

Evaluation of the Risk Factors for Postoperative Neurocognitive Disorder in Elderly Patients Following Coronary Artery Bypass Grafting.

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Research article

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Abstract

Background The incidence and risk factors of postoperative neurocognitive disorder (PND) following coronary artery bypass grafting (CABG) is still controversial. Exploring an effective and reliable predictor of PND is essential to the prevention of PND. This prospective observational study aimed to find the incidence rate as well as possible risk factors of PND in CABG.

Methods Patients who underwent CABG were included. A battery of neuropsychological tests was performed preoperatively and 7 days after surgery. We used the Z score to analyze and comprehensively evaluate PND. The clinical characteristics of the patients were recorded. The levels of TNF- α , IL-1 (interleukin-1), IL-6 (interleukin-6), S100 β , MDA (malondialdehyde) and T-AOC (total antioxidant capacity) were measured at different time points.

Results A total of 82 patients were enrolled in the study. The incidence of PND was 25.6% 7 days after surgery. Patients were divided into the control group (N = 61) and the PND group (N = 21). The average age of patients in the PND group was 68.1 years, which was 64 years in the control group ($P < 0.05$). The average years of education in the PND group were significantly shorter than those in the control group ($P < 0.05$). The serum levels of IL-6, MDA, IL-1, and S100 β in the PND group were significantly lower than those in the control group 1 day after surgery, and the T-AOC level was higher than that in the control group ($P < 0.05$) 1 day after surgery. The concentration of S100 β in the PND group significantly higher than that in the control group 3 days after surgery ($P < 0.05$). Age, years of education, IL6, TAOC, MDA, IL1, and S100B were included in the multiple regression to search for risk factors of PND. The results showed that higher age (95%CI = 0.776–0.984, $P = 0.026$), lower years of education (95%CI = 1.006–1.736, $P = 0.045$) and higher MDA level (95%CI = 0.304–0.964, $P = 0.037$) were risk factors for PND.

Conclusions Older age, lower educational level and higher MDA might be risk factors for PND 7 days after surgery. More researches in the future on this field needs to be conducted to prevent PND effectively and timely.

Trail registration: The trail has been registered to the Chinese Clinical Trail Registry (ID: ChiCTR1800015606) on April 11, 2018.

Background

Postoperative neurocognitive disorder (PND) is a common neurological complication, manifested as attention deficit, memory loss, thinking disorder, and even personality disorder [1–3]. Previous research has shown that PND may be related to poor prognosis, including prolonged hospitalization rate and increased mortality rate [4]. PND usually lasts from a few days to a year after surgery. PND occurs in about 12% of patients receiving cardiac or non-cardiac treatment, mainly in patients older than 65 [5]. Patients with less education and preoperative cognitive impairment are easier to develop PND. Cognitive decline is more common in patients with heart disease. 60% patients are reported to have mild cognitive impairment (MCI) [6]. Cerebral embolism, systemic inflammatory response, and cerebral hypoperfusion

resulting from hypoxia are generally considered as potential factors for short-term PND after cardiac surgery [7–8].

Although several risk factors for PND have been identified, the pathophysiological mechanisms behind PND remain unclear. The diagnosis of PND relies mainly on neuropsychological tests and lacks objective indicators. And there are no effective preventive measures and treatment methods for PND. Timely monitoring and early recognition of PND is of great significance to prevent and treat it. It is extremely urgent to find effective prevention methods and risk factors. In this study, all participants were diagnosed with coronary heart disease and underwent coronary artery bypass grafting (CABG). We collected perioperative clinical data of patients and biological indicators of the inflammatory response and oxidative stress response in the present study to find risk factors of PND.

Methods

This was an observational prospective cohort pilot study, which was approved by our Institutional Review Board and was registered by the Clinical Research Information Service (clinical trial registration number: ChiCTR1800015606). The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital affiliated to Capital Medical University. All patients received CABG from May 2018 to April 2019. All participants were informed of the study purpose and design and provided written consent before study enrolment. Patients who met all inclusion criteria and did not fall into any exclusion criteria were included in the study. Registered patients were asked to stay in close contact with the researchers. The inclusion criteria of the patients were: received CABG in Beijing Chao-Yang Hospital affiliated to Capital Medical University; aged 60–85 years old and with grade American society of anesthesiologists (ASA) classification I–II. The following patients were excluded: (1) those with a history of neurological diseases, mental illness or abnormal personality; (2) unable to communicate well, confused thinking, and failing to cooperate with investigators; (3) those with PND before operation; (4) those who need to take a sedative or depressive drugs during the perioperative period; (5) with central nervous system disease, psychological disease or long-term use of antidepressant drugs; (6) unable to effectively communicate with the researchers. 38 patients were excluded and 82 patients completed the study.

Anesthesia

All patients were fasting for 8 hours before the operation. The patients received oxygen supply with the Zeus anesthesia machine (Draeger, Germany) mask. Five lead electrocardiographs (ECG) and pulse oxygen saturation (SpO₂) were collected to monitor vital signs. Radial artery puncture and catheterization with local anesthesia were performed to monitoring invasive blood pressure. Induction: etomidate 0.1–0.3 mg/kg, sufentanil 1–2 µg/kg and rocuronium bromide 1 mg/kg. Ventilation with endotracheal intubation performed 5 to 10 minutes after induction with 8 mL/kg of tidal volume, the inspiratory-to-expiratory ratio of 2:1, and respiratory rate of 10–14 times/min. End-tidal carbon dioxide (ETCO₂) was maintained between 35–45 mmHg, propofol 3–8 mg.kg⁻¹.h⁻¹ was injected intravenously, bispectral

index (BIS) value was maintained at about between 40–60. A three-cavity central venous catheter was inserted through the right subclavian vein, and a swan-ganz floating catheter was inserted through the right internal jugular vein puncture to connect the vigilance heart output monitor (Edwards company, USA) and monitor the pulmonary arterial pressure and blood temperature. The operating room temperature 25–27°C, humidity 40–53%.

Data Collection

To measure TNF- α , IL-1 (interleukin-1), IL-6 (interleukin-6), S100 β , MDA (malondialdehyde) and T-AOC (total antioxidant capacity) levels, 5 mL venous blood samples were obtained at four time points: 5 min before operation (T_0), end of surgery (T_1), the first day after surgery (T_2), the third day after surgery (T_3). Plasma was separated by centrifugation at 3000 rpm for 10 min and stored at – 80 °C for further analysis.

Medical And Demographic Characteristics Of Patients

The clinical characteristics of the patients were recorded, including age, sex, height, weight, education years, preoperative diagnosis, ASA classification, intraoperative bleeding volume and urinary volume, operation time, the time from the end of surgery to extubation and the days of the intensive care unit (ICU).

Neuropsychological Assessment

According to the criteria that were used in the ISPOCD1 and ISPOCD2 studies [9], we used a validated battery of 5 neuropsychological tests, including Hopkins verbal learning test (HVLT), trail making test A (TMTA), digit span test (DST), revised brief visuospatial memory test (BVMT-R) and digit symbol-coding test (DSCT), to assess global cognitive status, short-term and intermediate-term memory, attention, concentration, and psychomotor skills. One day before the surgical procedure (T_0), for every patient we asked the investigator to perform neuropsychological tests to assess him/her in a quiet room at 9 a.m. Neuropsychological tests were repeated on the 7th day after surgery (T_4) in the same standardized fashion. A battery of tests of approximately 40 min duration was administered by the investigator.

Diagnose Of Pnd

The diagnostic standard of PND is the Z-score method [10]. We calculate the Z-score as follows: we record the difference of the mean value of postoperative and preoperative scores in the control group and obtain the standard deviation (SD) of the score difference in the control group. For every patient, we calculate the difference between the patient's postoperative and preoperative values and then compare

with the mean score of the difference of the control group, then divide SD to obtain the Z-score. In this experiment, we use the critical value of 0.05. This suggests that if the Z-score is higher than 1.96 (two standard deviations), we conclude that the result is significant. If the Z-score of two or more tests is higher than 1.96, we can conclude that PNCD occurred to the patient.

Preparation Of Blood Samples

5 mL venous blood was collected at T_0 , T_1 , T_2 , and T_3 . The serum was prepared via centrifugation (Z 400; Hermle Labortechnik GmbH, Wehingen, Germany) at 3000 rpm for 10 min. The concentration of TNF- α , IL-6, IL-1, and S100 β were tested using an enzyme-linked immunosorbent assay (ELISA) method (Deyi Clinical Laboratory, Beijing, China) according to the manufacturer's instructions. The concentration of MDA and T-AOC was tested using a colorimetric method (Nanjing Jiancheng Bioengineering Institute, China).

Statistical analysis

Data management and statistical analyses were performed in SPSS Statistics software version 25 (IBM Corp., Armonk, New York, United States). The data were presented as means \pm standard error (SEM) for continuous variables if normally distributed, as median (minimum, maximum) if not, and as percentages (%) for categorical variables. Statistical differences between the two groups were obtained using the t-test or Wilcoxon rank-sum test, as appropriate for continuous data. The chi-square test or Fisher exact test was used for categorical data. A binary logistic regression analysis was conducted to assess which factors were significantly associated with PND. All P values were based on two-sided tests, and P values of < 0.05 were considered statistically significant. All participants provided written informed consent and ethical approval was provided by the local medical ethics committee of the Beijing Chaoyang Hospital, Capital Medical University.

Results

Diagnosis of PND

A total of 82 patients were enrolled in the study. According to the diagnostic criteria, 21 patients were diagnosed with PND 7 days after surgery. The incidence of PND was 25.6%. The patients were divided into the PND group ($N = 21$) and the control group ($N = 61$) according to the occurrence of PND.

Clinical Characteristics Of The Two Groups

Collection sheet where data is expressed either as mean \pm standard deviation or as Number of cases, percentage. As we can see in Table 1, The average age of patients in the PND group was 68.1 years, which was 64 years in the control group ($P < 0.05$). The average years of education in the PND group were

significantly shorter than those in the control group ($P < 0.05$). No significant differences between the two groups were found in terms of other clinical characteristics, including age, sex, height, weight, diagnosis preoperatively, classification of ASA, intraoperative bleeding volume, operation time, time from the end of surgery to extubation and ICU length of stay.

Table 1
Clinical characteristics of the two groups

	All(n = 82)	Controls(n = 61)	POCD(n = 21)	<i>P</i>
Age, years	65.4 ± 6.1	64.4 ± 5.6	68.1 ± 7.0	0.016
Male sex, no. (%)		45(73.8)	14(66.7)	0.532
Height (cm)	167.0 ± 6.9	167.9 ± 6.4	164.6 ± 7.9	0.057
Weight (kg)	71.1 ± 9.3	71.2 ± 9.3	70.7 ± 9.7	0.836
Education years	9.3 ± 2.8	9.7 ± 3.0	8.3 ± 2.1	0.049
Hypertensive patients, no. (%)	49(59.8)	37(60.7)	12(57.1)	0.777
Diabetic patients, no. (%)	35(42.7)	27(44.3)	8(38.1)	0.622
Diagnose, no. (%)				0.393
Unstable angina pectoris	60(73.2)	47(77.0)	13(61.9)	
Effort angina	5(6.1)	3(4.9)	2(9.5)	
Acute myocardial infarction	17(20.7)	11(18.0)	6(28.6)	
ASA				0.687
I	17(20.7)	12(19.7)	5(23.8)	
II	65(79.3)	49(80.3)	16(76.2)	
Intraoperative bleeding volume (mL)	489.0 ± 222.5	480.3 ± 240.7	514.3 ± 160.6	0.55
Intraoperative urinary volume (mL)	1251.8 ± 644.8	1423.0 ± 576.6	1535.7 ± 822.5	0.566
Icu length of stay (d)	6.8 ± 2.4	6.9 ± 2.6	6.4 ± 1.4	0.318
Time from end of surgery to extubation (h)	15.6 ± 3.4	15.4 ± 3.5	16.3 ± 3.1	0.283
Operation time (min)	238.0 ± 46.2	238.3 ± 47.0	237.4 ± 44.8	0.939
Note: ASA: American society of anesthesiologists; ICU: intensive care unit.				

Neuropsychological Test Of The Two Groups

Higher scores indicate better test performance, except for TMTA, for which a shorter time indicates a better performance. The results of preoperative neuropsychological tests showed that the score of the TMTA in the PND group was significantly higher than that of the control group, while the score of the BVMT was significantly lower than that of the control group ($P < 0.05$). The scores of HVLT, DST and BVMT in the PND group were significantly lower than those in the control group at T_4 , while the TMTA scores were significantly higher than those in the control group ($P < 0.05$). There was no significant difference in the DSCT test between the two groups at T_4 . (Table 2)

Table 2
Neuropsychological test of the two groups

	ALL (n = 82)	Controls (n = 21)	POCD (n = 61)	<i>P</i>
HVLT (T_0)	21.4 ± 1.9	21.4 ± 2.1	21.5 ± 1.6	0.816
HVLT (T_4)	18.1 ± 3.8	19.9 ± 2.4	12.9 ± 1.6	< 0.001
TMTA (T_0)	58.8 ± 23.0	55.6 ± 20.6	68.2 ± 27.2	0.029
TMTA (T_4)	71.0 ± 28.6	61.0 ± 19.4	100.2 ± 31.4	< 0.001
DST forward (T_0)	10.2 ± 2.3	10.2 ± 2.2	10.5 ± 2.5	0.591
DST forward (T_4)	9.3 ± 2.1	9.6 ± 2.1	8.5 ± 1.9	0.027
DST backward (T_0)	4.9 ± 0.9	5.0 ± 0.9	4.9 ± 0.9	0.624
DST backward (T_4)	4.7 ± 0.7	4.8 ± 0.7	4.3 ± 0.6	0.003
BVMT (T_0)	12.1 ± 2.4	12.5 ± 2.3	11.2 ± 2.6	0.044
BVMT (T_4)	11.4 ± 2.7	12.0 ± 2.6	9.4 ± 2.0	< 0.001
DSCT (T_0)	18.5 ± 5.0	18.8 ± 4.8	17.6 ± 5.3	0.323
DSCT (T_4)	17.2 ± 4.5	17.7 ± 4.3	15.7 ± 4.9	0.073
<p>Values are presented as the mean ± SD. Higher scores indicate better test performance, except for TMTA, for which a shorter time indicates a better performance. $P < 0.05$ represents a significant difference in the neuropsychological test results between the control group and TEAS group patients at baseline and the 7th postoperative day. HVLT: Hopkins verbal learning test; TMTA: trail making test; DST: digit span test; BVMT-R: revised brief visuospatial memory test; DSCT: digit symbol-coding test; T_0: 1 day before surgery; T_4: 7 days after surgery; PND: postoperative neurocognitive disorder.</p>				

Table 3
Serum levels of TNF- α , IL-6, T-AOC, MDA, IL-1 and S100 of the two groups

$\alpha\beta$	T ₀	T ₁	T ₂	T ₃
TNF- α (pg/mL)				
Controls	2.5 \pm 1.7	12.7 \pm 8.1	19.6 \pm 12.8	7.8 \pm 3.0
PND	2.6 \pm 2.0	13.3 \pm 7.3	25.6 \pm 10.6	8.3 \pm 3.5
IL-6 (pg/mL)				
Controls	3.1 \pm 2.5	65.0 \pm 50.1	115.5 \pm 61.1	32.2 \pm 16.6
PND	3.6 \pm 2.5	62.6 \pm 51.6	157.1 \pm 47.8*	34.5 \pm 13.9
T-AOC (U/mL)				
Controls	22.6 \pm 2.5	18.3 \pm 3.6	16.1 \pm 3.0	19.2 \pm 3.1
PND	22.4 \pm 3.4	17.8 \pm 2.9	14.1 \pm 2.0*	19.1 \pm 2.4
MDA (nmol/mL)				
Controls	2.6 \pm 0.8	4.7 \pm 1.2	6.1 \pm 1.2	4.5 \pm 2.2
PND	2.9 \pm 0.9	5.3 \pm 1.2	7.1 \pm 1.4*	4.7 \pm 1.1
IL-1 (pg/mL)				
Controls	2.5 \pm 1.6	4.4 \pm 2.0	5.7 \pm 2.4	3.2 \pm 1.3
PND	2.3 \pm 2.1	4.6 \pm 2.5	6.9 \pm 2.2*	3.6 \pm 1.7
S100 β (pg/mL)				
Controls	74.6 \pm 24.6	193.2 \pm 60.7	245.6 \pm 90.5	165.3 \pm 46.7
PND	79.6 \pm 30.4	202.4 \pm 51.4	308.6 \pm 36.4*	199.3 \pm 40.5*
<p>Note: The level of TNF-α, IL-6, T-AOC, MDA, IL-1 and S100β at different time points. T₀ = 5 min before the operation, T₁: end of the surgery, T₂: the first day after surgery, T₃: the third day after surgery. Compared with group TEAS, *<i>P</i> < 0.05. IL-1: interleukin-1; IL-6: interleukin-6; T-AOC: total antioxidant capacity; MDA: malondialdehyde; PND: postoperative neurocognitive disorder.</p>				

The serum levels of TNF- α , IL-1, IL-6, S100 β , MDA and T-AOC

Table 4 shows the serum levels of TNF- α , IL-1, IL-6, S100 β , MDA and T-AOC in both groups at different time points. The serum levels of IL-6, MDA, IL-1 and S100 β in the PND group were significantly lower than

those in the control group at T₂, and the T-AOC level was higher than that in the control group ($P < 0.05$) at T₂. The concentration of S100 β in the PND group significantly higher than that in the control group at T₃ ($P < 0.05$). There was no significant difference between the two groups at any other time points.

Table 4
Multivariate logistic regression analysis

	B	Standard error	Wald	P	Exp (b)	95%CI
Age	-0.135	0.061	4.937	0.026	0.874	0.776–0.984
Education years	0.279	0.139	4.006	0.045	1.321	1.006–1.736
IL6 (T ₂)	0	0.008	0	0.987	1	0.985–1.016
TAOC (T ₂)	0.206	0.166	1.547	0.214	1.229	0.888–1.700
MDA (T ₂)	-0.614	0.294	4.347	0.037	0.541	0.304–0.964
IL1 (T ₂)	-0.211	0.172	1.491	0.222	0.81	0.578–1.136
S100B (T ₂)	-0.007	0.006	1.425	0.233	0.993	0.981–1.005
S100B (T ₃)	-0.012	0.011	1.254	0.263	0.988	0.968–1.009
Note: IL-6: interleukin-6; T-AOC: total antioxidant capacity; MDA: malondialdehyde.						

Regression Estimation

Age, years of education, IL6, TAOC, MDA, IL1 and S100B were included in the multiple regression to assess the risk factors of PND. The results showed that higher age (95%CI = 0.776–0.984, $P = 0.026$), lower years of education (95%CI = 1.006–1.736, $P = 0.045$) and higher MDA level (95%CI = 0.304–0.964, $P = 0.037$) were risk factors for PND.

Discussion

In the present study, we demonstrated that the incidence of PND was as high as 25.6% 7 days after CABG. Patients with PND were older, lower education, and have a higher inflammatory response after surgery. Regression results showed that older age, lower educational level and higher MDA level might be risk factors for PND 7 days after surgery.

With the development of an aging society, performing surgery in older patients becomes more and more frequent. And a significant percentage of patients suffer from PND. Increasing age, educational level, preoperative cognition and comorbidities are known contributory factors for PND [11]. Brain damage is particularly evident in patients after cardiac surgery. Moreover, brain impairment after heart surgery was

found to be more extensive and not confined to hippocampal brain regions in the animal study [12]. A review by Glumac et al. summarized that the current definition of PND is controversial and lacks consistency and the inflammatory response after cardiac surgery plays an important role in the pathogenesis of PND [13]. Which is worthy of further study. In this study, we also found that patients diagnosed with PND were associated with increased biological indicators of inflammation and oxidative stress reaction, which indicated those responses might play an important role in PND development. And the interaction mechanism between inflammation and oxidative stress response and PND merits further research.

Preoperative assessment of cognitive ability and risk factor recognition is imperative to ascertain the true extent of POCD and prevent it. Evidence has also shown that oxidative stress and inflammation are harmful to cognitive impairment and are thought to contribute to the pathogenesis of neurodegenerative diseases [14–15]. The interaction between inflammatory factors and oxygen free radicals impaired cognitive ability [16]. Reducing MDA level and oxidative stress response possess a neuroprotective effect via mechanisms involving its antioxidant and anti-inflammatory properties [17], which is consistent with the present study. An imbalance between higher cellular levels of reactive oxygen species (ROS) causes oxidative stress. Research showed that antioxidants had a neuroprotective effect that could be significant to neurological disorders [18]. And the brain is extremely vulnerable to oxidative damage induced by ROS. Oxidative stress caused by an imbalance between reactive oxygen species and detoxification ability of the body system is associated with many pathophysiological diseases, including neurodegenerative diseases. Postoperative memory impairment was closely associated with increased oxidative stress in elderly rats receiving tibial fracture surgery [19]. Our experiments also confirmed that the oxidative stress response with high MDA level impaired cognition. However, the mechanism underlying the effect of inflammation and oxidative stress on cognitive function is still unclear.

At present, the diagnosis of PND mainly relies on neuropsychological tests, and the tests and standards are not unified. Therefore, developing the definition of PND represents an absolute priority in POCD investigations. There had been considerable heterogeneity about the definition of the disease previously in this field. Therefore, different choices and combinations of the tests may result in different PND diagnosis results of PND. Although many researchers claimed that the occurrence of PND can be diagnosed using biomarkers or radiological investigations, it remains under development, because of the cost and mixed results of small studies. The newly proposed method of diagnosing PND with Z-score for the occurrence of PND measures the difference between preoperative and postoperative scores rather than a single value, which increases the validity of the test results.

Our founding is insistent with previous researche. The study from Feinkohl et al. concluded that patients with higher education levels are at reduced risk of POCD, with a 10% reduction in risk for each year increase in education [20]. PND is one of the most common postoperative complications. However, as a usual clinical phenomenon, there is no appropriate prevention method. Both animal experiments and clinical trials have shown that learning and memory function can be impaired by surgery and anesthesia, with the upregulation of proinflammatory cytokines in the blood and brain [21–22]. Identifying the risk

factors of PND, reducing the incidence of it and improving patients' cognitive ability is of great value for perioperative brain protection and improving the patient's prognosis.

We note there are several limitations to the present study. First, the number of total participants and the number of patients with PND were relatively small. Smaller quantities lack strong evidence for PND predictors. Second, the norms provided in our study concern only five tests. At present, the diagnostic criteria of PND are not unified, and the test assessment varies with different countries. Nevertheless, these tests cover different cognitive functions and are commonly used in the diagnostic process. To further explore the mechanism of oxidative stress in PND and its predictive value, it is crucial to find more reliable predictive risk factors.

Conclusions

Older age, lower educational level and higher MDA might be risk factors for PND 7 days after surgery. More researches in the future on this field needs to be conducted to prevent PND effectively and timely.

Abbreviations

PND

postoperative neurocognitive disorder; MCI:mild cognitive impairment; CABG:coronary artery bypass grafting; ASA:American society of anesthesiologists; ECG:electrocardiograph; SpO₂:pulse oxygen saturation; ETCO₂:end-tidal carbon dioxide; BIS:bispectral index; IL-1:interleukin-1; IL-6:interleukin-6; MDA:malondialdehyde; T-AOC:total antioxidant capacity; ICU:intensive care unit; HVLT:Hopkins verbal learning test; BVMT-R:revised brief visuospatial memory test; TMT:trail making test; DST:digit span test; DSCT:digit symbol-coding test; SD:standard deviation; ELISA:enzyme-linked immunosorbent assay; ROC:reactive oxygen species

Declarations

Acknowledgments

Not applicable.

Authors' contributions

Conception and design, critical revision for this study protocol: Anshi Wu, Ting Luo and Changwei Wei. Recruiting subjects: Juxia Zhang. Test performed and data collection: Xiao Huang. Blood collection: Juxia Zhang. Data analysis: Xiao Huang. The manuscript was written by Xiao Huang.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (clinical trial registration number: ChiCTR1800015606). All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The trial is carried out following the current version of the declaration of Helsinki from 2013.

Consent for publication

Specific written consent for data publication was signed by each patient involved.

Competing interests

The authors declare that they have no competing interests.

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