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Retrospective case–control study on screening risk factors of antibiotic-associated encephalopathy in patients with chronic kidney disease

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ABSTRACT

Objective The renal excretion function of patients with chronic kidney disease (CKD) is reduced, and the nervous system toxic reactions of antibiotics are prone to occur. The purpose of this study is to screen out some risk factors for patients with CKD to suffer from antibiotic-associated encephalopathy (AAE).

Design A case–control study.

Setting A tertiary hospital in China.

Participants The medical records of patients who were hospitalised for CKD and infectious diseases in our hospital from January 2010 to December 2019. All patients used antibiotics to treat infectious diseases during hospitalisation. All patients were divided into two groups according to whether they developed AAE during hospitalisation. The patients with CKD without AAE were selected as the control group (n=120), and the patients with CKD with AAE were regarded as the AAE group (n=102).

Interventions This study systematically analysed its clinical manifestations, laboratory examinations, prognosis, etc, and summarised the risk factors related to AAE in patients with CKD.

Primary outcome Screening risk factors of AAE in patients with CKD.

Results Logistic regression analysis showed that coronary heart disease, as well as abnormal indicators of haemoglobin, albumin, uric acid and blood phosphorus were independent risk factors for patients with CKD with AAE (OR values were 4.137, 0.963, 0.849, 0.996 0.161, respectively, all p<0.05). The case fatality rate (Pearson χ^2=7.524, p=0.006), rehospitalisation rate (Pearson χ^2=6.187, p=0.013) and treatment costs (t=−8.44, p<0.001) in encephalopathy group are significantly higher than the control group.

Conclusions Patients with CKD with AAE will increase the case fatality rate and cause poor prognosis. Coronary heart disease, as well as decreased levels of haemoglobin, albumin, uric acid, and blood phosphorus are independent risk factors for patients with CKD with AAE. Timely intervention of these risk factors may reduce the incidence of AAE and improve the prognosis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The survival analysis with Kaplan-Meier plots was used to show the association between the prognosis of patients with chronic kidney disease and the occurrence of antibiotic-associated encephalopathy.
⇒ The univariate logistic regression analysis was used to select the significant risk factors, then these factors were analysed by multivariate logistic regression analysis to define the final risk factors.
⇒ The sample size of this study is limited.

INTRODUCTION

Antibiotic-associated encephalopathy (AAE) is a series of neuropsychiatric dysfunction induced by the direct neurotoxicity of antibiotics or the interaction with other drugs during the use of antibiotics.[1 2] AAE often occurs in patients who use antibiotics such as cephalosporins, β-lactams, penicillins and quinolones. It is an antibiotic-induced disease.[3] The clinical manifestations of AAE include mental confusion, abnormal behaviour, personality changes, hallucinations, delusions and even induce epilepsy or psychotic seizures.[3] AAE can be divided into three categories based on clinical manifestations. Type 1 is mainly caused by penicillin and cephalosporin, and is characterised by myoclonus. Type 2 is mainly caused by procaine penicillin and sulfa antibiotics, and is characterised by psychosis. Type 3 is mainly caused by metronidazole antibiotics, mainly with cerebellar-related symptoms.[3 4]

Patients with chronic kidney disease (CKD) are prone to infection due to malnutrition and low immunity, so the probability of using antibiotics is high. As the renal excretion function of patients with CKD is reduced and antibiotics are prone to accumulate, central nervous system toxic reactions occur.[4 5] The diagnosis of CKD accompanied by AAE is based on the original diagnosis of CKD, and it also includes the history of antibiotic use, typical antibiotic-related neuropsychiatric symptoms, related laboratory tests and imaging indicators. In terms of treatment,

in addition to active treatment of underlying kidney disease, it also includes adjustment or discontinuation of suspected antibiotics.[4 6] To analyse the risk factors to develop AAE in patients with CKD, we selected the cases of hospitalised for CKD and infectious diseases and compared the clinical characteristics between patients who developed AAE or not. This study systematically analysed its clinical manifestations, laboratory examinations, prognosis, etc, and summarised the risk factors related to AAE in patients with CKD and compared the prognosis.

METHODS

Participants

This study is a retrospective case–control study. The medical records of patients who were hospitalised for CKD and infectious diseases in our hospital from January 2010 to December 2019 were collected. All patients used antibiotics to treat infectious diseases during hospitalisation. All cases were divided into two groups. One hundred and twenty patients with CKD without AAE were selected as the control group. The patients with CKD who developed AEE during hospitalisation were regarded as the AAE group, a total of 102 cases. This study has been carried out in accordance with

In this study, the diagnosis of CKD should meet the following two criteria: (1) Chronic kidney structure and dysfunction caused by various reasons (history of kidney damage is greater than 3 months), including renal pathological damage with normal or abnormal glomerular filtration rate (GFR), abnormal blood or urine composition, abnormal imaging examination or unexplained decrease in GFR (< 60 mL/min·1.73 m^2) for more than 3 months and (2) Estimate the GFR (according to the CKD-EPI formula) ≤60 mL/min·1.73 m^2. Exclusion criteria: (1) have a history of mental illness, (2) have a history of epilepsy, (3) diagnosed a new intracranial infection, (4) history of head trauma and (5) cranial CT was performed for patients who were suspected of AAE. Patients with new-onset cerebrovascular disease were excluded.[7 8]

Diagnosis criteria of AAE: (1) all patients adjusted the dosage of antibiotics according to the drug instructions and the renal function, (2) mental and neurological symptoms appear during the use of antibiotics, (3) exclude the history of uraemic encephalopathy and other neurological diseases through examinations of renal function, electrolytes, and head CT and (4) after stopping suspicious antibiotics, the symptoms of encephalopathy are relieved or even disappeared after active medical treatment.[2–4]

Patient and public involvement

Patients were involved in the conduct and reporting of this research. We confirmed that all methods were performed in accordance with the relevant guidelines and regulations. In addition, we confirmed that informed consent was obtained from all patients.

Procedures

This study systematically compared and analysed the data for the two group patients. White blood cells, haemoglobin, platelets, blood C reactive protein, serum procalcitonin, blood calcium, blood phosphorus, blood potassium, blood sodium, blood chlorine, plasma albumin, plasma globulin, blood creatinine, blood sugar, serum ferritin, serum immunoreactive parathyroid hormone (iPTH), blood PH value, application of antibiotics, antibiotic use time, history of diabetes, history of hypertension, history of coronary heart disease, history of smoking, history of drinking and history of cerebrovascular disease were systematically analysed. All above indicators were incorporate into logistic regression analysis to find independent risk factors that may cause AAE in patients with CKD. The follow-up period of this study is 1 year. The case case fatality rate, rehospitalisation rate, patients' hospitalisation expenditure, hospitalisation days and the prognosis of the two groups were compared. Furthermore, to evaluate the potential predictive power of these independent risk factors for the onset of AAE in patients with CKD.

There were 102 patients in the AEE group, of which 15 patients died during hospitalisation, 6 patients gave up treatment for different reasons and left the hospital automatically, and the rest 81 patients were discharged after their condition improved. There were 120 patients in the control group, of which 3 patients died during hospitalisation, 5 patients gave up treatment and discharged automatically, and the remaining 112 patients were discharged after their condition improved.

Statistical analysis

Data were expressed as mean±SD. Data were analysed with independent-sample t-test for two groups. χ^2 test was used to compare the count data of the two group patients. Two classifications, unconditional, univariate and multivariate logistic regression analysis were used to screen independent risk factors for AAE in patients with CKD, respectively. The receiver operating characteristic curve (ROC) and the area under the curve (AUC) were used to evaluate the predictive ability of the selected risk factors for the occurrence of AAE in patients with CKD. Survival analysis was shown in Kaplan-Meier survival curves. Survival comparisons between two subgroups were performed by the log-rank test. Statistical significance was assumed at $p<0.05$.

RESULTS

Descriptive analyses

In the control group, there were 44 males and 76 females, aged 59–88 years old, and antibiotics were used for 4–12 days. Among them, 64 patients were haemodialysis, and 56 were peritoneal dialysis. In the AAE group, there were 39 males and 63 females, aged 58–89 years old, and antibiotic application time were 3–14 days. Among them, 53 patients were haemodialysis and 49 were peritoneal

Table 1 Comparison of general conditions, laboratory test indexes and prognosis between the two groups

	Control group (n=120)	AAE group (n=102)	P value
Gender ratio (male: female)	44:76	39:63	0.810
Age (years)	71.88±8.84	72.20±7.97	0.779
Antibiotic application time (days)	7.10±2.01	7.24±3.04	0.693
Composition of infection types:			
Lung infection	46.7%	50%	0.952
Abdominal infection	26.7%	26.5%	
Urinary tract infection	20%	17.6%	
Others	6.6%	5.9%	
Composition of antibiotic types:			0.133
Cephalosporins	43.3%	41.2%	
Carbapenems	26.7%	28.4%	
Semi-synthetic penicillins	16.7%	14.7%	
Quinolones	13.3%	15.7%	
Haemoglobin (g/L)	95.87±15.91	85.82±17.25	<0.001
Albumin (g/L)	33.38±4.40	29.35±4.62	<0.001
White cell count ($\times 10^9$/L)	6.34±1.61	6.67±2.81	0.283
CRP (mg/L)	44.06±35.26	47.20±43.67	0.554
Serum sodium (mmol/L)	137.97±3.21	134.11±23.01	0.072
Blood calcium (mmol/L)	2.12±0.18	2.05±0.19	0.010
Uric acid (μmol/L)	342.17±86.57	313.74±79.12	<0.001
Blood phosphorus (mmol /L)	1.52±0.38	1.24±0.40	0.012
Ratio of patients with coronary heart disease	96:24	90:12	0.097
Ratio of patients with hypertension	108:12	90:12	0.673
Ratio of patients with diabetes	60:60	54:48	0.662
Case fatality rate (cases, %)	(19:120) 15.8	(32:102) 31.4	0.006
Rehospitalisation rate (cases, %)	(47:120) 39.2	(57:102) 55.9	0.013
Treatment cost (US$)	3520.22±1036.16	5486.25±2292.06	<0.001

AAE, antibiotic-associated encephalopathy; CRP, C reactive protein.

dialysis. According to statistics, the difference of general data such as gender composition, age, antibiotic application time, comorbidity, haemodialysis ratio and peritoneal dialysis ratio between the two groups were not statistically significant (table 1, all p>0.05).

The application of antibiotic

Analysis of the infection sites of the two groups of patients found that the most common was lung infection, followed by abdominal infection (including peritonitis, cholecystitis, appendicitis, etc), and urinary tract infection. There was no statistical significance on the composition ratio of infection types in the two groups (all p>0.05, see table 1). The two groups of patients were treated with antibiotics after infection. The types of antibiotics mainly included cephalosporins, carbapenems, semisynthetic penicillins and quinolones. The composition of the types of antibiotics used in the two groups was compared, and there was no statistical significance between the two groups (p>0.05, see table 1).

Clinical manifestations and prognosis

In the AAE group, the time interval from the use of antibiotics to the onset of disease is 3–14 days. The main clinical manifestations include hallucinations, delusions, myoclonus, disorientation, restlessness, ataxia, aphasia, seizures and other symptoms. About 70% of the patients had symptoms of sleep disturbance before the onset of severe symptoms. All patients in the AAE group underwent head CT scan, which showed no new cerebrovascular disease. However, 83% of patients were found to have multiple ischaemic foci, softening foci, sparse white matter and brain atrophy. Patients in the control group did not have the above-mentioned psychiatric symptoms during their hospitalisation. Regarding the prognosis, the follow-up period of this study is 1 year. By the end of the follow-up, 70 patients in the AAE group had improved, 32 died and the case fatality rate reached 31.4%. In the control group, 101 cases improved, 19 cases died and the case fatality rate was 15.8%. The case fatality rate of

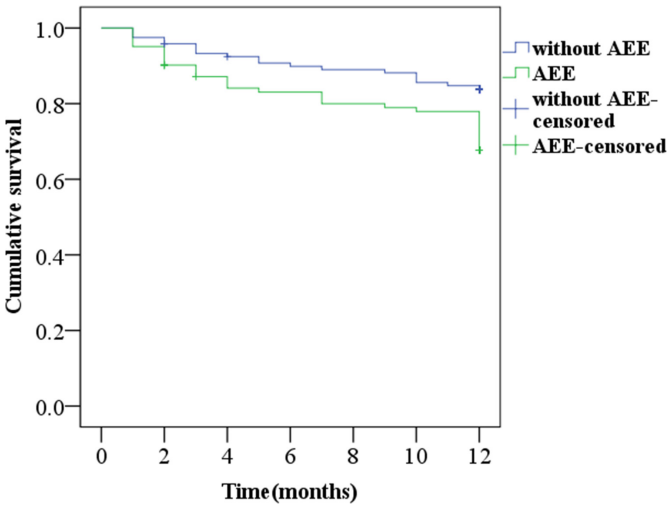

Figure 1 Comparison of survival analysis between two groups. All patients were followed up for 1 year. Kaplan-Meier survival curves was used to analyse the survival between AEE group and control group. The result showed that the survival rate of control group was significantly higher than that of AEE group (p=0.006).

the AAE group was significantly higher than that of the control group, and the difference was statistically significant (table 1, Pearson χ^2=7.524, p=0.006). Fifty-seven patients in the AEE group were readmitted during the follow-up period, while 47 patients in the control group were readmitted. As of the end of the follow-up, the rehospitalisation rate of the AAE group was also significantly higher than that of the control group, and the difference was statistically significant (table 1, Pearson χ^2=6.187, p=0.013). Statistics on the treatment cost of this admission show that the average treatment cost of patients in the AAE group is about US$5500, while the average treatment cost of the control group is about US$3500, and the difference is statistically significant (table 1, t=−8.44, p<0.001). We followed up all patients for 1 year, and then used Kaplan-Meier survival curves to analyse the survival of these two groups. The result showed that the survival rate of control group was significantly higher than that of AEE group (figure 1, p=0.006). Based on the above research results, it is proved that the prognosis of the AEE group is significantly worse than that of the control group.

Analysis of the risk factors in patients with CKD accompanied by AAE

In order to explore which factors are related to CKD with AAE, this study took the occurrence of AAE in all cases as the dependent variable, and used two classifications, unconditional, logistic regression analysis to screen risk factors from a variety of laboratory test indicators and history indicators. All indicators (including age, gender, application of antibiotics, history indicators and all laboratory test indicators) were tested through univariate logistic regression analysis to screen out significant risk factors. Statistical analysis showed that 10 risk factors were screened out (including haemoglobin, albumin, blood glucose, ferritin, serum calcium, uric acid, blood phosphorus, iPTH, coronary heart disease and cerebrovascular disease, all p<0.05). Then these factors were made multivariate logistic regression analysis to define the final risk factors. The results showed that a history of coronary heart disease, as well as abnormal indicators of haemoglobin, albumin, uric acid and blood phosphorus were independent risk factors for patients with CKD with AAE (table 2, OR values were 4.137, 0.963, 0.849, 0.996, 0.161, respectively, all p<0.05).

Based on the above-mentioned logistic regression analysis, this study also performed t-test statistical comparisons on the measurement data of these risk factors between the control group and the AAE group. The results showed that compared with the control group, the haemoglobin, albumin, uric acid and blood phosphorus of the patients in the AAE group decreased significantly, and the difference was statistically significant (table 1, all p<0.05).

Table 2 Logistic regression analysis of the risk factors in patients with CKD accompanied by AAE

					95% CI of OR	
Factor	**B**	**SE**	**P value**	**OR**	**Lower limit**	**Upper limit**
Haemoglobin	−0.038	0.012	0.001	0.963	0.941	0.985
Albumin	−0.164	0.049	0.001	0.849	0.771	0.935
Blood glucose	0.140	0.132	0.287	1.150	0.889	1.489
Ferritin	0.001	0.001	0.347	1.001	0.999	1.003
Serum calcium	−1.497	1.112	0.178	0.224	0.025	1.979
Uric acid	−0.004	0.002	0.048	0.996	0.992	1.000
Blood phosphorus	−1.825	0.564	0.001	0.161	0.053	0.487
iPTH	−0.001	0.001	0.341	0.999	0.997	1.001
Coronary heart disease	1.420	0.517	0.006	4.137	1.501	11.398
Cerebrovascular disease	0.865	0.540	0.109	2.375	0.825	6.840

AAE, antibiotic-associated encephalopathy; CKD, chronic kidney disease; iPTH, immunoreactive parathyroid hormone.

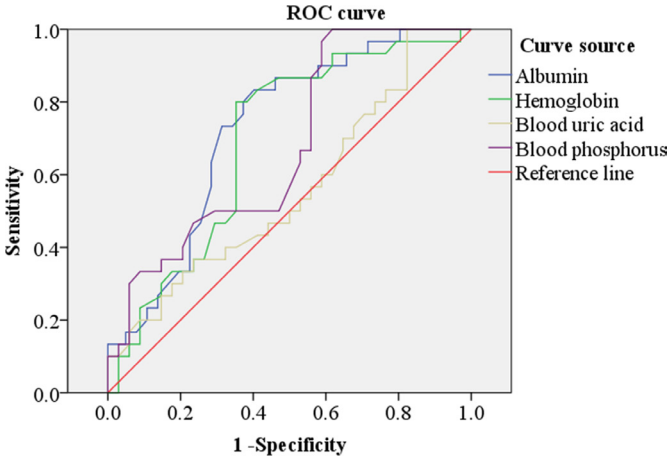

Figure 2 ROC curves of risk factors for evaluating patients with CKD with AAE. The risk factors, such as haemoglobin, albumin, uric acid and blood phosphorus, in patients with CKD accompanied by AAE all have large area under the curve (AUC). AAE, antibiotic-associated encephalopathy; CKD, chronic kidney disease; ROC, receiver operating characteristic curve.

The diagnostic value of independent risk factors for patients with CKD accompanied by AAE

The ROC curve was used to analyse the predictive ability of these risk factors such as haemoglobin, albumin, uric acid and blood phosphorus in patients with CKD accompanied by AAE. The above-mentioned risk factors all have a large AUC, as shown in figure 2. The specific values of the optimal cut-off value, AUC, sensitivity and specificity of each risk factor are shown in table 3. Among these risk factors, the numerical value of AUC in descending order is: haemoglobin>blood phosphorus>albumin>blood uric acid. However, there is no statistical significance in comparison of AUC among these risk factors (all p>0.05, table 3).

DISCUSSION

This study selected two groups of CKD cases after antibiotics were used for analysis. All cases were divided into AAE group and control group. There was no statistical significance between the two groups in terms of number of cases, male to female ratio, age of onset, renal replacement therapy and site of infection. Through the comparison of the indicators of the two groups of patients, it is found that the AAE group has a long time of hospitalisation, hospital stay, a high rehospitalisation rate, a high hospitalisation expenses, a high case fatality rate and a poor prognosis. It is suggested that if patients with CKD are accompanied by AAE, it will significantly increase the medical burden of patients and increase the poor prognosis. Therefore, the early detection and early treatment of CKD accompanied by AAE is very important. Analysis of the imaging examination results of patients in the during their hospitalisation revealed that the patients in the AAE group had imaging manifestations such as sparse white matter and brain atrophy in varying degrees. One of the reasons for this is that there may be underlying brain function decline, which may affect the responsiveness and permeability of brain cells to antibiotics. Studies have shown that the blood perfusion in the lesion area of patients with leukoaraiosis is significantly reduced, and the permeability of the blood–brain barrier is significantly increased.[9 10] Combined with the results of this study, it is suggested that these patients may be more likely to affect the central nervous system function through the blood–brain barrier after using antibiotics. Therefore, when such patients use antibiotics, they must strictly control the indications and dosage to avoid AAE. In this study, because many patients in the control group did not undergo head imaging examination, complete statistical analysis data could not be provided. Therefore, the relationship between basic brain diseases and AAE needs to be further studied and determined. This study also found that before the diagnosis of AAE in the AAE group, some patients had symptoms such as changes in sleep habits, while fewer patients in the control group had sleep disturbances. It is suggested that in the course of treatment of patients with CKD, sufficient attention should be paid to sleep disorders when antibiotics are used.

The results of logistic regression analysis showed that abnormal indicators such as haemoglobin, albumin, uric acid and blood phosphorus, as well as previous coronary heart disease, are independent risk factors for CKD accompanied by AAE. First of all, renal anaemia is a common complication of patients with CKD. Anaemia can cause chronic hypoxia in the brain, which in turn affects the function of the central nervous system.[11–13] Combined with the results of this study, haemoglobin reduction may be one of the causes of AAE by causing hypoxia in the brain. Second, many antibiotics need to be combined with albumin and transported after entering the body, such as

Table 3 AUC, best cut-off value, sensitivity and specificity of each risk factor in the evaluation of CKD with AAE

Factor	Best cut-off value	Sensitivity	Specificity	AUC (95% CI)	P value
Haemoglobin	88.50	0.800	0.667	0.710 (0.580 to 0.841)	0.622 (vs albumin), 0.654 (vs blood phosphorus)
Albumin	28.80	0.867	0.485	0.663 (0.527 to 0.799)	0.963 (vs blood phosphorus) 0.233 (vs blood uric acid)
Blood phosphorus	1.010	1.000	0.364	0.667 (0.532 to 0.802)	0.214 (vs blood uric acid)
Blood uric acid	228.5	1.000	0.152	0.542 (0.397 to 0.686)	0.090 (vs haemoglobin)

AAE, antibiotic-associated encephalopathy; AUC, area under the curve; CKD, chronic kidney disease.

carbapenems and cephalosporins. When the human blood albumin concentration drops, it can cause the concentration of free antibiotics to increase.[14–16] This further shows that the reduction of albumin level may promote the occurrence of AAE. Third, abnormal blood phosphorus concentration is also a common complication of CKD. Patients with long-term malnutrition and sepsis can induce hypophosphataemia, which can lead to central nervous system complications such as mental disorders and epilepsy.[17 18] These studies suggest that decreased blood phosphorus in patients with CKD may increase the chance of AAE. Fourth, normal concentration of uric acid has antioxidant capacity.[19–21] In this study, the level of uric acid in the AAE group was significantly lower than that in the control group. It is suggested that increasing uric acid may play a certain protective effect on the occurrence of AAE in patients with CKD. In addition, this study also showed that the patient's history of coronary heart disease is risk factor for CKD with AAE. Because coronary heart disease is high-risk factor for cerebral arteriosclerosis, patients with the history of coronary heart disease are more serious than ordinary patients with cerebral arteriosclerosis.[22]

In summary, once AAE occurs, it will increase the case fatality rate and cause a poor prognosis. In addition, AAE may be misdiagnosed in the clinical diagnosis and treatment process, and it is more likely to delay the disease. A history of coronary heart disease, as well as abnormal indicators of haemoglobin, albumin, uric acid, and blood phosphorus are independent risk factors for patients with CKD accompanied with AAE. Once a patient with CKD has a history of coronary heart disease, or a reduction in haemoglobin, serum albumin, uric acid and blood phosphorus levels, the patient is more likely to be accompanied by AAE. Then, early detection and early treatment must be achieved. In the treatment of CKD, attention should be paid to the emergence of the above-mentioned early warning factors. Timely intervention of the above risk factors will reduce the incidence of AAE and improve the prognosis.

Contributors HW: conceptualisation, methodology, formal analysis, data curation, funding acquisition, writing—original draft. DL: conceptualisation, methodology, formal analysis, data curation, supervision, writing—review and editing, and is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethics Committee of Tianjin Third Central Hospital (Ethics approval number: IRB2019-035-02). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All data generated or analysed during this study are included in this published article.

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