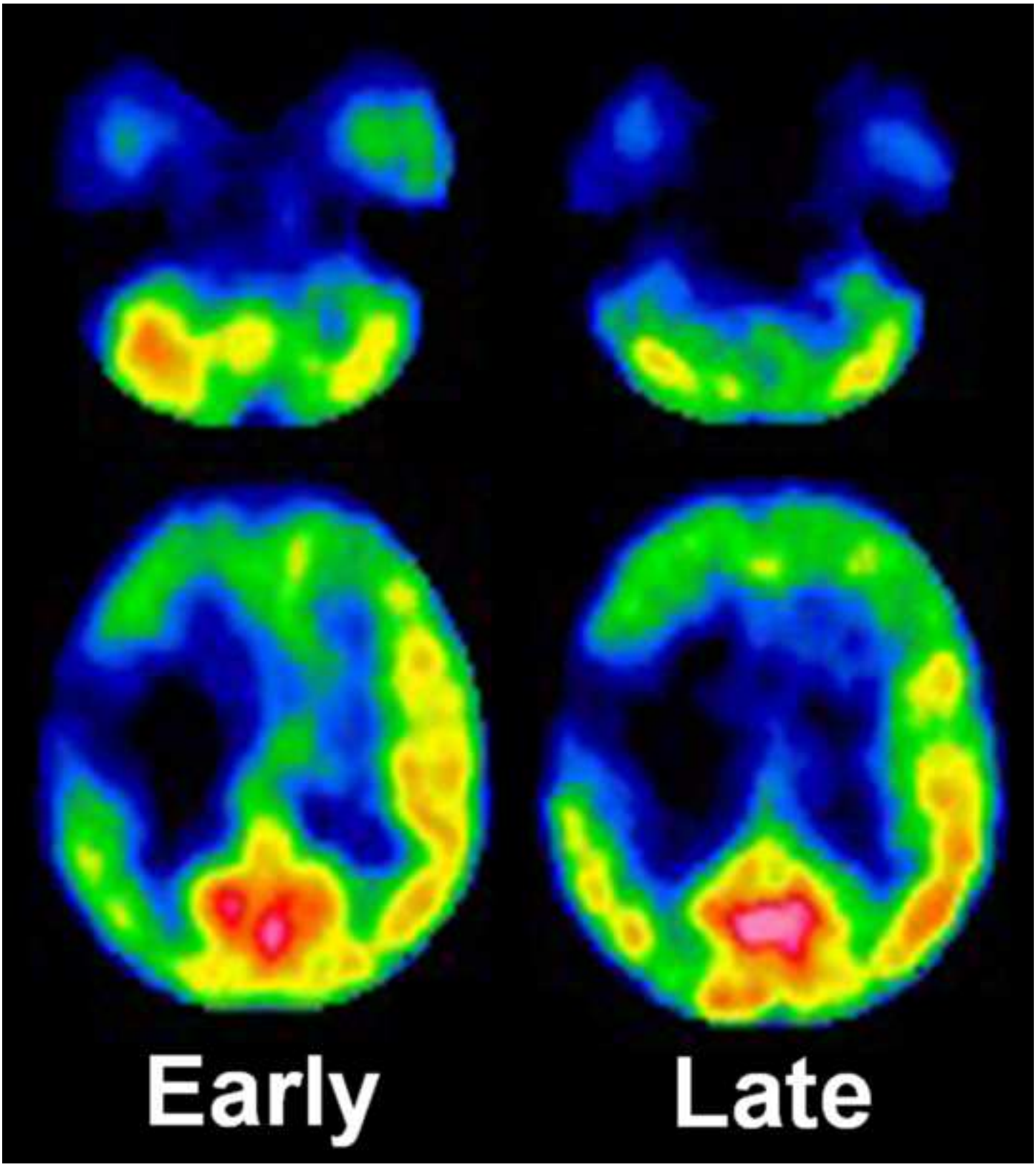

Figure 6

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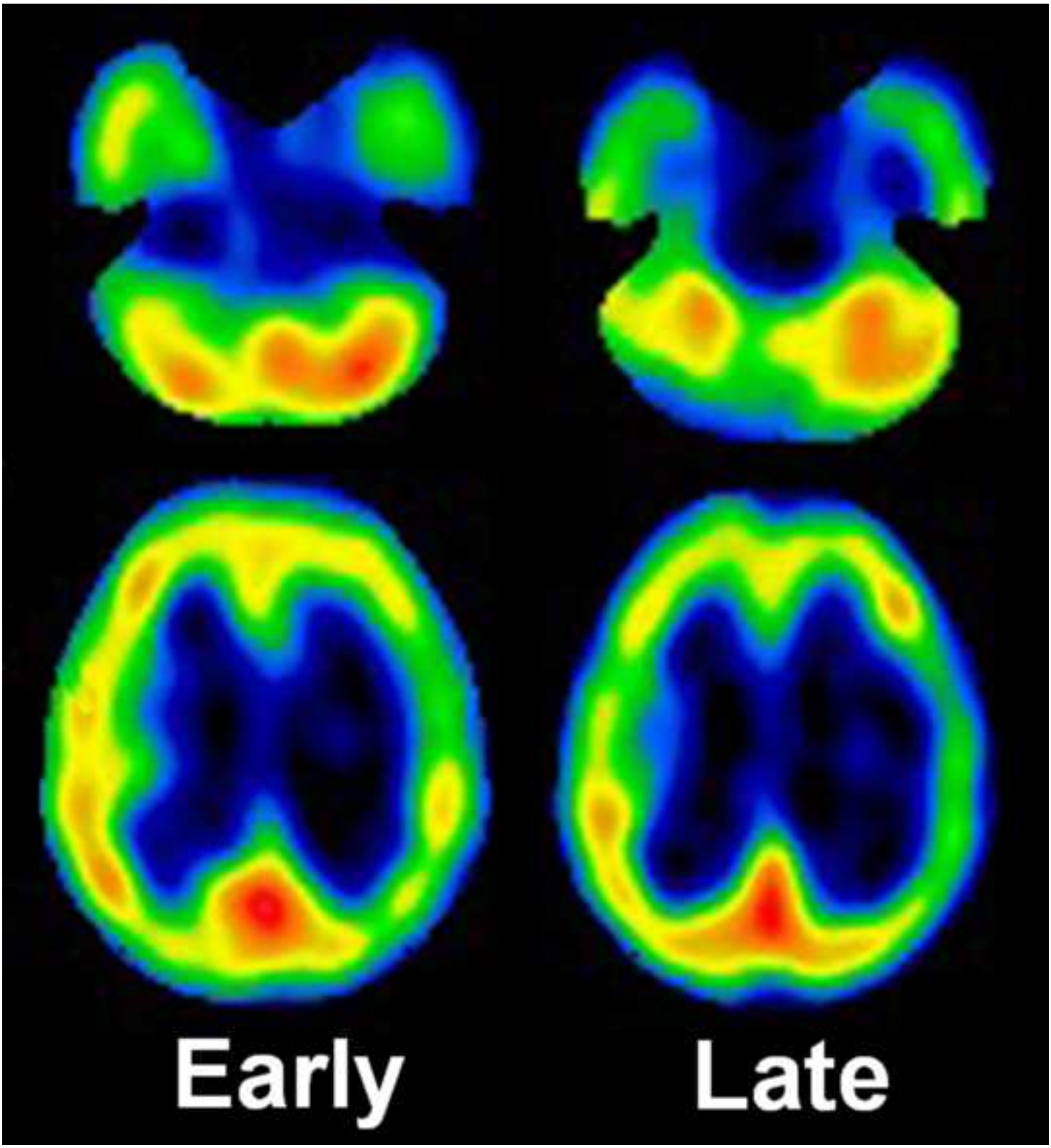

Table 1

Table 1 Factors related to the 3-month functional outcome in patients.

Factor	Univariate analysis			Multivariate analysis	
	Good outcome (n = 24)	Poor outcome (n = 22)	*P*	95% CI	*P*
Age (years)	60.2 ± 10.7	68.5 ± 8.9	0.0059	0.996 to 1.326	0.0561
Male gender	16 (67%)	15 (68%)	>0.9999		
Blood glucose at the time of hospitalization (mg/dl)	140 ± 45	147 ± 36	0.2861		
Left affected hemisphere	11 (46%)	8 (36%)	0.5616		
Thalamic hemorrhage	9 (38%)	11 (50%)	0.5525		
Hematoma volume (ml)	11.5 ± 10.4	18.3 ± 12.2	0.0275	0.845 to 1.122	0.7142
Intraventricular hemorrhage	1 (4%)	7 (32%)	0.0197	0.004 to 250.000	0.9657

Modified Rankin scale score immediately before SPECT	3.5 ± 1.0	4.5 ± 0.6	0.0004	0.458 to 111.111	0.1592
AR_{crb} in early image	0.936 ± 0.042	0.937 ± 0.057	0.8089		
AR_{cbl} in early image	0.977 ± 0.036	0.939 ± 0.035	0.0006	0.001 to 1964.262	0.7060
AR_{crb} in late image	0.976 ±0.038	0.958 ± 0.055	0.1945	0.001 to 3910.833	0.6524
AR_{cbl} in late image	1.010 ± 0.019	0.960 ± 0.041	<0.0001	0.001 to 0.003	0.0212

CI, confidence interval; SPECT, single photon emission computed tomography; AR_{crb}, asymmetry ratio in the cerebral hemispheric region of interest; AR_{cbl}, asymmetry ratio in the cerebellar hemispheric region of interest.