Clinically Optimal Neuropsychological Tests for Postoperative Cognitive Dysfunction in Heart Valve Surgeries

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Background: Postoperative cognitive dysfunction (POCD) is widely recognized and reported, but the lack of a uniform definition makes it difficult to evaluate its clinical impact. The aim of this study is to establish the optimal neuropsychological tests and definition of POCD relevant to clinical outcomes in heart valve surgeries.

Methods and Results: Between June 2015 and December 2019, 315 patients undergoing elective heart valve surgeries (age ≥65 years) were enrolled. The Mini-Mental Status Examination, Montreal Cognitive Assessment (MoCA), and the Trail Making Test A and B were performed to evaluate cognitive function. Clinical endpoints were defined as readmission and death. The postoperative readmission and death rate were 17% and 3% (54/315 and 8/315; follow-up 266–1,889 days). By multivariable Cox hazard analysis, Short Physical Performance Battery (adjusted hazard ratio [HR]: 0.84, 95% confidence interval [CI]: 0.49–0.98, P=0.001), MoCA change rate (adjusted HR: 0.64, 95% CI: 0.01–1.22, P=0.024), and intensive care unit stay (adjusted HR: 0.55%, 95% CI: 0.99–1.12, P=0.054) were detected as independent risk factors for combined events. The cutoff value was −12% in the change rate of MoCA.

Conclusions: MoCA was the only neuropsychological test that predicted the clinical impact on complex events and has the potential to define POCD.

Key Words: Cardiac surgery; Heart valve disease; Neuropsychological test; Postoperative cognitive dysfunction

In 1995 Bedford was the first to report cognitive disorder after surgery with general anesthesia at an incidence of 7%. Since then, postoperative cognitive dysfunction (POCD) has been widely recognized and reported. With advancements in both surgical techniques, such as minimally invasive surgery, and postoperative management, cardiac surgery is increasing being performed in elderly patients. During cardiac surgeries, hemodynamic instability and cardiopulmonary bypass increase the risk of POCD, and many studies have reported a high incidence of POCD (30–65%). As POCD has several adverse effects on quality of life (QOL) and leads to early readmission and death, focusing on the prevention of POCD would improve the outcomes of cardiac surgeries.

Surprisingly, there is no international definition and diagnostic criteria for POCD. In other studies, selected neuropsychological tests ranged from 1 to 16 tests. We have used multiple neuropsychological tests to evaluate POCD (the Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), Trail Making Test A and B, Grooved Pegboard, Rey Auditory Verbal Learning Test, Stroop Color Word Test, Digit Span, etc.) and different definitions (≥1 SD, ≥20% on ≥2 of tests, Z-score (sum) >1.96 SD). Because the lack of a uniform definition makes it difficult to evaluate the clinical effect of POCD, optimal tests and criteria are required for objective analysis. Based on this, we sought to establish the optimal neuropsychological tests and definition of POCD relevant to clinical outcomes in heart valve surgeries.

**Methods**

**Cohort and Data Collection**

There were 757 consecutive elective heart valve surgeries performed in patients aged ≥65 years between June 2015 and December 2019 at the Sakakibara Heart Institute of Okayama, Japan. Of them, 315 patients were enrolled. Age <65 years, emergency cases, concomitant aortic surgery (to avoid the influence of isolated cerebral perfusion and circulatory arrest), dialysis patients, patients diagnosed with delirium by CAM-ICU examination at the time of postoperative evaluation, and patients with postoperative
These tests were performed before and after surgery. Re-evaluation timing after surgery and the criteria for defining POCD differ across reports. Because POCD at 1 week after surgery has been reported as an independent risk factor of POCD at 1 year after surgery, we set the postoperative evaluation date as 5–7 days after returning from the intensive care unit (ICU) to the ward. All tests were completed on the same day by an occupational therapist, and all 4 of the pre- and postoperative studies were completed by all patients. Postoperative evaluations were all performed by the same evaluator.

Neuropsychological Examinations

There is no internationally determined evaluation of POCD. However, in 1995 a statement was issued regarding neuropsychological tests after cardiac surgery, and 4 tests, including the Trail Making Test, were proposed. Because preoperative cognitive decline is a risk for POCD, we added 4 other tests as follows.

**MMSE** The MMSE assesses 6 cognitive domains: memory, orientation, registration, attention, language, and visual construction ability. The maximum score is 30 and the recommended cutoff score for dementia is <24.

**MoCA** MoCA measures language, memory, attention, abstraction and orientation on a maximum of 30 points. A cutoff score <26 indicates mild cognitive impairment.

**Trail Making Tests (TMTs) A and B** The TMTs provide information on attention, processing speed, and execution functions; TMT-A is a line connecting 25 numbers on paper; TMT-B is a similar task except that the numbers and letters are drawn alternately (e.g., 1, A, 2, B, 3, C, etc.). The score for each part represents the time required to complete the task.

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Clinical Endpoints and Main Outcomes
Clinical endpoints were defined as readmission and death. Readmission and death after discharge (follow-up min. 266 to max. 1,889 days) were obtained from the medical records, and the cause of either was also investigated. The main purpose was to evaluate the influence of a change in cognitive function on readmission and death, and determine the optimal neuropsychological examinations with clinical impact.

Statistical Analysis
Continuous data are presented as mean±standard deviation. Categorical variables are given as a count and percentage of patients. The sensitivity and specificity of the postoperative rate of change in neuropsychological tests that affected readmission and death were calculated using receiver operating characteristic (ROC) curve analysis. A univariate Cox regression analysis was performed to independently detect the factors associated with readmission and death, followed by multivariate analysis using variables with P=0.10 in the univariate analysis. Survival analyses were performed using the Kaplan-Meier method. A P value of 0.05 was considered significant. All data were analyzed using the Statistical Analysis Systems software JMP 12.0 (SAS Institute Inc., Cary, NC, USA).

Results
Baseline Patients’ Characteristics and Operative Data
Preoperative patient characteristics and operative data are shown in Table 1. Mean age was 75±10 years, and 55% were female. The mean left ventricular ejection fraction was 65±12%. Single valve surgery was performed in 54% (171/315), double valve surgery in 22% (69/315), triple valve surgery in 3% (12/315), and concomitant coronary artery bypass grafting in 20% (63/315) of patients.

Preoperative Physical and Cognitive Function
Regarding preoperative physical function, SPPB was 11±1 and gait speed was 0.92±0.2 m/s. As for preoperative neuropsychological tests, MMSE, MoCA, TMT-A and TMT-B results were 26±3, 23±4, 147±73s and 227±110s, respectively.

Perioperative Data and Rehabilitation
There was no operative deaths. The mean intubation time and ICU stay were 12±15h and 3±1 days, respectively. The occurrence of acute kidney injury was 7% and of delirium was 15%. Regarding the rehabilitation course, the mean time to walking independence was 6±3 days and the postoperative hospital stay was 22±9 days (Table 2).

Changes in Postoperative Cognitive Function Tests
Postoperative cognitive function declined in 33%, 36%, 59% and 44% of patients on the MMSE, MoCA, TMT-A and -B tests; however, the change in the MMSE and MoCA was not significant (P=0.50 and 0.27, respectively). The parameters of the TMT-A were significantly increased (P=0.001) and those of TMT-B significantly decreased (P=0.007). Among the individual domains of MoCA, language, delayed memory, and orientation significantly declined (Supplementary Table). Changes in the respective cognitive function tests between patients with and without combined events are shown in Figure 2. MoCA significantly decreased in the group with adverse events.

Table 1. Baseline Characteristics of Preoperative Patients
<table>
<thead>
<tr>
<th>Variable</th>
<th>(n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>75±10</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>174 (55)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>215 (68)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>97 (30)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>131 (42)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>71 (23)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Respiratory dysfunction, n (%)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>Chronic kidney injury, n (%)</td>
<td>31 (10)</td>
</tr>
<tr>
<td>Orthopedic diseases, n (%)</td>
<td>51 (16)</td>
</tr>
<tr>
<td>Biochemical</td>
<td></td>
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<tr>
<td>Albumin (g/dL)</td>
<td>3.9±0.4</td>
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<tr>
<td>HbA1c (%)</td>
<td>5.9±0.6</td>
</tr>
<tr>
<td>Cre (mg/dL)</td>
<td>0.9±0.3</td>
</tr>
<tr>
<td>Operative data</td>
<td></td>
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<tr>
<td>Operation time (min)</td>
<td>398±80</td>
</tr>
<tr>
<td>Extracorporeal circulation time (min)</td>
<td>170±50</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>116±38</td>
</tr>
<tr>
<td>Bleeding (mL)</td>
<td>1,294±799</td>
</tr>
<tr>
<td>Blood transfusion (mL)</td>
<td>961±975</td>
</tr>
<tr>
<td>Total balance* (mL)</td>
<td>2,053±2,609</td>
</tr>
</tbody>
</table>

*Volume of fluids lost vs. infused.

Table 2. Perioperative Data and Rehabilitation Process
<table>
<thead>
<tr>
<th>Variable</th>
<th>(n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation time (h)</td>
<td>12±15</td>
</tr>
<tr>
<td>Intensive care unit stay (days)</td>
<td>3±1</td>
</tr>
<tr>
<td>Benzodiazepine use, n (%)</td>
<td>78 (25)</td>
</tr>
<tr>
<td>Acute kidney injury, n (%)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Delirium, n (%)</td>
<td>46 (15)</td>
</tr>
<tr>
<td>Sitting start (postoperative day)</td>
<td>1±0.8</td>
</tr>
<tr>
<td>Standing start (postoperative day)</td>
<td>2±1</td>
</tr>
<tr>
<td>Walking start (postoperative day)</td>
<td>3±1</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>22±9</td>
</tr>
</tbody>
</table>

Postoperative Data Including Readmission and Mortality
The readmission rate after surgery was 17% (54/315) and the causes included 21 heart failure, 7 stroke, 5 arrhythmia, 3 peripheral artery disease, 4 myocardial infarction, 1 infectious endocarditis, 3 wound infection, 3 gastrointestinal bleeding, and 7 falls. A total of 8 patients (3%) died after surgery, and causes were 4 heart failure, 1 stroke, 1 cancer and 2 sudden death.

Univariable and Multivariable Cox Hazard Analyses for Risk of Combined Events (Readmission and Mortality)
Univariable analysis detected diabetes mellitus, myocardial infarction, chronic kidney injury, ejection fraction, SPPB, MoCA rate of change, TMT-B rate of change, intubation time, ICU stay, benzodiazepine usage and delirium as risk...
The Kaplan-Meier model and the log-rank test revealed a significantly lower event-free ratio in patients with lower preoperative SPPB, lower postoperative MoCA and prolonged ICU stay (P=0.001, 0.001 and 0.023, respectively) (Figure 4).

**Discussion**

In terms of QOL after discharge from hospital, POCD is a serious complication with a long-term effect on patients and their families due to the loss of memory, decline in physical function and withdrawal from the workforce.\(^6\)\(^7\)
Postoperative Cognitive Dysfunction With Valve Surgery

Postoperative Cognitive Dysfunction With Valve Surgery

surgeries, POCD is primarily assessed after coronary artery bypass grafting (CABG) and postoperative assessment can be performed within a very short time (7 days), a short time (1–3 months) or long-term (1–5 years) after the procedure. Reported incidence rates of POCD are 37–71% in the very short term, 20–24% in the short term, and 10–47% in the long term after CABG.2–3,17–19

Various neurological symptoms have been reported as clinical manifestations of POCD. In particular, memory function, executive function, and brain processing speed are reduced.20 MoCA is a test that covers attention, memory, executive function and brain processing speed. In our study, the MoCA rate of change was an independent risk factor for combined events, and a decline in memory, orientation and language was observed in the comparison of the domains of MoCA before and after surgery. Generally, the clinical picture of POCD can be drawn from a patient’s MoCA score, so this test seems most appropriate as an evaluation of POCD.

Risk factors for combined events after discharge from hospital were preoperative physical function and MoCA rate of change, as well as length of ICU stay. It is also reported that a preoperative decline in physical function is associated with a 2- to 3.5-fold higher risk of lower 1-year

![Figure 3](image.png)  
**Figure 3.** Receiver operating characteristic curve analysis to detect the cutoff value for the Short Physical Performance battery (SPPB), Montreal Cognitive Assessment (MoCA), and intensive care unit (ICU) stay.

![Figure 4](image.png)  
**Figure 4.** Kaplan-Meier model for combined risk in the Short Physical Performance battery (SPPB), Montreal Cognitive Assessment (MoCA), and for intensive care unit (ICU) stay (days).

Therefore, it is very important to establish the risk factors of POCD to improve QOL after cardiac surgery. However, in previous studies there are wide differences in the definition, incidence rate and timing of assessment of POCD.

We explored the definition of POCD from combined events after valvular heart disease. Our main findings are as follows.

1) In the 4 cognitive tests, univariable analysis revealed the change rates of TMT-B and MoCA as influential factors for postoperative combined events, readmission and death.

2) By multivariable analysis, the SPPB and MoCA change rate, and ICU stay were detected as independent risk factors for combined events.

3) MoCA was the only neuropsychological test that predicted the clinical impact on complex events. The cutoff value for the MoCA change rate was a 12% decline from preoperative values.

After the risk factors of POCD of noncardiac surgeries were investigated in a multicenter study by Moller et al in 1998 (the International Study of Postoperative Cognitive Dysfunction: ISPOCD-1),11 several studies reported old age, low educational background, preoperative cognitive decline, and frailty as risks for POCD.10–16 Regarding cardiac surgeries, POCD is primarily assessed after coronary artery bypass grafting (CABG) and postoperative assessment can be performed within a very short time (7 days), a short time (1–3 months) or long-term (1–5 years) after the procedure. Reported incidence rates of POCD are 37–71% in the very short term, 20–24% in the short term, and 10–47% in the long term after CABG.2–3,17–19

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survival after cardiac surgery; and prolonged ICU stay can lead to a decline in both physical and mental function after discharge. Poor baseline physical function causes further decline in physical function after a long ICU stay, leading to a worse prognosis.

In our study, heart failure (38%) and falls (13%) were common causes of readmission and death. Inappropriate self-care and cognitive decline are reported as independent risk factors for readmission due to heart failure. Postoperative physical and cognitive decline may reduce self-care ability and affect post-discharge events. It has also been reported that decreased attention and executive function increases the risk of falls. In our study, we reported changes in cognitive function in patients undergoing valvular heart surgeries. We believe that elucidation of and intervention for POCD will contribute to improving the QOL of patients after hospital discharge. Additionally, MoCA appeared to be the clinically optimal neuropsychological test with clinical impact.

Study Limitations
First, the sample size was small and assessment of preoperative physical and cognitive function could not be performed for all patients. Second, postoperative cognitive tests could not be performed for all patients for various reasons (difficulty in completing the tests, refusal, stroke and delirium). Therefore, selection bias cannot be ruled out. Finally, 4 neuropsychological tests were administered, but as there is no internationally standardized testing, a different array of tests may deliver different results.

Conclusions
We investigated the effects of POCD on the readmission and death of patients after heart valve surgery. Its detection was significantly associated with increased readmission and death after discharge. We propose MoCA –12% as a definition of POCD with clinical impact.

Conflict of Interest / Funding Statement
None.

Disclosures
The authors declare that there are no conflicts of interest.

IRB Information
The study was approved by the Ethics Committee of the Sakakibara Heart Institute of Okayama (reference no. 20151102)

References