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Age, preoperative higher serum cortisol levels, and lower serum acetylcholine levels predict delirium after percutaneous coronary intervention in acute coronary syndrome patients accompanied with renal dysfunction

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ABSTRACT

Background: The objective of the study is to investigate the incidence and risk factors of delirium after percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS) patients accompanied with renal dysfunction.

Materials and Methods: This was a prospective and cohort study, performed in a medical center from July 2014 to June 2017, which enrolled ACS patients accompanied with renal dysfunction who were treated with PCI. Univariate analysis and binary logistic regression analysis was used to determine the incidence and risk factors of delirium.

Results: Data were analyzed from 119 patients. The 7-day incidence of delirium after PCI in ACS patients accompanied with renal dysfunction was 15.97% ($n = 19/119$). The binary logistic regression analysis results indicate that age (odd ratio [OR] 1.463; 95% confidence interval [CI] 1.070–2.001; $P = 0.017$), preoperative higher serum cortisol (COR) (OR 1.025; 95% CI 1.002–1.048; $P = 0.030$), and lower serum acetylcholine (Ach) (OR 0.965; 95% CI 0.937–0.993; $P = 0.016$) were significant differences in delirium and nondelirium groups.

Conclusions: Age, preoperative higher serum COR levels, and lower serum Ach levels were independent risk factors for delirium after PCI in ACS patients accompanied with renal dysfunction.

Key words: Acute coronary syndrome, delirium, delirium biomarkers, percutaneous coronary intervention, risk factors

INTRODUCTION

Acute coronary syndrome (ACS) is one of the main causes of morbidity and mortality in the modern world.^[1] ACS patients accompanied with renal dysfunction have a poorer prognosis than those with normal renal function. Percutaneous

coronary intervention (PCI) is widely used in the treatment of ACS clinically.^[2] Despite PCI is more effective in restoring coronary blood flow compared with other interventions and are now conducted more safely than ever before,^[3] postoperative delirium after PCI cannot be ignored.

Delirium is an acute onset of a fluctuating disturbance in the following cognitive functions: attention; environmental awareness; and cognition and/or perception, and may

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be most readily identified in patients with sleep/wake cycle disturbances, emotional lability, hallucinations or delusions.^[4] Delirium is a rare complication after PCI, the early literature reports that the incidence is 0.06%.^[5] In patients older than 80 years after PCI, the reported incidence is 29.8%.^[6] When compared to the general population, the prevalence of delirium is higher in individuals with renal dysfunction.^[7] Impaired renal function was identified as a high-risk independent factor for subsequent cardiovascular events.^[8] Renal disease severity walks hand in hand with loss of neurocognitive function.^[9] Delirium is commonly seen in any stage of renal dysfunction, renal dysfunction patients with delirium generally associated with more complications and poorer prognosis.^[10]

While postoperative delirium after cardiac surgery has been the subject of intense research and numerous review articles, little attention has been placed on the unique aspects of delirium related to patients after PCI. The purpose of the present report is to investigate the incidence and risk factors of delirium after PCI in ACS patients accompanied with renal dysfunction.

MATERIALS AND METHODS

Patient populations

This was a prospective cohort study. Continuous sampling was used to enroll ACS patients with renal insufficiency who underwent PCI in our cardiovascular department from July 2014 to June 2017. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Institutional Review Board of the Second Affiliated Hospital of Shenyang Medical College.

Inclusion criteria: (1) patients with renal dysfunction were defined as those with an estimated glomerular filtration rate (eGFR) <90 ml/(min 1.73 m²);^[8] (2) patients with ACS defined as those diagnosed with ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) or unstable angina (UA). The diagnosis of STEMI refers to the guidelines developed by the American College of Cardiology Foundation/American Heart Association (ACC/AHA) in 2013,^[11] the diagnosis of NSTEMI and UA refers to the non-ST-segment elevation ACS (NSTEMI-ACS) guidelines developed by the American College of Cardiology/AHA in 2014.^[12] The eGFR was calculated using the modification of diet in renal disease study formula as follows:^[13]

$$\text{GFR} = 186.3 \times (\text{serum creatinine mg/dl})^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if black)} \quad (1)$$

Exclusion criteria: (1) the patient had delirium prior to PCI; (2) patients with eGFR <20 ml/(min 1.73 m²); (3) previous history of mental illness; (4) previous history of craniocerebral injury; (5) language, vision, hearing impairment causes failure to cooperate with normal

inspection; (6) does not have the basic level of education; (7) can only communicate in dialect; and (8) postoperative condition deteriorates.

Collection of baseline data

The baseline data include: (1) gender, age, history (history of hypertension, diabetes, atrial fibrillation, cerebrovascular disease, anemia, etc.), and psychological pressure; (2) degree of coronary artery disease; (3) duration of PCI surgery and dosage of contrast agent; and (4) left ventricular ejection fraction (LVEF).

The gender, age, and history of the patient were collected using self-report questionnaires, and electronic medical charts. Psychological stress refers to the Hamilton Anxiety Scale, which consists of 14 items, each with a 5-point scale of 0–4 points, with more than 7 points classified as having anxiety state. In this study, psychological stress is a categorical variable. The operation records were used to collect the degree of coronary artery disease, duration of PCI surgery, and dosage of contrast agent. LVEF examination was performed using a commercial ultrasound system (IE33, Philips Healthcare, Inc.)

Laboratory assays

Laboratory indicator: blood urea nitrogen (BUN), serum creatinine (Cr), Serum interleukin-6 (IL-6), serum cortisol (COR), serum dopamine (DA), serum acetylcholine (Ach), serum γ -aminobutyric acid (GABA), serum 5-hydroxytryptamine (5-HT), eGFR, etc.

Blood samples of elective PCI patients were obtained from fasting patients, and emergency PCI patients were obtained from preoperative PCI. Two milliliters of venous blood was collected directly in an ethylenediaminetetraacetic acid vacutainer in sitting position from antecubital vein and analyzed directly using standard laboratory techniques. In addition, 2 mL samples of IL-6, COR, DA, Ach, GABA, 5-HT were taken and centrifuged at 4°C for 10 min (3000 rpm) to determine the plasma levels. Thereafter, the supernatant was taken and stored for a maximum of 1 month at –80°C until biochemical parameters were determined. The plasma samples were analyzed by applying a commercial kit (Jianglai biological, china). The levels of serum IL-6, COR, DA, Ach, GABA, 5-HT were measured through enzyme-linked immunosorbent assay (Jianglai biological, china). The precision performance of these assays was within the manufacturer's specifications.

Delirium assessment

Patients were screened for delirium preoperative PCI and evaluated for delirium within 7 days after PCI by two psychiatrists. If the results of delirium assessment by two psychiatrists were inconsistent, the delirium was evaluated by the third psychiatrist. The diagnostic criteria for delirium refer to the diagnostic and statistical manual for mental disorders.^[14]

Statistical analysis

All statistical analyses were performed using SPSS (version 22.0, SPSS, Chicago, IL, USA). Results were presented as means standard deviation for continuous variables and as percentages of the total number of patients for categorical variables. Chi-square and the Fisher's exact test were used for categorical variables and *t*-test was used for comparison of continuous variables. Levene's test was used to check the homogeneity of variance. Equivalent nonparametric tests were used when Kolmogorov–Smirnov was in favor of nonnormal distribution. Results with $P < 0.05$ were regarded as statistically significant. The independent variables with statistical differences in univariate analysis were substituted into the binary logistic regression analysis model, and the independent risk factors of delirium were obtained by the backward likelihood ratio method. Risk factors are expressed as odds ratios (OR) with 95% confidence intervals (CIs).

RESULTS

Incidence of postoperative delirium

A total of 119 cases met the criteria from July 2014 to June 2017. No patient had delirium prior to PCI, and 19 patients had delirium within 1 week after PCI. The incidence of delirium was 15.97%, including 13 males and 6 females, ranging in age from 57 to 88 years with an average of 75.74 ± 8.22 years old. In order to protect the renal function, the two groups of patients were given intravenous 250 ml saline hydration (1 ml/min) from 2 h before PCI to 24 h after PCI. Only delirium group was given haloperidol 10 mg, scopolamine 0.3 mg, intramuscular injection four times a day, not all patients received prophylactic haloperidol to prevent delirium. All the 19 patients were acute onset, and they were discharged after active support for symptomatic treatment.

Comparison between the two groups

Patients were divided into delirium group and nondelirium group according to whether delirium occurred. There were significant differences between the two groups in age, preoperative serum BUN, Cr, COR, Ach, eGFR, GABA, 5-HT, DA, and postoperative psychological stress. The remaining risk factors were not significant in univariate analysis [Table 1].

Binary logistic regression analysis

The result of 10 factors identified as significant in univariate analysis were included into binary logistic regression analysis. The results indicate that age (OR 1.463; 95% CI 1.070–2.001; $P = 0.017$), serum COR (OR 1.025; 95% CI 1.002–1.048; $P = 0.030$), and serum Ach (OR 0.965; 95% CI 0.937–0.993; $P = 0.016$) were significant differences in delirium and nondelirium groups [Table 2].

DISCUSSION

Delirium is a common postoperative complication that is manifested by a change of mindset and attention deficit

over time.^[15] In our study, the incidence of postoperative delirium after PCI was 15.97%, consistent with previous literature has described that the incidence of delirium in hospitalized patients.^[16]

Delirium is frequently caused by multifactorial etiologies and the exact pathophysiology of delirium remains poorly understood.^[17,18] Our analyses revealed that older age was an independent risk factor of delirium. Aging is associated with the loss of neurons and glucocorticoid (GC) receptors in the hippocampal region and with impaired hypothalamic–pituitary–adrenal axis feedback inhibition.^[19,20] Besides, aging exaggerate brain microglial activation after peripheral inflammation,^[21] and the increased vulnerability to harmful stimuli from outside world due to a lack of physiologic reserve.^[22]

According to the results of the present study, a higher level of serum COR prior to PCI is associated with an increased risk of postoperative delirium. Serum COR is one of the most important GCs,^[23] and responsible for the stress response.^[24] PCI is a kind of stress for ACS patients accompanied with renal dysfunction; this results in stimulation of the sympathetic nervous system and activation of the hypothalamic–pituitary–adrenal axis. Following activation of the hypothalamus, there is an increase serum COR release from the adrenal medulla.^[24] GCs are steroid hormones that modulate metabolism, salt balance, development, reproductive processes, and immune function.^[25] High levels of GCs might have harmful effects on the brain and cause psychiatric symptoms,^[26,27] particularly the glucocorticoid receptor-rich hippocampus.^[28] In addition, impaired renal function may be associated with increased inflammation and oxidative stress,^[8] these maybe the essential for delirium in ACS patients accompanied with renal dysfunction. Higher levels of serum COR of patients with delirium in line with the hypothesis of a 'aberrant stress response' of delirium.^[29-31]

In our study, we also demonstrated that lower levels of serum Ach were a risk factor of delirium. However, serum DA and serum GABA were not significant differences in delirium and nondelirium groups. The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain. Impairment of the cholinergic system may cause delirium.^[32] Ach nicotinic receptor is mainly related to learning and memory.^[25] The inhibition of Ach muscarinic (M) 1 receptor in the postsynaptic membrane can lead to hallucinations, confusion, and other clinical symptoms of cognitive impairment.^[33] GABA is the major inhibitory neurotransmitter in the human central nervous system (CNS), plays a part in regulating neuronal excitability.^[25] Aging is associated with a reduction in GABAergic.^[34] Decreased GABAergic activity is also often reported in delirium patients.^[35] Studies indicated that increased serum DA transmission also contribute to the

Table 1: Baseline characteristics of two groups

Variables	Nondelirium group (n=100), n (%)	Delirium group (n=19), n (%)	P
Age (years)	67.67±9.90	75.74±8.22	0.001
Male gender	74 (74)	13 (68.4)	0.615
Weight (kg)	70.30±10.85	71.61±11.55	0.644
Hypertension	71 (71)	12 (63.2)	0.495
Diabetes mellitus	40 (40)	9 (47.4)	0.550
Anemia	26 (26)	1 (5.3)	0.093
Atrial fibrillation	4 (4)	2 (10.5)	0.535
Previous cerebrovascular disease	15 (15)	4 (21.1)	0.750
Postoperative psychological stress	10 (10)	7 (36.8)	0.002
Coronary artery lesions			
Single vessel	60 (60)	10 (52.6)	0.391
Double vessel	30 (30)	5 (26.3)	
Triple vessels	10 (10)	4 (21.1)	
Dosage of contrast agent (ml)			
<100	25 (25)	2 (10.5)	0.389
100–150	44 (44)	9 (47.4)	
150–200	24 (24)	5 (26.3)	
>200	7 (7)	3 (15.8)	
Duration of PCI surgery (min)	71.37±19.31	79.67±20.91	0.101
BUN (mmol/L)	9.42±3.24	7.48±3.51	0.020
Cr (μmol/L)	131.84±46.76	93.07±31.62	0.000
IL-6 (pg/ml)	13.17±15.21	19.78±31.20	0.695
COR (nmol/L)	216.81±83.80	319.20±134.97	0.000
eGFR (ml/[min·1.73 m ²])	49.15±18.32	71.66±28.37	0.001
GABA (μmol/L)	6.01±1.40	4.54±1.84	0.002
5-HT (pg/ml)	1772.22±445.27	1414.74±410.97	0.000
Ach (nmol/L)	294.46±106.93	123.84±91.47	0.000
DA (pg/ml)	33.15±9.28	38.66±9.63	0.013
LVEF (%)	58.08±8.45	60.73±5.52	0.317

Data are shown as n (%) or mean±SD. BUN – Blood urea nitrogen; Cr – Creatinine; IL-6 – Interleukin-6; COR – Cortisol; eGFR – Glomerular filtration rate; GABA – γ-aminobutyric acid; 5-HT – 5-hydroxytryptamine; Ach – Acetylcholine; DA – Dopamine; LVEF – Left ventricular ejection fraction; SD – Standard deviation; PCI – Percutaneous coronary intervention

Table 2: Binary logistic regression analysis results

Variables	OR (95% CI)	P
Age (years)	1.463 (1.070–2.001)	0.017
BUN (mmol/L)	1.176 (0.982–1.317)	0.133
Cr (μmol/L)	1.087 (0.991–1.192)	0.077
COR (nmol/L)	1.025 (1.002–1.048)	0.030
eGFR (ml/[min·1.73 m ²])	1.151 (0.999–1.325)	0.051
GABA (μmol/L)	0.415 (0.165–1.044)	0.062
Ach (pg/ml)	0.965 (0.937–0.993)	0.016
DA (pg/ml)	1.355 (0.996–1.844)	0.053

BUN – Blood urea nitrogen; Cr – Creatinine; COR – Cortisol; eGFR – Glomerular filtration rate; GABA – γ-aminobutyric acid; Ach – Acetylcholine; DA – Dopamine; CI – Confidence interval; OR – Odds ratio

development of delirium.^[36] Elevation in serum DA leads to neurobehavioral change observed in delirious patients through three pathways: the direct excitatory activity of DA; DA gives rise to cognitive impairment through oxidative stress; and the regulation of DA strengthens glutamate and results in behavioral changes.^[37-39] PCI is a kind of invasive operation, intraoperative will cause mechanical stimulation and damage to blood vessels, the constant stimulation and damage can led to a large number of inflammatory factors release, cause the body and blood vessels of acute and chronic inflammation.^[40] Acute inflammatory reactions may affect physiologic processes implicated in neuronal

and synaptic function with consequent neurochemical disturbances and functional disconnection between different anatomic structures.^[41] Thus, the disturbances of neuronal and synaptic function may be a risk factor of delirium after PCI in ACS patients accompanied with renal dysfunction.

Studies have shown that intravascular contrast agent produces renal vasoconstriction, medullar ischemia, and decreases renal blood flow.^[42,43] Thus, the blood creatinine levels should be increased after the administration of contrast agent. However, our data suggest that patients have lower Cr levels. The reason may be that we performed hydration therapy before and after PCI to reduce the damage of renal function to ACS patients accompanied with renal dysfunction.

Typically, under normal conditions, contrast agent does not cross the blood–brain barrier (BBB), when the integrity of the BBB is disrupted, and contrast agent permeates the CNS, subsequently causing injury by direct neuronal toxicity, patients may show delirium.^[44] Larger doses of contrast agent are considered a risk factor of delirium.^[45] In renal dysfunction patients, the metabolic rate of the brain is reduced,^[46] and the metabolic ability of contrast agent in patients with renal dysfunction is worse than that in patients

with normal renal function. These maybe the reason of ACS patients accompanied with renal dysfunction occurred delirium after PCI. While in the present study, we found that the contrast agent was not associated with delirium, which maybe related to our sample size. In addition, Lahariya *et al.*^[47] studies have shown that the presence of atrial fibrillation, diabetes mellitus, anemia, and LVEF <30 has significant predictive value for the development of delirium. While in our study, we found that these factors were not associated with delirium.

There are some limitations in our study. First, our sample size was relatively small and only a small sample of population (119 patients) was enrolled. Second, our study was carried out in a single center and therefore, its results cannot be extrapolated to other centers. Third, among the patients we included, there may be patients who underwent emergency PCI. The venous blood sample levels are preoperative results. Fourth, due to individual differences, some patients are overweight or treatment is not ideal given haloperidol 10 mg intramuscularly, four times a day, for a total of 1 day. Finally, we did not have a long-term follow-up after discharge for all patients included in the study.

Despite these limitations, our study suggests that age, preoperative higher serum COR levels and lower serum Ach levels were independent risk factors for delirium after PCI in ACS patients accompanied with renal dysfunction. Clinicians should screen for delirium in ACS patients accompanied with renal dysfunction who are prepare for PCI treatment. In particular, patients who are older or who have a higher COR levels and lower Ach levels prior to PCI may benefit from preoperative preventative and postoperative screening for delirium. Future studies with a much greater sample size and multicenter data collection would be needed to determine the causality of certain risk factors for delirium.

CONCLUSIONS

Delirium among ACS patients accompanied with renal dysfunction after PCI showed an incidence of 15.97%. Our data suggest that older age, higher serum COR levels, and lower serum Ach levels prior to PCI that acts as an independent risk factor for delirium. The levels of serum COR and serum Ach prior to PCI may as several biomarkers for early recognition of delirium.

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Conflicts of interest

There are no conflicts of interest.

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