

Original Article

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An MRI-Based Quantification for Correlation of Imaging Biomarker and Clinical Performance in Chronic Phase of Carbon Monoxide Poisoning

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Purpose: The purpose of this study was to determine the relation between quantitative magnetic resonance imaging biomarkers, and clinical performances in chronic phase of carbon monoxide intoxication.

Materials and Methods: Eighteen magnetic resonance scans and cognitive evaluations were performed, on patients with carbon monoxide intoxication in chronic phase. Apparent diffusion coefficient (ADC) ratios of affected versus unaffected centrum semiovale, and corpus callosum were obtained. Signal intensity (SI) ratios between affected centrum semiovale, and normal pons in T2-FLAIR (fluid-attenuated inversion recovery) images were obtained. The Mini-Mental State Exam, and clinical outcome scores were assessed. Correlation coefficients were calculated, between MRI and clinical markers. Patients were further classified into poor-outcome and good-outcome groups based on clinical performance, and imaging parameters were compared. T2-SI ratio of centrum semiovale was compared, with that of 18 sex-matched and age-matched controls.

Results: T2-SI ratio of centrum semiovale was significantly higher in the poor-outcome group, than that in the good-outcome group and was strongly inversely correlated, with results from the Mini-Mental State Exam. ADC ratios of centrum semiovale were significantly lower in the poor outcome group than in the good outcome group, and were moderately correlated with the Mini-Mental State Exam score.

Conclusion: A higher T2-SI and a lower ratio of ADC values in the centrum semiovale, may indicate presence of more severe white matter injury and clinical impairment. T2-SI ratio and ADC values in the centrum semiovale, are useful quantitative imaging biomarkers for correlation with clinical performance in individuals with carbon monoxide intoxication.

Keywords: Carbon monoxide intoxication; MRI; MMSE

INTRODUCTION

Carbon monoxide (CO) poisoning is common, and, in the United States, ~50,000 patients annually visit the emergency department because of CO poisoning (1). Clinical symptoms of acute CO poisoning are non-specific, and patients can present a variety of symptoms such as headache or dizziness resulting from mild exposure, confusion, loss of consciousness, or even death, after severe exposure (2). Apart from acute symptoms of cerebral impairment after exposure to CO, delayed onset of neuropsychiatric symptoms has been reported in 10–30% of survivors, after three to 240 days of exposure. However, there are no clinical or laboratory results available to correlate occurrence of these complications (3).

Conventional MRI findings of CO poisoning, are well described. Most imaging findings of damaged brains from CO poisoning, are bilateral hyperintensities in the globus pallidus, periventricular white matter (WM), and centrum semiovale (CS) on T2-weighted images (4). Additionally, high signal intensity (SI) on DWI and low value on apparent diffusion coefficient (ADC) map in the globus pallidus in the acute phase, and in the cerebral WM in the acute through chronic phases following CO intoxication, have been demonstrated (5, 6). These neuroimaging findings were related to necrosis in the globus pallidus and demyelination in the cerebral WM, as documented in a report of autopsy findings by Lapresle and Fardeau (7, 8).

Several studies focused on using neuroimaging findings to predict clinical outcomes in patients with CO intoxication, have been performed; however, they have not shown consistent results. Chen et al. (9) reported that ADC values of globus pallidus and corpus callosum, correlated with multiple cognitive test scores. Chang et al. (10) described that extensive areas of decreased fractional anisotropy

in various regions of the WM tract were detectable after four to six months of hyperbaric-oxygen treatment, and correlated with cognitive deficits. In a study by McKinney et al. (11), conducted on four patients with CO intoxication and 28 patients with other various toxic causes of leukoencephalopathy, none of the imaging markers seemed to correlate with clinical outcomes. In a series of 21 individuals, significantly reduced total hippocampal volumes were observed in CO-poisoned patients, and overall neuropsychological impairment was correlated with hippocampal volume obtained from quantitative MRI (12). In a study by Parkinson et al. (13), WM hyperintensity in CS was significantly associated with cognitive impairment based on a four-point semiquantitative rating method, not on quantitative measurement.

Accordingly, we performed the current investigation in subacute and chronic phase to determine quantitative MRI biomarkers correlating the MRI markers of ADC value and T2-signal intensity ratios with clinical outcomes.

MATERIALS AND METHODS

Patient Enrollment

Patients recruited to this study were admitted to our hospital November 2011–March 2015. Entry criterion for this study, was clinical diagnosis of CO intoxication. CO intoxication was diagnosed based on clear evidence of exposure. We excluded patients in persistent vegetative state who would not be capable of undergoing cognitive evaluations, as well as those with previous history of brain disorders such as stroke, trauma, or demyelinating disease. We retrospectively reviewed 18 MR scans, and cognitive evaluations of 15 patients. There were nine men and nine women with mean age of 56.4 ± 15.7 (range: 34–79).

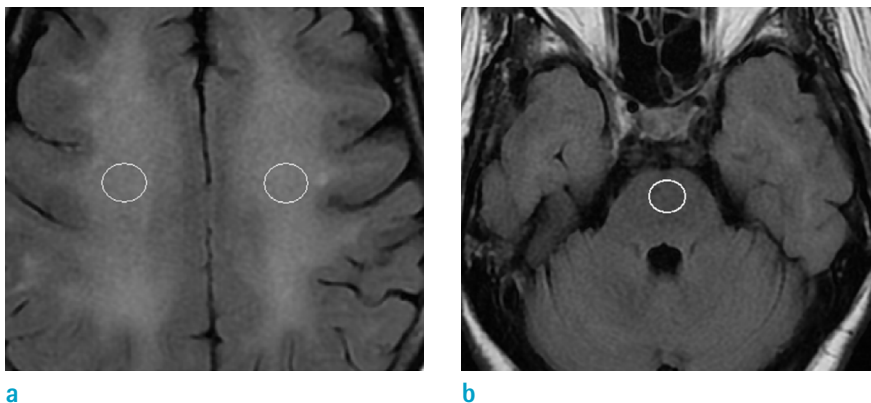


Fig. 1. Forty-eight-year-old male with CO intoxication. (a, b) Measurement of T2 signal intensity in CS (a) and normal appearing ventral pons (b). SI ratios between affected CS and normal pons on T2-FLAIR images are calculated.

Nine patients (50%) were accidentally exposed to CO, and eight patients (44%) attempted suicide. Classification of the clinical phase was based on elapsed time between CO exposure and MRI, as previously described: ultra-acute phase, within 24 hours; acute phase, between one and seven days; subacute phase, between eight and 21 days; chronic phase, from 22 days and thereafter (4). We classified both of subacute and chronic phase as early chronic phase, which covers all included patients in our study. Control subjects were selected from a normative database, and were age-matched and sex-matched with CO-exposed patients.

This study was approved by our Institutional Review Board.

MRI Acquisition

MRI was performed using 1.5T and 3T MR (Signa HDxt, GE Healthcare, Milwaukee, WI) for 7 and 11 patients, respectively. MRI parameters varied, with field strength. At 3T, conventional MR images were obtained with axial T2-weighted fast-spin echo (repetition time [TR]/echo time [TE] = 4000/105.2), axial fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time [TI]=9502/121.068/2250), and sagittal T1-weighted spin-echo (2578.92/12.824)

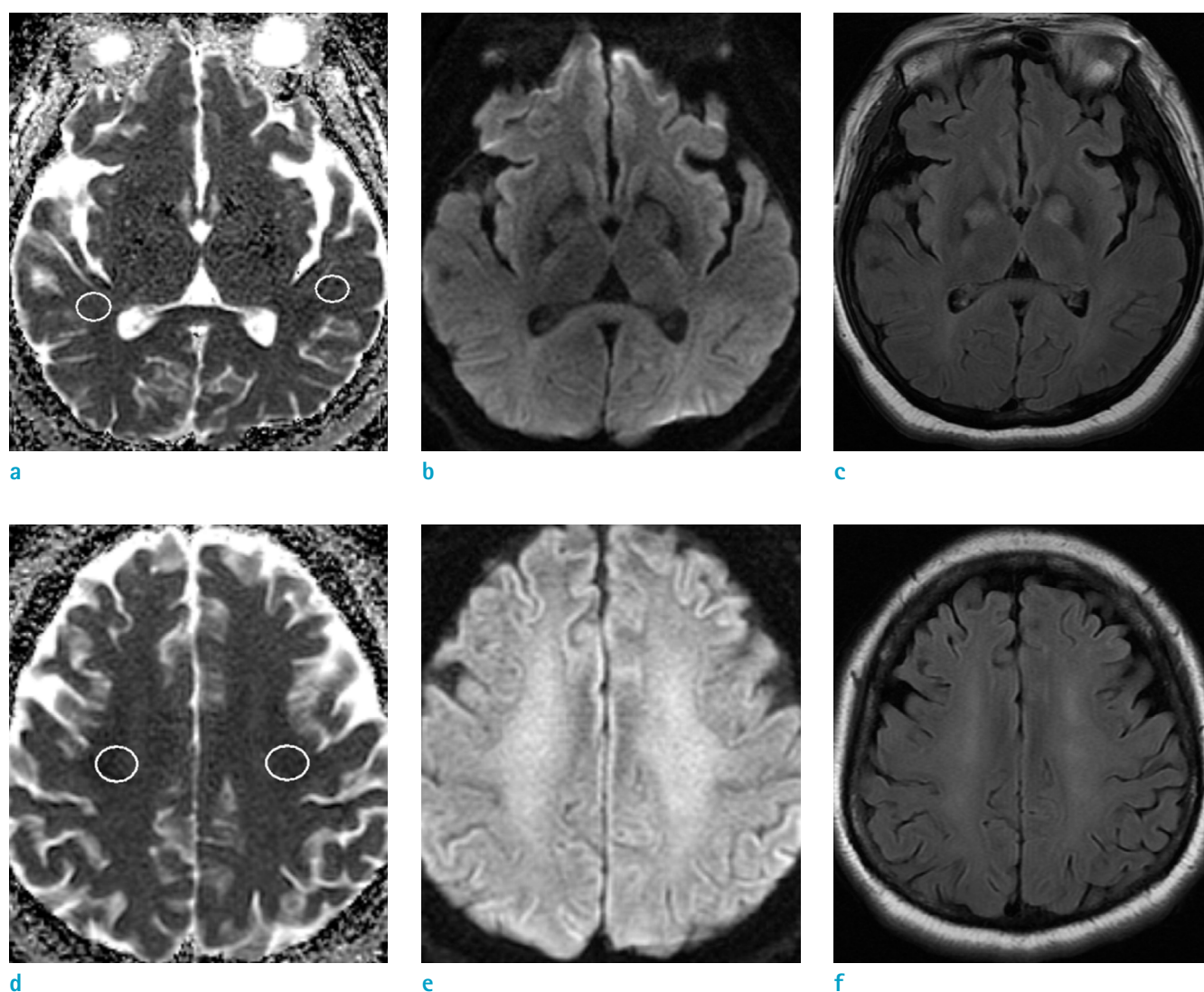


Fig. 2. Forty-one-year-old female with CO intoxication. (a–f) ADC map (a), DWI (b), T2-FLAIR image (c) at the level of temporal lobe and ADC map (d), DWI (e), T2-FLAIR image (f) at the level of CS. T2-FLAIR image (c) shows normal-looking peripheral WM. T2-FLAIR image (f) shows bilateral symmetric confluent areas of high SI, in the CS. ROIs are placed on the involved CS (d) and normal-looking peripheral WM (a) on ADC maps. Bilateral involvement of basal ganglia, is also noted. There is no discernable SI change, in the corpus callosum.

sequences. DWIs and ADC maps were obtained in the axial plane by using single-shot spin-echo echo-planar imaging sequence with the following parameters: TR/TE/number of excitations (NEX) of 8000/76.1/2, 192×192 matrix, 24×24 -cm² field of view, and 5-mm section thickness with a 6-mm gap. At 1.5T, conventional MR images were obtained with axial T2-weighted fast spin echo (TR/TE 4750/122.9), axial FLAIR (TR/TE/TI=8802/123.8/2200), and sagittal T1-weighted spin-echo (566.668/14) sequences. DWIs and ADC maps were obtained in the axial plane, by using single-shot spin-echo echo-planar imaging sequence with the following parameters: TR/TE/NEX of 8000/91.3/2, 128×160 matrix, 24×24 -cm² field of view, and 5-mm section thickness with a 6-mm gap. Diffusion gradients were applied, along three orthogonal directions. A b value of 1000 s/mm² was used.

Acquisition of T2-FLAIR SI Ratio

Two radiologists blinded to patient outcome, confirmed radiographic findings in 18 MR scans. Quantitative analysis of CS injury was conducted, with axial T2-FLAIR image and the average values were adopted. However, absolute signal intensity measurements possibly relied on the position of the head surface coil, and the amplifier gain of image reconstruction circuitry. So, we used normal appearing ventral pons as an internal standard, to minimize variations (14, 15). Finally, SI ratios between affected CS and normal pons on T2-FLAIR images were measured. Regions of interest were manually drawn, and the area of ROIs was

1 cm², in general (Fig. 1). The same procedures described above were conducted for 18 age-matched and sex-matched healthy subjects, *i.e.*, controls. Additionally, inter-observer reproducibility for assessment of T2-SI ratios was evaluated.

Acquisition of ADC Ratio

Fifteen MRI scans were reviewed, for measurement of ADC ratio in the CS and corpus callosum. 3 MRI scans were assessed on only T2-FLAIR images, not available for ADC map. Mean ADC values were calculated from affected CS, and compared with those of normal-looking peripheral WM on T2-FLAIR images (5). Measurements were performed bilaterally, and mean ADC ratios were calculated for statistical evaluation (Fig. 2). Additionally, mean ADC values were calculated from affected genu or splenium of corpus callosum, and compared with those of normal-looking corpus callosum on T2-FLAIR images. When no involved area was visible, ratio was assumed to be 1 (Fig. 3). ROIs were manually drawn on ADC maps using the corresponding FLAIR image as reference, and were 1 cm² for CS and 0.2 cm² for corpus callosum, respectively.

Inter-observer reproducibility for assessment of mean ADC ratios in CS and corpus callosum were evaluated.

Evaluations of Clinical Performances

Patients were subjected to the Mini-Mental State Examination (MMSE) at each MR scan, to evaluate general

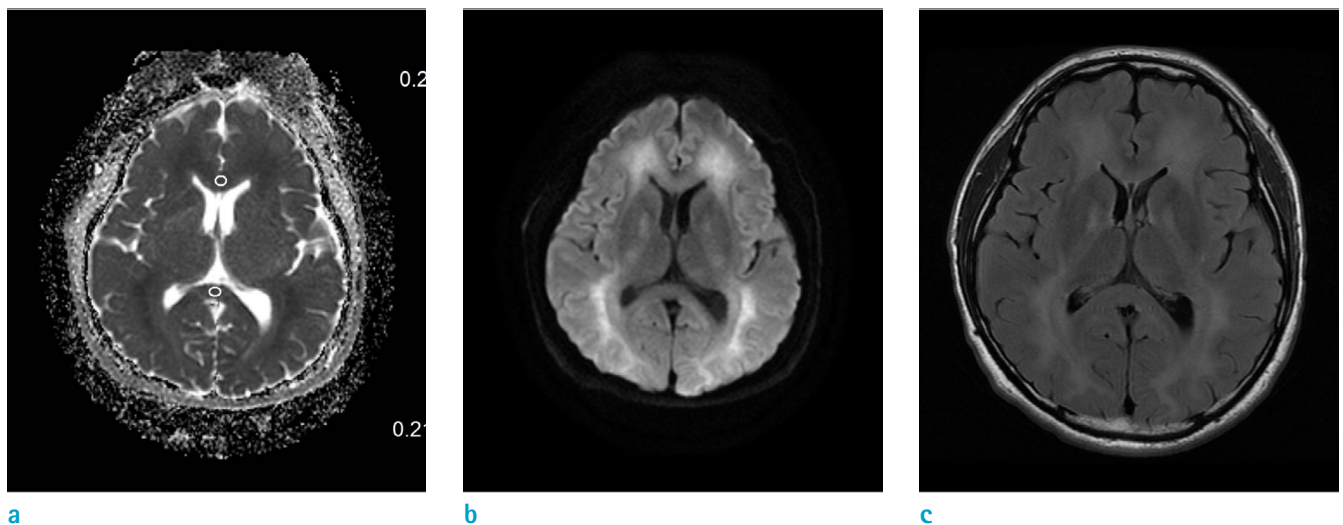


Fig. 3. Thirty-six-year-old male with CO intoxication, in poor-outcome group (28 days after CO exposure). (a–c) T2-FLAIR image (c) show high SI in genu of corpus callosum. ADC map (a) and DWI (b) show restricted diffusion in genu. To obtain mean ADC values, ROIs are placed on the genu and normal-looking area of splenium on ADC map, using T2-FLAIR image as reference.

cognitive function (16). We defined an MMSE score <10 as severe dementia and a poor outcome, and an MMSE score ≥ 10 as a good outcome (16). We reviewed the neurologic examination on the medical records at the furthest time-point after exposure to CO and MRI scans during hospitalization, and scored relative degree of improvement compared to the initial presentation. We adopted the scoring system of clinical outcomes used in literature, and

graded them on a scale of 0 to 4: 0, complete recovery; 1, minimal residual neurological deficit; 2, moderately improved; 3, mildly improved, and 4, not improved or coma (11). For analysis, we defined clinical outcome scores ≥ 3 as a poor outcome and ≤ 2 as a good outcome.

Table 1. Demographic and Clinical Characteristic of All Subjects

Variable	Total
By patient	
Age (year)	56.4 $\pm$ 15.7*
Sex, n (%)	
Male	9 (50)
Female	9 (50)
Status, n (%)	
Chronic	17 (94.4)
Subacute	1 (5.6)
Days to evaluation (day)	46 $\pm$ 48*
By lesion	
CS T2 ratio, median (IQR)	1.241 (1.092-1.323)
CS ADC ratio, median (IQR)	0.836 (0.740-1.091)
CC ADC ratio, median (IQR)	1.000 (0.859-1.000)
By clinical result	
MMSE score, median (IQR)	14 (8-19)
Clinical outcome score, median (IQR)	3 (1.25-3)

* Data are expressed as mean $\pm$ standard deviation.

ADC = apparent diffusion coefficient; CC = corpus callosum; CS = centrum semiovale; IQR = interquartile range; MMSE = Mini-Mental State Examination

Statistical Evaluation

Statistical analysis was conducted using the Statistical Package for Social Sciences software (version 13 for Windows, SPSS Inc., Chicago, IL, USA) and R (version 3.1.3, The R Foundation for Statistical Computing, Vienna, Austria). Spearman's rank correlation analysis was used to assess correlation of clinical performances with MR measurements, including ADC values and T2-SI ratios in CO-intoxicated patients. The Mann-Whitney U test was used, to compare continuous variables between groups. The Wilcoxon signed rank test was used, to assess differences in age and T2-SI ratios, and the Chi-square test was used, to assess sex-based differences between patients and controls. Statistical significance was established at the $P < 0.05$ level in all analyses.

Inter-observer agreement

Inter-observer reproducibility was evaluated by calculating the intra-class correlation coefficients (ICC), to assess T2-SI ratios, ADC ratios of CS, and ADC ratios of the corpus callosum. An excellent agreement was determined as an ICC > 0.8.

Table 2. Comparison of Characteristics Between Good and Poor Outcome Groups

Variable	Good (n = 10)	Poor (n = 7)	Comparison (P-value)
MRI measurements			
A. MMSE scores			
WM T2 ratio, median (IQR)	1.105* (1.069-1.177)	1.323* (1.317-1.398)	0.003
WM ADC ratio, median (IQR)	0.957* (0.836-1.126)	0.713* (0.692-0.778)	0.036
CC ADC ratio, median (IQR)	1.000 (0.822-1.000)	0.961 (0.902-1.000)	0.855
B. Clinical outcome scores			
WM T2 ratio, median (IQR)	1.131* (1.037-1.165)	1.312* (1.241-1.359)	0.044
WM ADC ratio, median (IQR)	1.007 (0.900-1.108)	0.795 (0.715-0.836)	0.224
CC ADC ratio, median (IQR)	1.000 (1.000-1.000)	0.922 (0.822-1.000)	0.361

Patients were classified into two groups on the basis of MMSE scores (A) and clinical outcome scores (B).

* $P < 0.05$

ADC = apparent diffusion coefficient; CC = corpus callosum; CS = centrum semiovale; IQR = interquartile range; MMSE = Mini-Mental State Examination; WM = white matter

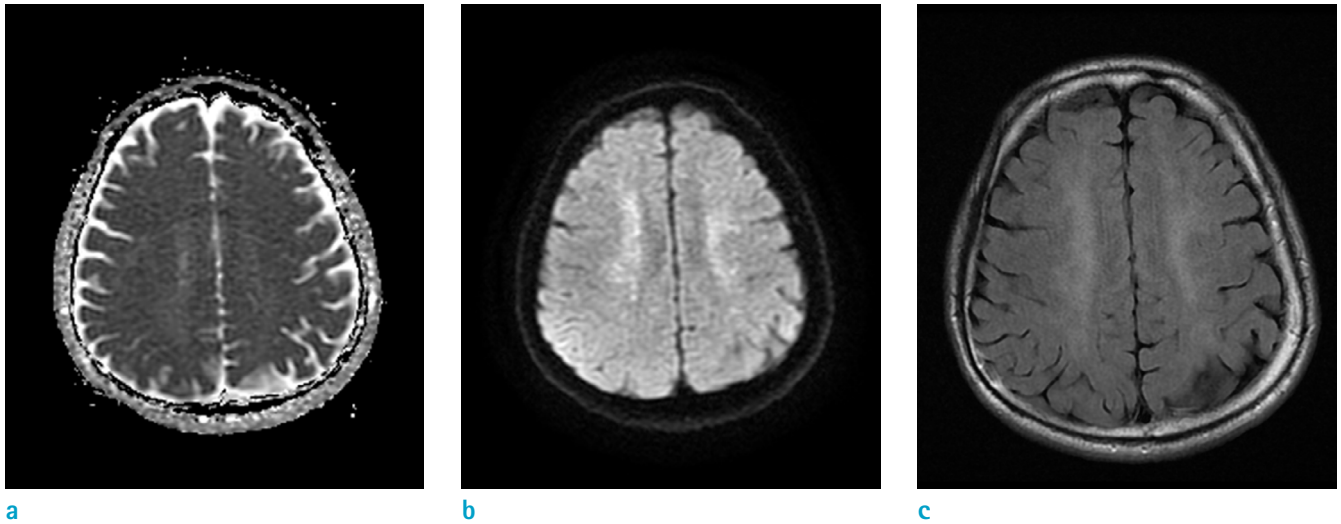


Fig. 4. Thirty-four-year-old male with CO intoxication in good-outcome group (52 days after CO exposure). ADC map (a) shows iso to slight hyperintensity, and T2-FLAIR image (c) and DWI (b) show hyperintensity in the bilateral CS.

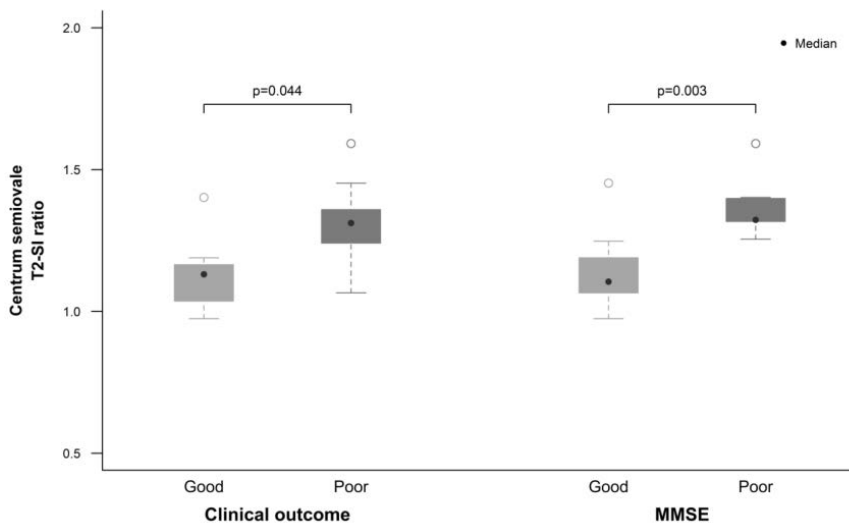


Fig. 5. Differences of mean T2-SI ratios in CS between good-outcome and the poor-outcome groups based on clinical outcome scoring and Mini-Mental State Examination.

RESULTS

Patient Characteristics

The patients' clinical features are summarized in Table 1. Supplemental Tables 1 and 2 show the patients' demographic data. MR images were obtained in subacute phase in one patient and in early chronic phase in the remaining patients. The mean time interval between exposure to CO and MRI acquisition was 46 ± 48 days.

Comparison of MR Parameters between Good-Outcome and the Poor-Outcome Groups

T2-SI ratios of CS and ADC ratios of CS and corpus

callosum were compared, between the good and the poor outcome groups. Figures 3 and 4 show MR images, of two representative cases from both groups. Table 2 shows ranges and means of ADC values, and T2-SI ratios for each group. ADC ratio of CS is significantly lower in the poor-outcome group, than in the good-outcome group, when patients are classified based on MMSE scores ($P = 0.036$), whereas no significant differences were found in ADC ratios of corpus callosum between the two groups. T2-SI ratio of CS is significantly higher in the poor-outcome group than in the good-outcome group, when patients are classified based on MMSE ($P = 0.003$) and clinical outcome scores ($P = 0.044$) (Fig. 5).

Correlation between MR parameters and clinical performance

Correlation between MR parameters and clinical performances in CO-poisoned patients are shown in Table 3. White matter hyperintensities in the CS, were found in all 18 MR scans. T2-SI ratio of CS showed a strong, inverse correlation with MMSE, representing general intellectual function ($r = -0.739$, $P = 0.004$). ADC ratio of CS had moderate correlation with MMSE ($r = 0.669$, $P = 0.032$). No significant correlation was found, between ADC ratio of the corpus callosum and all clinical parameters.

Comparison of MR Parameters between Patients and Control Groups

Table 4 shows ranges and means, of T2-SI ratios of CS for each group. There were no significant differences, in age and sex between the groups. T2-SI ratio of CS is significantly higher in the patient group, than in the control group ($P < 0.001$).

Inter-Observer Reproducibility

An excellent inter-observer agreement was observed, for assessment of T2-SI ratios (ICC: 0.963, 95% CI: 0.906 to 0.986), ADC ratios of CS (ICC: 0.979, 95% CI: 0.938 to 0.993), and ADC ratios of the corpus callosum (ICC: 0.993, 95% CI: 0.980-0.998) in patients.

DISCUSSION

Neuropathological hallmarks in CO intoxication are bilateral areas of necrosis in the globus pallidus and bilateral demyelination in the central WM, with sparing of subcortical arcuate U-fibers (7, 8). WM lesions seem to be produced, by relative ischemia superimposed on tissue hypoxia (7). Evolution of brain lesions, after CO

intoxication is also described. Within hours or days, cerebral edema and necrosis of globus pallidus and of substantia nigra are present. After days or weeks, edema usually disappears; however, changes related to degeneration and demyelination are usually present (17).

The most characteristic neuroradiological findings in CO poisoning are bilateral T2 hyperintensities in the globus pallidus and in cerebral WM in chronic phase, and may also show lesions in the corpus callosum (18). The most commonly involved WM regions in CO intoxication, are the periventricular WM and central semiovale (19). MR imaging shows diffuse and confluent hyperintensity on T2-weighted images and hypointensity on T1-weighted images, reflecting the demyelination process (19). WM demyelination is considered associated with delayed encephalopathy, and chronic symptoms arise predominantly from demyelination of white relative to gray matter (4, 5).

In our studies, we reviewed WM change based on quantitative measurement. T2-SI ratio of CS showed strong correlation with the cognitive test. Further, the poor-outcome group showed significantly higher T2-SI ratio of the CS, than the good-outcome group. These results can be explained by the hypothesis that increased signal intensity in the CS on T2-FLAIR images reflects more severe brain

Table 3. Correlation Between MRI Measurements and Clinical Performances

MRI measurement	Clinical performance	
	MMSE score	Clinical outcome
CS T2 ratio	-0.739* ($P = 0.004$)	0.538 ($P = 0.085$)
CS ADC ratio	0.669* ($P = 0.032$)	-0.456 ($P = 0.264$)
CC ADC ratio	0.266 ($P = 0.338$)	-0.419 ($P = 0.264$)

* $P < 0.05$

ADC = apparent diffusion coefficient; CC = corpus callosum; CS = centrum semiovale; IQR = interquartile range; MMSE = Mini-Mental State Examination

Table 4. Comparison of Characteristics Between Patient and Control Groups

Variable		Patient	Control	Comparison (P-value)
By patient				
Age, median (IQR)		54.5 (42.25-69.75)	54.5 (42.25-69.75)	0.281
Sex, n (%)	Male	9 (50)	11 (61.11)	0.737
	Female	9 (50)	7 (38.89)	
By lesion				
CS T2 ratio, median (IQR)		1.241 (1.092-1.323)	1.006 (0.947-1.046)	< 0.001

CS = centrum semiovale; IQR = interquartile range

injury and demyelination process, resulting in poor clinical prognosis. Our data are supported by several previous studies that reported WM hyperintensities in CO-poisoned patients, were closely related to prognosis (13, 20, 21). Parkinson et al. (13) studied 73 consecutive CO-poisoned patients, and found that hyperintensities in the CS, but not those in the periventricular WM, significantly correlated with cognitive measures in all clinical phases. In that study, semiquantitative measurement based on a 4-point rating was used, which showed only mild correlation when compared to our study.

Some studies have reported findings of DWI, in CO-poisoned patients in different clinical phases. Diffusion-weighted MRI is more useful for early identification of WM damage, than conventional MRI during the acute phase. In the ultra-acute or acute phase, areas of high SI on DWI and reduced ADC values were observed as early as 12 hours after exposure, reflecting restriction of mobility of water molecules and cytotoxic edema (22). Reduced ADC values were reported to be relatively persistent, indicating slowly progressive cytotoxic edema in the WM demyelination (5, 6). According to several studies of radiological findings on serial follow-up DWI in the subacute and chronic phases, reduction in ADC values was observed within three months after exposure followed by a slow increase (5, 23). From a pathological perspective, this sequence can be explained by changes from cytotoxic to vasogenic edema, destruction of cell membrane, and eventually cell necrosis, as in ischemic brain tissue (24).

Results of this study show that ADC ratio of CS, significantly correlated with cognitive function. Most of the MRI scans in our study were performed within three months, when progressive decline in ADC values was ongoing. So, we can speculate that the low ADC values in CS represent the severity of cytotoxic edema in WM demyelination, leading to poor prognosis. Results of our study are supported by a previous report in which the ADC map of a patient, who did not clinically improve and presented the lowest ADC value in the group, showed persistent low signal intensity after six months (5).

In this study, T2-SI and the ADC ratios of CS, are shown to be useful imaging markers in predicting clinical impairment. Also, there are some previous studies supporting our results and suggesting CS as a key region, responsible for chronic neurological symptoms (13, 25, 26). Fujiwara et al. (26) performed voxel-based analysis with diffusion tensor imaging, covering the whole brain in 22 patients in subacute phase (26). Among various regions, absolute

fraction anisotropy (FA) values in CS were significantly lower in patients displaying chronic neurological symptoms, than in asymptomatic patients or controls. Beppu et al. (25) investigated FA values in CS and major basic protein concentration in cerebrospinal fluid, from 26 patients in subacute phase. Mean FA values were significantly lower in patients displaying chronic neurological symptoms, and significantly correlated with major basic protein concentration. The authors speculated that, in their study, low FA value represents demyelination in the WM fibers in CS of patients presenting chronic symptoms.

Corpus callosum is the largest fiber bundle in the central nervous system and consists of topographically organized fibers, providing the main connection between corresponding regions in the two cerebral cortices (27). Porter et al. (18) found 15-mm² loss in the cross-sectional surface area of the corpus callosum between baseline and six-month follow-up MRI scans, although neuropsychological test results in that study did not correlate. A previous study reported gradual increment of ADC values of the corpus callosum during shifting of acute, delayed subacute, and chronic phases (9). The study observed inverse correlation between ADC values in the corpus callosum and MMSE, partly explained by reduced connectivity between different cortical regions. In our study, no significant correlation was observed between mean ADC values of corpus callosum, and clinical evaluations. Further, mean ADC values of corpus callosum did not differ significantly between good-outcome and poor-outcome groups. Use of different measurement methods of ADC values between the studies, may also explain the discrepancy. In our study, ADC ratios were used to reduce image-dependent factors; however, absolute mean ADC values had been used in a previous study (9).

There were several limitations in this study. First, because of the broad range of symptoms in CO-poisoned patients including motor impairment, cognitive dysfunction, or personality, comparison of MRI findings and clinical performances may be complex. Second, in our study, only patients with limited time interval of early chronic phase from CO exposure to MR scan were included and patients in acute phase of CO intoxication were omitted. Third, the individuals in this study were biased to severe cases referred to a tertiary center, and patients with subclinical CO intoxication may have not been included. In fact, WM hyperintensities were detected in all patients in our study. Fourth, only a limited cognitive test was performed; hence, cognitive dysfunction may have been underestimated.

Further studies are needed to investigate changes of ADC value and T2-SI in the CS, of patients with a wide severity of CO poisoning.

This is the first report to find high T2-SI in the CS, may indicate presence of more severe WM injury and clinical impairment. Further, ADC values in the CS in the chronic phases after CO exposure, significantly correlated with clinical performances, demonstrating severe cytotoxic edema and demyelination.

In conclusion, T2-SI and ADC values in the CS were found to be useful quantitative imaging biomarkers, in predicting clinical outcomes in individuals with CO poisoning, reflecting neurodegenerative changes in the brain.

Supplementary Material

Supplementary Table 1. Summary of All Patients: T2-SI ratio, Days to MR scans, Symptoms, and Clinical Results(<https://doi.org/10.13104/imri.2019.23.3.241>)

Supplementary Table 2. Summary of All Patients: ADC ratio, Days to MR scans, Symptoms, and Clinical Results(<https://doi.org/10.13104/imri.2019.23.3.241>)

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