Establish a Nomogram of Cardiac Postoperative Cognitive Dysfunction

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ABSTRACT

Objectives: Cardiac postoperative cognitive dysfunction (c-POCD) is a common complication. This article established a nomogram by analyzing preoperative and intraoperative data to help identify high-risk patients and take effective management for prevention of c-POCD in early stage.

Measurements and main results: A total of 265 patients were enrolled in this study, 27 of whom were diagnosed as cardiac postoperative cognitive dysfunction (c-POCD). Patients were divided into a control group and c-POCD group. Univariate analysis suggested that gender, smoking, drinking history, hypertension, white blood cell (WBC) count, aspartate aminotransferase (AST), high-sensitivity troponin (hs-CRP), arrhythmia, left atrial diameter (LAD), cardiopulmonary bypass (CPB) time, and the ascending aortic block (AAB) time were correlated with postoperative cognitive dysfunction after cardiac surgery. Multivariate regression analysis indicated that CPB time ($P=0.0015$, OR (95% CI) = 6.696 (2.068-21.673), hypertension ($P=0.0098$, OR (95% CI) = 3.776 (1.377-10.356), WBC count ($P=0.0227$, OR (95% CI) = 3.358 (1.184-9.522), AST ($P=0.0128$, OR (95% CI) = 3.966 (1.340-11.735), and arrhythmia ($P=0.0017$, OR (95% CI) = 5.164 (1.855-14.371) were the independent risk factors of cognitive dysfunction after cardiac surgery and used to establish a nomogram for clinical use. The initial C-index of the nomogram was 0.8182 and good calibration. Corrected C-index value of 0.793 was reached after internal validation. The area under ROC curve of this model was 0.8188 (95% CI: 0.7185-0.9190). The positive odds ratio (PLR) was 1.21 (95% CI: 1.1-1.3), and the negative odds ratio (NLR) was 0.18 (95% CI: 0.03-1.3).

Conclusion: This nomogram incorporating the CPB time, hypertension, WBC count, AST, and arrhythmia to predict the risk of c-POCD. The internal validation shows a good forecasting effect.

INTRODUCTION

Cardiac postoperative cognitive dysfunction (c-POCD) is receiving increasing attention, with an incidence of 13.5%-41.7% [Koster 2008; Mangusan 2015; Zhang 2015]. It always shows symptoms of alienation, anxiety, delirium, memory impairment, personality change, and changes in social integration capabilities. As a result, patients often do not cooperate in diagnosis and treatment, and the treatment is difficult to conduct. However, the etiology and pathogenesis of c-POCD are still unclear, and it may include surgery-, anesthesia- and patient-related factors [van Harten 2012]. Once cognitive dysfunction after cardiac surgery occurs, it is difficult to control and reverse, and the treatment effect often is unsatisfactory. Therefore, it is important to improve the identification and quantification of risk factors for c-POCD, as this will assist clinicians and patients in the decision-making process, when invasive procedures are planned.

Nomogram was introduced to oncology research by Kattan from Memorial Sloan-Kettering Cancer Center in 1998 to predict the recurrence rate after radical prostatectomy. Due to its simple and intuitive characteristics, nomogram now widely has been used in the prognostic analysis of various diseases [Jasonos 2008; Kawai 2015]. This article was a retrospective research to screen the risk factors for c-POCD and establish a nomogram to help identify high-risk patients early and then provide timely intervention.

PATIENTS AND MEASUREMENTS

A total of 265 patients who underwent routine open cardiac surgery [Yuan 2012; Di Tomasso 2015; Hessel 2015] in Fujian Medical University Affiliated First Quanzhou Hospital from January 2015 to January 2018 were enrolled in this study. Twenty-seven of these patients were diagnosed with cardiac postoperative cognitive dysfunction (c-POCD), and they were divided into a control group and an experimental group. Patients who underwent valve surgery and coronary artery bypass grafting (CABG) were included our research. Exclusion criteria: (1) non-routine open cardiac surgery; (2) clinical data missing; (3) perioperative cognitive dysfunction; (4) psychotropic drugs abuse and alcoholism; (5) suffer from mental illness or family history of mental illness. Data such as demographic, diseases, preoperative examinations, CPB time, and the ascending aortic block (AAB) time of the included patients were collected from medical records. (Table 1)

Assessment of cardiac postoperative cognitive function: This study refers to the Montreal Cognitive Assessment (MoCA) [Nasreddine 2005] and Mini-mental state (MMSE) [Folstein 1975] assessment scale to evaluate cardiac postoperative cognitive function from orientation, attention, memory, execution, language and visual-spatial functions. c-POCD...
| Variables            | Total (N = 265) | Normal (N = 238) | c-POCD (N = 27) | Z/\chi^2 | P-value |
|----------------------|-----------------|------------------|-----------------|----------|---------|
| Age, year            | 58.00(46.00-65.00) | 58.00(46.00-65.00) | 60.00(48.00-68.50) | -1.003   | 0.316   |
| Gender               |                 |                  |                 | 6.436a   | 0.011   |
| Male                 | 135(50.94%)     | 115(48.32%)      | 20(74.07%)      |          |         |
| Female               | 130(49.06%)     | 123(51.68%)      | 7(25.93%)       |          |         |
| BMI, kg/m^2          | 22.51(20.00-24.75) | 22.37(19.96-24.56) | 23.69(21.42-27.36) | -1.766   | 0.077   |
| Smoking history      |                 |                  |                 | 8.208a   | 0.004   |
| No                   | 182(68.68%)     | 170(71.43%)      | 12(44.44%)      |          |         |
| Yes                  | 83(31.32%)      | 68(28.57%)       | 15(55.56%)      |          |         |
| Drinking history     |                 |                  |                 | 7.586a   | 0.006   |
| No                   | 231(87.17%)     | 212(89.08%)      | 19(70.37%)      |          |         |
| Yes                  | 34(12.83%)      | 26(10.92%)       | 8(29.63%)       |          |         |
| Operation history    |                 |                  |                 | 1.054a   | 0.305   |
| No                   | 207(78.11%)     | 188(78.99%)      | 19(70.37%)      |          |         |
| Yes                  | 58(21.89%)      | 50(21.01%)       | 8(29.63%)       |          |         |
| Hypertension         |                 |                  |                 | 6.001a   | 0.014   |
| No                   | 174(65.66%)     | 162(68.07%)      | 12(44.44%)      |          |         |
| Yes                  | 91(34.34%)      | 76(31.93%)       | 15(55.56%)      |          |         |
| Diabetes             |                 |                  |                 | 0.18a    | 0.893   |
| No                   | 228(86.04%)     | 205(86.13%)      | 23(85.19%)      |          |         |
| Yes                  | 37(13.96%)      | 33(13.87%)       | 4(14.81%)       |          |         |
| Diagnosis            |                 |                  |                 | 5.485a   | 0.064   |
| CHD                  | 85(32.08%)      | 71(29.83%)       | 14(51.85%)      |          |         |
| Other                | 48(18.11%)      | 44(18.49%)       | 4(14.81%)       |          |         |
| CVD                  | 132(49.81%)     | 123(51.68%)      | 9(33.33%)       |          |         |
| ECG                  |                 |                  |                 | 12.055a  | 0.001   |
| No                   | 185(69.81%)     | 174(73.11%)      | 11(40.74%)      |          |         |
| SR                   | 80(30.19%)      | 64(26.89%)       | 16(59.26%)      |          |         |
| WBC, 10^9/L          | 7.06(5.82-9.11) | 6.91(5.73-8.78)  | 8.70(6.99-10.79) | -2.764   | 0.006   |
| Hb, 110-130 mg/L     | 131.00(117.00-140.00) | 131.00(118.00-141.00) | 130.00(115.50-139.50) | -0.323   | 0.746   |
| PLT, 10^9/L          | 214.00(169.00-258.00) | 214.00(168.00-261.00) | 213.00(187.00-238.50) | -0.062   | 0.950   |
| NEUT%, 40%-70%       | 63.00(55.30-70.40) | 62.95(55.30-69.78) | 67.00(53.40-73.25) | -0.901   | 0.368   |
| ALT, 9-50U/L         | 21.00(17.00-31.00) | 21.00(16.00-29.00) | 34.00(20.00-45.50) | -3.023   | 0.003   |
| AST, 15-40U/L        | 23.00(17.00-31.00) | 22.50(16.00-30.00) | 27.00(18.50-46.50) | -2.189   | 0.029   |
| Creatinine, 44-138umol/L | 90.00(77.00-105.00) | 89.00(76.00-103.00) | 102.00(89.50-123.50) | -2.527   | 0.012   |
| hs-CRP, 0-3umol/L    | 4.00(1.36-6.60)  | 3.80(1.20-6.00)  | 4.70(3.10-20.26) | -2.228   | 0.026   |
| PT-INR, 0.82-1.15    | 1.05(1.00-1.13)  | 1.04(1.00-1.14)  | 1.07(1.02-1.11)  | -0.567   | 0.570   |
| N-BNP, 0-125ng/L     | 730.30(276.30-2391.00) | 679.45(267.90-2297.00) | 1106.00(610.70-2592.00) | -1.286   | 0.198   |
| Thyroxine T3, 11.5-22.7nmol/L | 16.92(15.46-16.92) | 16.92(15.46-16.92) | 16.92(16.13-18.35) | -1.077   | 0.281   |
| LAD (< 30mm)         | 41.00(35.00-48.00) | 41.00(35.00-48.00) | 39.00(33.50-46.00) | -1.275   | 0.202   |
was diagnosed when any one of the symptoms occurs: (1) delirium; (2) language disorder; (3) persecuted delusion; (4) indifference; (5) memory disorder.

**Statistical analysis:** All statistical analyses were performed with SPSS (version 23.0) and R (Version 3.5.3; The R Foundation for Statistical Computing, Vienna, Austria) software. The measurement data were expressed as mean ± standard deviation (X±S), group t test was used for comparison among groups, and chi-square test was used for comparison of count data. Risk factor analysis: First, single factor analysis was used to screen out possible risk factors, then logistic multivariate regression analysis was used to screen out independent risk factors, and the “rms” package of R language was used to express the effect of the nomogram. All statistical tests were bilateral tests and were of statistical significance (P < 0.05).

**RESULTS**

The demographics of included patients: The postoperative cognitive function of 265 patients in this research was analyzed, and 27 patients were diagnosed c-POCD. Univariate analysis results showed that the patient's gender, smoking history, drinking history, hypertension, white blood cell count (WBC), aspartate aminotransferase (AST), high-sensitivity C-reactive protein (hs-CRP), International standard ratio of prothrombin time; N-BNP, N-terminal brain natriuretic peptide; LAD, left atrial diameter; LVD, left ventricular diameter; RVD, right ventricular diameter; LVEF, left ventricular ejection fraction; AAB, ascending aortic block.

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**DISCUSSION**

In 1955, Bedford proposed the concept of postoperative cognitive dysfunction. Postoperative cognitive dysfunction is also a common complication of cardiac surgery, which often results in patients not cooperating in treatment, the increase of postoperative mortality, extension of hospital stays, and waste of more medical resources. Therefore, early intervention is very important for high-risk patients [Gottesman 2010;
However, there is no prediction model to estimate the risk of c-POCD. This research established a nomogram, which has good predictive value. Compared with traditional prediction models, the nomogram is easier to be used by clinicians and also can achieve individualized predictions.

This research reported an occurrence probability of c-POCD of 10.18%, which is close to the probability reported in past research [Koster 2008; Mangusan 2015; Zhang 2015]. The etiology and pathogenesis of c-POCD are unclear so far and are closely related to preoperative, intraoperative, and surgical factors. General diagnosis and treatment methods often lead to delay in treatment. At present, it is believed that c-POCD is induced by surgery and anesthesia and is a kind of neurological hypofunction caused by the combined action of multiple factors, involving the disorders of central nervous system, endocrine, and immune systems [Bi 2014].

### Table 2. Univariate analysis between baseline characteristics and c-POCD

| Variables                  | Normal (N = 238) | c-POCD (N = 27) | B   | S.E.   | OR (95%CI)     | P-value |
|----------------------------|------------------|-----------------|-----|--------|----------------|---------|
| Age (>58 y)                | 117 (49.16%)     | 15 (55.56%)     | 0.257 | 0.408  | 1.293 (0.581-2.878) | 0.5296 |
| Gender, Female             | 123 (51.68%)     | 7 (25.93%)      | 1.117 | 0.458  | 3.056 (1.246-7.497) | 0.0147 |
| BMI (>22.5)                | 116 (48.74%)     | 16 (59.26%)     | 0.425 | 0.413  | 1.530 (0.681-3.434) | 0.3028 |
| Smoking (yes)              | 68 (28.57%)      | 15 (55.56%)     | 1.139 | 0.413  | 3.125 (1.391-7.021) | 0.0058 |
| Drinking (yes)             | 26 (10.92%)      | 8 (29.63%)      | 1.233 | 0.470  | 3.433 (1.367-8.623) | 0.0087 |
| Operation history (yes)    | 50 (21.01%)      | 8 (29.63%)      | 0.459 | 0.451  | 1.583 (0.655-3.828) | 0.3078 |
| Hypertension (yes)         | 76 (31.93%)      | 16 (59.26%)     | 0.980 | 0.411  | 2.664 (1.189-5.969) | 0.0172 |
| Diabetes (yes)             | 33 (13.87%)      | 4 (14.81%)      | 0.077 | 0.573  | 1.080 (0.351-3.323) | 0.8927 |
| Diagnosis                  | -                | -               | -   | -      | -              | -       |
| CHD                        | 71 (29.83%)      | 16 (55.56%)     | -   | -      | -              | 1       |
| CVD                        | 123 (51.68%)     | 9 (33.33%)      | 0.217 | 0.426  | 1.242 (0.364-4.238) | 0.7288 |
| Other                      | 44 (18.49%)      | 4 (14.81%)      | 0.991 | 0.452  | 2.695 (1.110-6.542) | 0.0285 |
| WBC, >9.5×10^9/L           | 47 (19.75%)      | 12 (44.44%)     | 1.179 | 0.420  | 3.251 (1.427-7.407) | 0.0050 |
| PLT, >125×10^9/L           | 14 (5.88%)       | 3 (11.11%)      | 0.693 | 0.671  | 2.000 (0.536-7.458) | 0.3020 |
| NEUT%, >70%                | 70 (29.41%)      | 11 (40.74%)     | 0.501 | 0.417  | 1.650 (0.729-3.734) | 0.2295 |
| ALT, >50U/L                | 18 (7.56%)       | 5 (18.52%)      | 1.022 | 0.553  | 2.778 (0.940-8.208) | 0.0646 |
| AST, >40U/L                | 24 (10.08%)      | 10 (37.04%)     | 1.657 | 0.453  | 5.245 (2.159-12.744) | 0.0003 |
| Creatinine, >133μmol/L     | 23 (9.66%)       | 5 (18.52%)      | 0.754 | 0.542  | 2.125 (0.735-6.144) | 0.1643 |
| hs-CRP, >3μmol/l           | 141 (59.24%)     | 20 (74.07%)     | 0.890 | 0.410  | 2.434 (1.090-5.437) | 0.0300 |
| PT-INR, >1.5               | 55 (23.11%)      | 4 (14.81%)      | -0.547 | 0.563  | 0.579 (0.192-1.745) | 0.3131 |
| N-BNP, >125ng/L            | 211 (88.66%)     | 24 (88.89%)     | 0.023 | 0.646  | 1.024 (0.289-3.628) | 0.9711 |
| Thyroxine T3, >22.7mmol/L  | 16 (6.72%)       | 4 (14.81%)      | 1.012 | 0.611  | 2.750 (0.831-9.105) | 0.0977 |

- c-POCD, cardiac postoperative cognitive dysfunction; BMI, body mass index; CHD, coronary atherosclerotic heart disease; Other, CHD + CVD; CVD, valvular heart disease; WBC, white blood cell count; Hb, Hemoglobin; PLT, platelet count; NEUT%, neutrophil percentage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein; PT-INR, International standard ratio of prothrombin time; N-BNP, N-terminal brain natriuretic peptide; LAD, left atrial diameter; LVD, left ventricular diameter; RVD, right ventricular diameter; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; AAB, ascending aortic block

Koster 2012].

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Univariate analysis found that age and diabetes history were of no statistical significance. However, many studies showed that age was a main risk factor for the occurrence of c-POCD [Canet 2003; Evered 2011; Gao 2005]. In addition, the research of Launer also showed that diabetes was associated with c-POCD [Launer 1993; Shaw 2003]. This may be due to the sample size not being large enough to detect weak statistical correlations.

Although gender, smoking history, drinking history, high-sensitivity troponin (hs-CRP), arrhythmia, left atrial diameter (LAD), and ascending aortic block (AAB) time were related to the c-POCD in univariate analysis, they were not statistically significant in multivariate regression analysis, so they were not included in the prediction model. The nomogram showed that the patients with longer CPB time, hypertension, arrhythmia, higher WBC count, and AST were more likely to have c-POCD.

CPB is a non-physiological process. It is common practice for the arterial pressure to be maintained at around 60 mmHg, which may disrupt cerebral autoregulation, particularly in patients with a history of hypertension, eventually leading to poor cerebral perfusion and oxygenation and c-POCD. At present, it is not possible to directly measure intraoperative cerebral blood flow or perfusion. Real-time assessment of regional (frontal) cortical oxygenation by near-infrared spectroscopy is promising technology, which offers a non-invasive method of assessing cerebral haemoglobin oxygen saturation, thereby giving an indication of the overall balance between oxygen delivery, requirements, and uptake. It thus has the potential to demonstrate untoward intraoperative consequences of off-pump surgery. Early work also suggests that the technique can be used to assess cerebral autoregulation [Brady 2010]. On the other hand, on-pump cardiac surgery induces a widespread systemic inflammatory response that is associated with c-POCD [Hudetz 2011], which ultimately leads to cognitive dysfunction [Kalman 2006; Wan 2007]. In addition, the permeability of the blood-brain barrier will increase under pathological conditions; the inflammatory factors can through the blood-brain barrier to result in c-POCD [Rasmussen 2006; Wan 2010]. Therefore, immune system modulation is required to further work, not only an anti-inflammatory one, such as the corticosteroid dexamethasone, but also by other agents that may exert beneficial effects on the balance between pro- and anti-inflammatory mediators, such as interleukin-6 or tumor necrosis factor-a, and interleukin-4 or interleukin-10, respectively.

In this article, arrhythmia is considered to be the strongest independent risk factor for cognitive dysfunction after cardiac surgery, particularly in atrial fibrillation and cognitive dysfunction after cardiac surgery. Its possible mechanisms mainly follow three aspects: First, abnormal fluctuating rhythm often leads to insufficient stroke volume, which leads to insufficient cerebral perfusion and c-POCD [Cacciato 2012]; second, the microthrombi in the atrium fall during the preoperative and intraoperative operations and block the cerebral microvessels, causing c-POCD [Richards 1997]; and third, the use of anticoagulant drugs before the operation can cause tiny hemorrhagic foci in the brain. Unfortunately, there currently are no effective measures to prevent the c-POCD of patients with arrhythmia [Wu 2016; Akoudad 2014]. Although in our study, AST is an independent risk factor for c-POCD, there is little past research. This may be because abnormal liver function often leads to slow metabolism of anesthetic drugs and eventually c-POCD [Bucak 2014; Silverstein 2007].

In addition, this research also found that the patients with hypertension had higher occurrence of c-POCD. This may be related to the cerebral ischemia caused by the decrease in the mean arterial pressure of the systemic circulation during the operation. The patient’s blood pressure is maintained at a high level for a long time, the perfusion pressure under CPB is low during operation, and patients with long-term hypertension have cerebral arteriosclerosis, poor vascular elasticity, and weakened autonomic regulation [Heyer 2002; Monk 2008], which will increase the risk of c-POCD.

There currently are no safe and effective interventions for c-POCD. Adequate preoperative education can significantly reduce the probability of cognitive dysfunction after surgery [Gao 2005]. In addition, correcting the inflammation and abnormal liver function before the operation also is of great significance for preventing cognitive dysfunction after cardiac surgery [Bi 2014].

**Table 3. Multivariate regression analysis screen independent risk factors of c-POCD**

| Variables            | B    | S.E.  | OR (95%CI)         | P-value |
|----------------------|------|-------|--------------------|---------|
| CPB time, >127min    | 1.901| 0.599 | 6.696 (2.068-21.675) | 0.0015  |
| Hypertension         | 1.329| 0.515 | 3.776 (1.377-10.356) | 0.0098  |
| AST, >40U/L          | 1.378| 0.554 | 3.966 (1.340-11.735) | 0.0128  |
| Arrhythmia           | 1.642| 0.522 | 5.164 (1.855-14.371) | 0.0017  |
| WBC, >9.5*10^9/L     | 1.211| 0.532 | 3.358 (1.184-9.522)  | 0.0227  |

c-POCD, cardiac postoperative cognitive dysfunction; CPB, cardiopulmonary bypass; AST, aspartate aminotransferase; WBC, white blood cell count

**LIMITATIONS**

There are several of limitations of this research. First, we only collected data from a single center, without a large sample. Second, this research is a retrospective analysis, and
many data cannot be further verified. Third, anesthesia-related factors are considered to be independent risk factors for c-POCD, but we have not been able to provide detailed anesthesia records. All in all, it requires multi-center, large-sample, and prospective study in the future.

CONCLUSION

In our research, CPB time, hypertension, arrhythmia, WBC, and AST level were independent risk factors for c-POCD. Based on these five factors, the nomogram established has higher accuracy in predicting c-POCD. Compared with the traditional prediction models, the nomogram is more intuitive and convenient for the clinicians.

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