# White-Matter Hyperintensities Predict Delirium After Cardiac Surgery

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**Objectives:** *Postoperative delirium is a common psychiatric disorder among patients who undergo cardiac surgery. Although several studies have investigated risk factors for delirium after cardiac surgery, the association between delirium and cerebral white-matter hyperintensities (WMH) on magnetic resonance (MR) imaging has not been previously studied. The aim of this study was to identify general risk factors for delirium, as well as to examine the specific relationship between WMH and delirium.* **Design:** *Retrospective chart review.* **Setting:** *University hospital.* **Participants:** *A total of 130 patients who underwent cardiac surgery.* **Measurements:** *Variables recorded included patient demographics, comorbidities, mental health, laboratory data, surgical information, and cerebrovascular disease. The presence of WMH was assessed using MR images. Two groups of patients were compared (patients with and without delirium) using both univariate and multiple logistic analyses.* **Results:** *Delirium occurred in 18 patients (13.8%) and patients with delirium were significantly older than patients who did not develop delirium. The prevalence of severe WMH (Fazekas score = 3) was significantly higher in patients with delirium. Three independent predictors of delirium were identified: abnormal creatinine (odds ratio [OR]: 4.5; 95% confidence interval [CI]: 1.4–13.9), severe WMH (OR: 3.9; 95% CI: 1.2–12.5), and duration of surgery (OR: 1.4; 95% CI: 1.0–1.8).* **Conclusions:** *The results of this study suggest that white-matter abnormality is one of the most important risk factors for development of delirium after cardiac surgery. These factors can be used for prediction and prevention of delirium following cardiac surgery.* (Am J Geriatr Psychiatry 2013; 21:938–945)

**Key Words:** Cardiac surgery, delirium, magnetic resonance imaging, white matter

Delirium is an acute state of confusion characterized by disturbed consciousness and cognitive dysfunction. Delirium is a complication of many physical disorders and is a common postoperative state, particularly among hospitalized patients.[1] The development of delirium after surgery has been associated with prolonged hospital stays, increased costs, and increased mortality.[2–4]

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As medical techniques continue to evolve, the patient population eligible for cardiac surgery will continue to expand to include even *older adults* and patients with other risk factors including hypertension, diabetes, heart failure, hyperlipidemia, severe angina, and emergent surgery.[5–7] These populations are particularly susceptible to the development of delirium in the postoperative period. Some studies have demonstrated beneficial effects of early pharmacologic intervention and intensive nursing care on the severity and duration of postoperative delirium.[8,9] Moreover, one study indicated that early pharmacological intervention reduced the number of days in the hospital.[8] Therefore, prevention or early recognition of delirium is an important goal.

Previous studies have demonstrated high rates of ischemic change in the brains of patients with cardiac disease.[10,11] Several studies have shown that white matter hyperintensities (WMH), identified on brain magnetic resonance (MR) imaging, represent cerebral ischemic change and neural degeneration.[12,13] In recent years, several researchers have suggested that WMH are related to mental disorders, such as cognitive dysfunction in older patients, and late-life depression.[14–19] Some of these studies suggest a relationship between WMH and specific cognitive deficits such as attention deficits, processing speed decrease, and executive function deficits.[15,16,18] Some other studies also suggest that WMH predict worse outcomes in patients with depression.[17,19] Although several studies have identified risk factors for delirium after cardiac surgery,[20–29] the association between delirium and cerebral WMH has not been thoroughly examined. Therefore, the hypothesis of this study is that WMH are associated with the development of delirium, with symptoms including both cognitive and emotional disturbance. The objectives of this study were to identify risk factors for postoperative delirium in patients who have undergone cardiac surgery and to examine the relationship between WMH and delirium.

## METHODS

### Participants

A total of 164 patients underwent cardiac surgery between April 2009 and March 2010 at Kyoto Prefectural University of Medicine (KPUM). To evaluate for the presence of cerebrovascular disease and to rule out organic brain diseases, cardiovascular department guidelines call for preoperative brain and carotid artery MR scans in all patients scheduled to undergo cardiac surgery. All MR scans were performed prior to surgery at KPUM. Among the 164 eligible patients, 29 were excluded because brain MR images were not obtained (19 patients did not undergo MR imaging due to acute admission and 10 patients had a previous brain MR from another institution). An additional five patients were excluded, namely, two patients with delirium before surgery, two patients who had undergone reoperation for graft repair, and one patient who died soon after surgery. The single patient who had a stroke after surgery was included in this study. Three patients with mental disorders such as mental retardation, epilepsy, and mild depression were also included in the analysis. In total, 130 participants who underwent cardiac surgery were analyzed using retrospective chart review. Patient characteristics (age, sex ratio, and type of surgery ratio) were not significantly different between patients who were included and excluded from this study (Appendix 1). The study was approved by the institutional review board at KPUM.

### Clinical Variables

Clinical and laboratory data were obtained from medical charts and, with the exception of MR image assessment, all variables were reviewed by HY (lead author). Potential risk factors for postoperative delirium were selected on the basis of previously published literature.[20–29] Risk factors assessed included patient demographics, comorbidities, mental health, laboratory profile both prior to and after surgery, type and duration of surgery, and cerebrovascular disease. In all patients, the presence of hypertension, hyperlipidemia, diabetes, atrial fibrillation, and arteriosclerosis obliterans was recorded. Mental health information included the presence of mental disease, a history of use of psychotropic medications, and/or use of anxiolytics, including benzodiazepines, zolpidem, and zopiclone. Other medications such as steroids, $H_2$ receptor antagonists, and hydroxyzine were also included. Body mass index was collected from the preoperative anesthesia record. The last preoperative and first postoperative laboratory values were used; these included the albumin level, hematocrit, blood urea nitrogen, and creatinine. Types of surgery were categorized as coronary artery bypass graft surgery (CABG), off-pump coronary artery bypass graft surgery (OPCAB, bypass surgery without the use of cardiopulmonary bypass), valve replacement/repair with/without CABG, and other. The "other" category included maze procedures with CABG, maze procedures with valve replacement/repair, ventricular septal defect closures, and Bentall procedures. Cerebrovascular disease was recorded using the presence of carotid artery stenosis, a prior stroke or transient ischemic attack, and degree of WMH. Carotid artery stenosis was defined as either moderate or severe stenosis and the degree of stenosis was diagnosed under blinded conditions by a trained radiologist (YK) using MR angiography.

### Delirium Assessment

The diagnosis of delirium was made from medical charts reviewed under blinded conditions by trained psychiatrists (Y. Hatano and Y. Hata). Mental status descriptions in the medical record were most often entered by the treating physician and/or primary nurse. However, mental status descriptions made by consulting psychiatrists were also reviewed. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* diagnostic criteria were used to define delirium.[30] Interrater reliability was calculated using intraclass correlation coefficients (ICCs). There was good reliability between raters for the assessment of delirium (ICC: 0.883; 95% CI: 0.835−0.917).

*Magnetic resonance.* All patients in this study were scanned using a 1.5 T whole-body scanner (Gyroscan Intera; Philips Healthcare, Best, the Netherlands). The routine brain imaging protocol at our institute requires 14 minutes and consists of T1-weighted images (repetition time: 611 ms; echo time: 13 ms), T2-weighted images (repetition time: 4754 ms; echo time: 100 ms), and fluid level-attenuated inversion recovery images (delay time: 2200 ms; repetition time: 8000 ms; echo time: 100 ms). Time-of-flight MR angiography (repetition time: 30 ms; echo time: 2.3 ms) is also routinely included in the protocol.

### MR Scan Analysis

MR images were randomized and assessed under blinded conditions by two authors (MT and TS) using T2-weighted images and fluid attenuated inversion recovery. WMH were assessed using the modified Fazekas criteria.[31] The Fazekas criteria describe WMH on MR imaging in three regions and follow an ascending degree of severity and frequency for hyperintensities. Deep white-matter hyperintensities (DWMH; 0: absent; 1: punctate foci; 2: initial confluence of foci; 3: large confluent area) and periventricular hyperintensities (PVH; 0: absent; 1: caps; 2: smooth halo; 3: irregular with extension into deep white matter) were assessed. Interrater reliability was calculated separately using ICCs. Interrater reliability calculations showed good agreement (DWMH ICC: 0.884; 95% CI: 0.836−0.918; PVH ICC: 0.882; 95% CI: 0.832−0.916).

Table 1 presents grades of baseline WMH in all 130 patients analyzed in this study. The results of this study demonstrated a 96.2% prevalence of DWMH and a 100% prevalence of PVH among participants. Indeed, 21.5% of patients had severe DWMH (n = 28) and severe PVH was found in 39.2% of patients (n = 51).

### Statistical Analysis

All variables were compared between two groups (patients with delirium and patients without delirium). Student's *t*-test was used for continuous variables, and the $\chi^2$ test was used for dichotomous variables. If an expected frequency was less than 5, Fisher's exact test was used for analysis. Variables that demonstrated a different prevalence between the two groups ($p < 0.1$) were entered into a logistic regression analysis. Continuous variables that demonstrated a nonlinear correlation with the presence or absence of delirium were converted into dichotomous variables. For example, creatinine was categorized as either normal (≤1.1 mg/dL) or abnormal (>1.1 mg/dL), and albumin was categorized as either normal (≥3.9 g/dL) or abnormal (<3.9 g/dL), based on local clinical guidelines from KPUM. Patient age was also dichotomized into two groups (age: <70 or ≥70 years) based on criteria suggested in previous studies.[20,26] Using the Fazekas score, DWMH and PVH were divided into two groups (severe: Fazekas score = 3; moderate or less: Fazekas score = 0−2). For a logistic regression analysis, a forward selection method (likelihood ratio) was used to determine the predictors of delirium. A p value of <0.05 was used to enter and eliminate variables. Goodness of fit was determined using the

TABLE 1. Baseline Grades of White-Matter Hyperintensities

| Fazekas Score | Delirium (n = 18) | Percent | No Delirium (n = 112) | Percent |
|---|---|---|---|---|
| Deep white-matter hyperintensities | | | | |
| 0 | 0 | 0.0 | 5 | 4.4 |
| 1 | 5 | 27.8 | 44 | 39.3 |
| 2 | 5 | 27.8 | 43 | 38.4 |
| 3 | 8 | 44.4 | 20 | 17.9 |
| Periventricular hyperintensities | | | | |
| 0 | 0 | 0.0 | 0 | 0.0 |
| 1 | 1 | 5.6 | 31 | 27.7 |
| 2 | 6 | 33.3 | 41 | 36.6 |
| 3 | 11 | 61.1 | 40 | 35.7 |

Hosmer−Lemeshow test. The capacity to distinguish between patients with and without delirium was estimated using the area under the receiver operating characteristic (ROC) curve. Statistical data were analyzed with SPSS version 19.0 (IBM, Armonk, NY). Fisher's exact test was performed in tables larger than $2 \times 2$ using R version 2.1 (http://www.r-project.org/).

## RESULTS

Demographic and medical characteristics of patients are shown in Table 2. The mean age of the patient population was 66.6 ± 10.9 years, with 41.5% of the population older than 70 years (n = 54). Eighty-nine (68.5%) patients were men. Fifty-seven patients (43.8%) underwent valve replacement or repair with or without CABG and 43 patients (33.1%) underwent OPCAB. Delirium occurred in 18 patients (13.8%).

The prevalence of delirium did not vary significantly among the four types of surgeries. Although there was no significant difference between patient groups, the average length of postoperative hospital stay in patients with delirium (35.4 ± 37.0 days) was longer than in patients without delirium (18.5 ± 7.5 days; p = 0.071). There were no patients with head injuries during the study period.

Results of univariate analysis comparing candidate predictor variables of delirium between patients with and without delirium are shown in Table 2. Patients with delirium were significantly older and patients with arteriosclerosis obliterans were significantly more likely to develop delirium. The prevalence of severe WMH was significantly higher in patients with delirium. Patients with delirium had a significantly higher prevalence of pre- and postoperative lower albumin and higher creatinine values. Patients whose surgical procedures were of a longer duration tended to develop delirium. To avoid confounding by multicollinearity, postoperative creatinine values that demonstrated a strong correlation with preoperative creatinine values (Spearman's $r = 0.83$; p <0.01) were excluded. There was also a high correlation between the DWMH Fazekas scores and the PVH Fazekas scores (Spearman's $r = 0.77$; p <0.01). Therefore, the DWMH Fazekas score was chosen for further analysis as the DWMH Fazekas score (p = 0.041) demonstrated better differentiation between groups (DWMH: p = 0.041; PVH: p = 0.026).

A multiple logistic analysis identified three independent predictors of postoperative delirium: abnormal creatinine (OR: 4.5; 95% CI: 1.4−13.9), severe DWMH (OR: 3.9; 95% CI: 1.2−12.5), and duration of surgery (OR: 1.4; 95% CI: 1.0−1.8) (Table 3). The Hosmer−Lemeshow test showed that the goodness of fit for the final prediction model containing these three factors was strong (p = 0.37; a high p value indicates better fit). The area under the ROC curve was also calculated using the model. The area under the curve was 0.82 (95% CI: 0.73−0.91; p <0.001).

## DISCUSSION

This study identified that severe DWMH predicts delirium after cardiac surgery. Other independent predictors of delirium were identified, including abnormal creatinine and duration of surgery. A final predictive model including these three predictors showed a high degree of reliability and the capacity to correctly classify patients into two groups: those with delirium and those without delirium.

WMH represent diffuse areas of brain white-matter loss associated with local increases in brain water

**TABLE 2. Univariate Analysis of All Candidate Predictor Variables**

| Characteristics | Delirium (n = 18) | | No Delirium (n = 112) | | p |
|---|---|---|---|---|---|
| **Age, mean (SD), years** | **71.3** | **(8.5)** | **65.9** | **(11.1)** | **0.05**[a] |
| **≥ 65 years** | **12** | **(67)** | **42** | **(38)** | **0.02**[b] |
| Sex, women, n (%) | 4 | (22) | 37 | (33) | 0.43[c] |
| Types of surgery, n (%) | | | | | 0.66[c] |
| CABG | 1 | (6) | 6 | (5) | |
| OPCAB | 4 | (22) | 39 | (35) | |
| Valve with or without CABG | 10 | (56) | 47 | (42) | |
| Other | 3 | (17) | 20 | (18) | |
| Psychotropic drug use, n (%) | 4 | (22) | 23 | (21) | 1.00[c] |
| Anxiolytic use, n (%) | 4 | (22) | 20 | (18) | 0.74[c] |
| Steroid (predonizolone), n (%) | 0 | (0) | 3 | (3) | 1.00[c] |
| Hydroxyzine, n (%) | 1 | (6) | 0 | (0) | 0.14[c] |
| $H_2$ receptor antagonist, n (%) | 2 | (17) | 20 | (83) | 0.74[c] |
| Hypertension, n (%) | 14 | (78) | 81 | (72) | 0.78[b] |
| Hyperlipidemia, n (%) | 9 | (50) | 54 | (48) | 0.89[b] |
| Diabetes mellitus, n (%) | 9 | (50) | 39 | (35) | 0.22[b] |
| Prior stroke/TIA, n (%) | 4 | (22) | 18 | (16) | 0.51[c] |
| Carotid artery stenosis, n (%) | 4 | (22) | 23 | (21) | 1.00[c] |
| **Arteriosclerosis obliterans, n (%)** | **3** | **(17)** | **4** | **(4)** | **0.06**[c] |
| Atrial fibrillation, n (%) | 6 | (33) | 19 | (17) | 0.11[b] |
| Preoperative infection, n (%) | 0 | (0) | 2 | (2) | 1.0[c] |
| Postoperative infection, n (%) | 2 | (11) | 3 | (3) | 0.14[c] |
| **Severe DWMH (Fazekas score 3), n (%)** | **8** | **(44)** | **20** | **(18)** | **0.03**[b] |
| **Severe PVH (Fazekas score 3), n (%)** | **11** | **(61)** | **40** | **(36)** | **0.04**[b] |
| Body mass index, mean (SD) | 22.6 | (3.9) | 22.4 | (3.3) | 0.82[a] |
| LVEF (%), mean (SD) | 58.8 | (14.9) | 61.8 | (11.1) | 0.31[a] |
| **Albumin <3.9 g/dL, n (%)** | **7** | **(39)** | **19** | **(17)** | **0.05**[b] |
| **Creatinine >1.1 mg/dL, n (%)** | **10** | **(56)** | **23** | **(21)** | **0.03**[b] |
| Hematocrit <36%, n (%) | 9 | (50) | 37 | (33) | 0.16[b] |
| Blood urea nitrogen (mg/dL), mean (SD) | 19.6 | (9.1) | 18.8 | (8.0) | 0.71[a] |
| **Albumin <3.9 g/dL (postoperative), n (%)** | **18** | **(100)** | **94** | **(84)** | **0.08**[b] |
| **Creatinine >1.1 mg/dL (postoperative), n (%)** | 7 | **(39)** | **16** | **(14)** | **0.02**[b] |
| Hematocrit <36% (postoperative), n (%) | 17 | (94) | 97 | (87) | 0.35[b] |
| Blood urea nitrogen (mg/dL) (postoperative) | 16.0 | (9.1) | 15.7 | (6.5) | 0.86[b] |
| **Duration of surgery, mean (SD), hour** | **8.3** | **(2.2)** | **6.7** | **(1.9)** | **0.001**[a] |

*Notes*: Boldface text/values indicate the variables that demonstrated a different prevalence between the two groups and p value was less than 0.1 ($p < 0.1$). CABG: coronary artery bypass graft surgery; DWMH: deep white-matter hyperintensities; LVEF: left ventricular ejection fraction; OPCAB: off-pump coronary artery bypass graft surgery; PVH: periventricular hyperintensities; TIA: transient ischemic attack.
[a]Student's *t*-test.
[b]Chi-square test.
[c]Fisher's exact test.

content.[12] WMH are commonly observed on brain MR images of elderly patients.[32,33] Several studies have demonstrated the association between WMH and vascular risk factors.[12,34,35] Recent studies have shown that the major factor in the pathogenesis of WMH is cerebral arteriosclerosis of the small vessels.[12] Several studies have suggested that patients with higher grades of WMH are more likely to develop psychiatric disorders such as depression or cognitive dysfunction.[14–19] However, little literature exists on the association between white-matter abnormalities and delirium. Recently, Shioiri et al.,[24] using a diffusion tensor imaging method, showed that abnormalities in several white-matter regions predisposed patients to delirium after cardiac surgery. However, the association between WMH and delirium was not mentioned. This study suggests the possibility that higher grades of WMH predispose patients to developing delirium through white-matter deterioration. The pathogenesis

**TABLE 3. Multiple Logistic Regression Analysis for Predictors of Postoperative Delirium**

| Variable | Odds Ratio | 95% CI | p |
|---|---|---|---|
| Creatinine >1.1 mg/dL | 4.5 | 1.4–13.9 | 0.01 |
| Severe DWMH (Fazekas score 3) | 3.9 | 1.2–12.5 | 0.02 |
| Duration of surgery, hour | 1.4 | 1.0–1.8 | 0.02 |

of postoperative delirium is associated with several etiologies.[1] Inflammatory response syndrome and hypermetabolism are induced by surgery under general anesthesia. The inflammatory response syndrome is known to stimulate macrophage enzymes and excess enzyme activity leads to oxidative stress, which can cause dysregulation of central neuronal function. Central nervous system resident cells react to the presence of peripheral immune signals, leading to the production of cytokines and other mediators in the brain. Neuroinflammation promotes a cholinergic deficit with associated imbalances in other neurotransmitters, including dopamine, serotonin, and norepinephrine.[36] Delirium develops via neurotransmitter dysfunction in several subcortical structures such as the amygdala and hippocampus, which are connected through basal ganglia-thalamo-cortical loops.[1]

A postmortem study showed that WMH correspond to heterogeneous pathologies with varying degrees of myelin attenuation, arteriolosclerosis, and gliosis.[13] These pathologic changes in white-matter pathways may be factors that induce delirium by promoting the vulnerability of the central nervous system.

Abnormal creatinine values and prolonged duration of surgery were also identified as predictive factors for the development of delirium, in agreement with previous studies.[22,27,29] Renal dysfunction frequently reflects the presence of several secondary diseases, including poorly controlled hypertension, hypoalbuminemia, and cerebrovascular disease.[29] These factors may contribute to developing delirium by impairing metabolism and promoting neuronal dysfunction. A prolonged duration of surgery has also been implicated as a risk factor for delirium.[22] During the intraoperative period, there are several potential factors (e.g., fluid balance, urine output, body temperature, anesthetic time, and time on cardiopulmonary bypass [CPB]) that may play a role in the development of delirium.[21] In particular, an association between prolonged duration of CPB and delirium has been shown.[22,29] However, in this study, the prevalence of delirium was not significantly different when the OPCAB group was compared with other surgical groups that required CPB (OPCAB: 9.3%; CPB: 16.1%; $p = 0.42$). The effects of prolonged anesthetic time on the potential for developing delirium are also controversial.[22] Further investigation is needed to identify specific intraoperative factors that predispose a patient to developing delirium.

There was a high prevalence of baseline WMH in patients in this study (Table 1). Greater than half of the included patients had white-matter lesions of moderate or severe hyperintensity (Fazekas score = 2 or 3). These results support other previous studies, which have indicated higher rates of ischemic changes in the brain of patients with cardiac disease than in people without cardiac disease.[10,11,32,33] In addition, recent studies have shown that patients with cardiac disease are more likely to have baseline cognitive impairment and the association between cerebral ischemic change and cognitive impairment has also been shown.[10,37] These results indicate that patients with cardiac disease have a tendency toward increased cerebral vulnerability, which leads to the development of neuropsychiatric complications, including cognitive dysfunction and delirium.

The results of this study must be viewed in light of its limitations. This study employed a retrospective analysis in which the quality of medical information depends on descriptions provided by treating physicians or nurses. Therefore, it is possible that the prevalence of delirium is underestimated in this study. No rating scales were used to assess delirium. However, the diagnosis of delirium and WMH assessments were conducted carefully by two blinded psychiatrists and the strength of the results are supported by the interrater reliability values, demonstrating a high degree of agreement. In terms of cognitive function, because of the retrospective design, we did not assess any rating of cognitive function and diagnosis of dementia. Several studies have suggested that cognitive impairment was one of the major risk factors for the development of delirium in older adults.[21,24] Therefore, a prospective study might be needed to examine the degree of effect of cognitive impairment on the development of delirium compared with other factors, including WMH.

In conclusion, severe DWMH was identified as a predictor for the development of delirium following cardiac surgery. Other predictors of delirium were abnormal creatinine values and duration of surgery. These factors can be used for prediction and prevention of delirium. In addition, this study identified a high baseline prevalence of WMH in patients with cardiac disease. Further prospective studies are needed to validate a clinical prediction rule based on the risk factors identified in this study. Future studies are also needed to investigate the pathogenesis of delirium using volumetric analysis of specific regions of WMH.

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**APPENDIX 1. Demographics of patients included and excluded**

| Characteristics | Included (n = 130) | | Excluded (n = 30) | | p |
|---|---|---|---|---|---|
| Age, (mean (SD), years | 66.6 | 10.9 | 64.3 | 14.3 | 0.32 |
| Sex, women, n (%) | 41 | (32) | 12 | (40) | 0.40 |
| Types of surgery, n (%) | | | | | 0.43 |
| CABG | 7 | (5) | 4 | (13) | |
| OPCAB | 43 | (33) | 8 | (27) | |
| Valve with or without CABG | 57 | (44) | 14 | (47) | |
| Other | 23 | (18) | 4 | (13) | |

*Notes*: CABG: coronary artery bypass graft surgery; OPCAB: off-pump coronary artery bypass graft surgery.