Risk Factors for Herpes Zoster Infection in Patients With Chronic Kidney Disease: A Case-control Study

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Abstract

**Background:** Chronic kidney disease (CKD) increases the susceptibility to the infection of herpes zoster (HZ). Less is known about the risk factors of HZ in CKD patients.

**Methods and Participants:** This is a case-control study. CKD patients diagnosed with HZ infection between January 2015 and October 2020 in a tertiary hospital were identified. One age- and gender-matched control was paired for each case, matched to the date of initial HZ diagnose. The uni- and multivariate analysis were used to evaluate the risk factors for development of HZ in CKD patients.

**Results:** Forty-six HZ patients and controls were identified. In general, about 80% (72 out of 92) patients were classified at end-stage renal disease (ESRD, CKD V to VI). Multivariate analyses revealed that immunosuppressive agents (odds ratio: 12.50, 95% CI: 1.53-102.26, P=0.021) and dialysis (odds ratio: 3.33, 95% CI: 1.13-9.78, P=0.029) were independent risk factors of HZ in patient with CKD.

**Conclusion:** Immunosuppressive medication and dialysis were associated with HZ infection in CKD. Further guideline may highlight the necessity of zoster vaccine for patients with CKD, who undertake immunosuppressive or dialysis treatment.

Introduction

The burden of chronic kidney disease (CKD) has become a great challenge of global healthcare system, affected almost 15% of adults in the United States. As progression of CKD, costly therapy such as dialysis or kidney transplant may be required to maintain the function of kidney. Moreover, patients with CKD exhibit great risk to develop cardiovascular disease, in both dialysis- and non–dialysis dependent population. Infectious disease is the second most common cause of morbidity and mortality in CKD, accounting for 30–36% of death. The mechanism underlying the immune dysfunction of CKD includes poor nutritional condition, immunosuppressive medication and uremic toxins. Consequently, infectious-related mortality increased significantly in patients with CKD, especially for those have progressed to end-stage renal disease (ESRD).

Herpes zoster (HZ), also known as shingles, is a common viral infection that occurs with reactivation of the varicella-zoster virus. Accumulating evidence has suggested that CKD as an important risk factor for HZ. Incidence of postherpetic neuralgia (PHN), the most common complication of HZ, also increases significantly among CKD cohort. PHN patients often present physical, occupational, social, and psychosocial disabilities as a result of the unremitting pain. Furthermore, the overall risk for developing cardiovascular event also increased after zoster attack.

One effective approach to reduce the morbidity of HZ and postherpetic neuralgia is to apply zoster vaccine. Recent study has demonstrated that zoster vaccine was effective against incident zoster for the elderly with CKD. In addition to advancing ages, less is known about the other risk factors for HZ
lesion in CKD population. To achieve better clinical outcome of CKD, early recognition of potential HZ infection and subsequent protective vaccine therapy is urgently needed. In current study, we aim to examine the potential risk factors to develop HZ in CKD patients.

Methods

Study Population

The study was approved by the ethics committee of the Third Xiangya Hospital, Central South University (NO.2050-s388), and informed consent was waived due to the observational design in this study.

Cases

Ninety-two CKD patients diagnosed with HZ (ICD-10-CM codes: B02) between January 2015 and October 2020 at the Third Xiangya Hospital of Central South University were identified. Forty-six cases who underwent transplant were not included in this study.

Controls. The controls were randomly retrieved from the remaining CKD patients, age- and sex- matched with the HZ cases. One control was identified for each case and matched to the date of initial herpetic diagnose.

Data Collection

Two colleagues (Q. W and ZX. L) independently reviewed the medical record of all cases and controls. One standard data collection form was applied to record the general characteristics and clinical information. The age of patient was identified as the onset of herpes rash. The first data available follow admission was recorded and applied for further analysis.

Statistical Analysis

Chi-squared test or Fisher exact test were conducted to compare categorical data. The Student t test or Mann-Whitney U test was used when appropriate to analyze continuous data. Uni- and multivariate logistics analysis was performed to evaluate the independent risk factors associated with HZ infection in CKD patient. Only variables with a p value < 0.05 between cases and controls were included for multivariate logistics analysis. All continuous data are presented as mean ± standard deviation. Estimation of risk was presented as odds ratios (ORs) with 95% CIs, and two-tailed p value < 0.05 was considered statistically significant. All data analysis was processed with SPSS (version 16.0, Chicago, IL).

Result

General Characteristics

The research of medical database initially identified a total of 46 CKD cases with a diagnose of HZ. Next, forty-six age- and sex-matched controls were selected randomly from the remaining CKD cohort. The
mean duration of CKD was approximately 45 months in HZ group, almost 2 times longer compared with control group (P = 0.07). Only one out of 46 patients (2.1%) took regular immunosuppressive agents in the control group, and 22.7% (n = 10/44) for HZ group respectively (P = 0.004). Compared with control group, more patients required the renal replacement therapy of dialysis (71.7% versus. 45.7%, P = 0.003). The majority of patients (80.4%) in this study were identified as ESRD (CKD 3 to 5). However, no significant difference of disease severity was found between groups (P = 0.46). The general information of enrolled participants is given in Table 1.

**Laboratory Result**

The diagnostic detail of laboratory test is shown as Table 2. In general, the HZ patients presented a significant dysfunction of immune system, characterized by reduced total lymphocyte account (P = 0.003) and neutrophil-to-lymphocyte ratio (P = 0.04). Meanwhile, the concentration of albumin was 31.65 ± 6.05 g/L in HZ cohort, significantly lower than control group (P = 0.004). No obvious difference of renal function was found between groups according to current data.

**Logistic Regression**

In the univariate regression analysis, total lymphocyte account, neutrophil-to-lymphocyte ratio, serum albumin, immunosuppressive and dialysis treatment predicted the onset of HZ (Table 3). Among the risk factors for development of HZ, multivariate logistic regression revealed that immunosuppressive agents (odds ratio: 12.50, 95% CI: 1.53-102.26, P = 0.021) and dialysis treatment (odds ratio: 3.33, 95% CI: 1.13–9.78, P = 0.029) were independent risk factors for HZ infection.

**Discussion**

In this case-control study, we investigated 92 patients with CKD at a tertiary hospital and aimed to evaluate the potential risk factors for development of HZ infection. To our knowledge, it is the first time we identified immunosuppressive agents and dialysis treatment as independent risk factors for development of HZ in CKD population.

Kidney disease severity is classified into five stages according to the level of glomerular filtration rate. Previous study has demonstrated that ESRD as a risk factor for development of HZ infection. Similarly, we found that most of HZ cases (74%, n = 34/46) were identified at the ESRD in this study. The overall incidence of ESRD increases with age and the majority of patients who reach ESRD are 65 years or older. Despite disease severity, herpes zoster is also of particular concern in the elderly. The mean age of subjects in this study was around 60 years old. Given the advancing age, we did NOT find significantly increased disease severity in HZ patients compared with control group.

Consistent with previous reports, our data indicated an increased risk of HZ in patients who regularly take immunosuppressive medication. In our study, we found that patients who took immunosuppressive drugs were at almost fourteen-fold increased risk of HZ compared with control group. The common co-morbidity of CKD patients who use immunosuppressive therapy, includes rheumatoid arthritis and
systemic lupus erythematosus. Despite immunosuppressive treatment, we found that dialysis was associated with greater risk of zoster. There were 33 out of 46 cases (71.7%) treated with dialysis, and 45.7% for control group respectively. The large cohort study conducted by Lin et al. showed similar results, that both peritoneal dialysis and hemodialysis patients presented higher incidence of HZ compared with control. The highest risk of HZ infection was reported in patients underwent renal transplant. Although we identified 46 HZ cases after renal transplant in the initial research. We did not enroll these patients due to the complex factors in the status of renal transplant.

There are some correlations between the immune deficiency and the incidence of infectious complications in CKD patient, characterized by a significant lymphopenia. Similarly, we found that the total lymphocyte account was significantly lower in HZ patient compared with control group. The mechanism underlying the lymphopenia in CKD is that lower T cell homeostatic proliferation. It is not surprising that total leukocyte counts showed no significant difference between groups, mainly due to routine medication to prevent leukopenia. Thus, combination of mild neutrophilia and significant lymphopenia potentially caused an increased neutrophil-to-lymphocyte ratio.

A plethora of corroborative evidence in CKD population has suggested inverse relationship between serum albumin and poor prognosis. However, the context in herpetic infection remains unclear. In our study, we found significant reduction of serum albumin in CKD patient with HZ, compared with control group. Although the prognostic value of serum albumin was not statistically significant in the logistic regression analysis. The allocation of CKD patient based on serum albumin levels is helpful in prediction of infection-related death, but not available in this study due to limited number of subjects.

Our study has some limitations beyond the limited sample size. First, the retrospective nature of this study design is likely to omit the feature data. The data we collected were derived from general characteristics and routine laboratory test. Specific examination of immune function such as lymphocyte subset analysis and interleukin 2. Second, information regarding the patient’s course after discharge was not available for control group. This supports the need for future research to conduct long-term follow-up.

In conclusion, immunosuppressive and dialysis therapy are independent risk factors for the development of HZ infection in patients with CKD. Further guideline may highlight the necessity of zoster vaccine for patients with CKD, who undertake immunosuppressive or dialysis treatment.
Table 1
General characteristics of herpetic and non-herpetic patients with CKD.

| Variables                     | HZ        | Non-HZ     | P value |
|-------------------------------|-----------|------------|---------|
| N                             | 46        | 46         |         |
| Age (years)                   | 58.89 ± 13.85 | 56.15 ± 13.37 | 0.340   |
| Sex (female, %)               | 21 (45.6) | 21 (45.6)  | 1.000   |
| Body Mass Index (kg/m$^2$)    | 21.97 ± 3.20 | 22.94 ± 30.41 | 0.540   |
| Known CKD duration (months)   | 44.64 ± 48.7 | 22.94 ± 30.41 | 0.070   |
| Intervention (n, %)           |           |            |         |
| Immunosuppressive agents      | 10/44, (22.7) | 1/46, (2.1)  | 0.004   |
| Dialysis therapy              | 33/46, (71.7) | 21/46, (45.7) | 0.003   |
| CKD stage (n, %)              |           |            | 0.460   |
| ✸                             | 0 (0)     | 0 (0)      |         |
| ✷                             | 6 (13)    | 2 (4)      |         |
| ✶                             | 6 (13)    | 4 (9)      |         |
| ✸                             | 5 (11)    | 14 (30)    |         |
| ✷                             | 29 (63)   | 26 (57)    |         |

CKD: Chronic Kidney Disease; HZ: Herpes Zoster.
Table 2
Laboratory findings of CKD patients.

| laboratory indicators                  | HZ                  | Non-HZ             | P value |
|----------------------------------------|---------------------|---------------------|---------|
| White blood cell count, 10^9/L          | 6.42 ± 2.41         | 7.00 ± 2.29         | 0.240   |
| Neutrophil count, 10^9/L               | 4.88 ± 2.20         | 5.10 ± 2.27         | 0.640   |
| Lymphocyte count, 10^9/L               | 0.93 ± 0.50         | 1.24 ± 0.46         | 0.003   |
| Eosnophils count, 10^9/L               | 0.14 ± 0.15         | 0.20 ± 0.49         | 0.379   |
| Basophil count, 10^9/L                 | 0.02 ± 0.02         | 0.03 ± 0.03         | 0.103   |
| Platelet count, 10^9/L                 | 173.33 ± 86.17      | 174.98 ± 72.38      | 0.921   |
| Red blood cell count, 10^9/L           | 3.08 ± 0.77         | 3.00 ± 0.85         | 0.649   |
| Hb (g/L)                               | 93.43 ± 22.93       | 89.89 ± 25.21       | 0.482   |
| Hematocrit(%)                          | 28.80 ± 6.77        | 27.82 ± 7.35        | 0.508   |
| Neutrophils-lymphocytes ratio(%)       | 7.01 ± 5.44         | 4.97 ± 5.32         | 0.040   |
| C-reactive protein (mg/L)              | 23.43 ± 47.60       | 15.91 ± 36.85       | 0.580   |
| Erythrocyte sedimentation rate(mm/hr)  | 40.25 ± 27.29       | 45.06 ± 32.36       | 0.500   |
| Glucose(mmol/L)                        | 5.39 ± 2.07         | 5.23 ± 1.66         | 0.680   |
| Procalcitonin (ng/ml)                  | 1.0 ± 0.97          | 0.86 ± 1.77         | 0.800   |
| Serum albumin(g/L)                     | 31.65 ± 6.05        | 35.17 ± 5.18        | 0.004   |
| Serum globulin(g/L)                    | 25.14 ± 6.09        | 24.91 ± 4.16        | 0.830   |
| Ratio of albumin to globulin           | 1.32 ± 0.38         | 1.46 ± 0.33         | 0.070   |
| Alanine aminotransferase(U/L)          | 18.62 ± 13.65       | 17.18 ± 13.31       | 0.616   |
| Aspartate aminotransferase(U/L)        | 20.22 ± 15.52       | 20.54 ± 10.43       | 0.912   |
| Total bilirubin(umol/L)                | 7.65 ± 5.25         | 8.29 ± 5.56         | 0.572   |
| Direct bilirubin(umol/L)               | 2.40 ± 3.31         | 2.29 ± 2.18         | 0.854   |
| Total bile acid(umol/L)                | 5.02 ± 5.69         | 3.56 ± 2.58         | 0.126   |
| Low-density lipoprotein(mmol/L)        | 2.09 ± 0.72         | 2.06 ± 0.78         | 0.857   |
| High-density lipoprotein(mmol/L)       | 1.17 ± 0.41         | 1.13 ± 0.36         | 0.697   |
| Total cholesterol(mmol/L)              | 4.46 ± 1.21         | 4.11 ± 1.28         | 0.196   |
| Triglyceride(mmol/L)                   | 2.17 ± 1.85         | 1.71 ± 1.89         | 0.248   |
### Table 3
Uni- and multivariate analysis of risk factors for herpes zoster in patients with chronic kidney disease.

| Covariates               | Univariate | P     | Multivariate | P     |
|--------------------------|------------|-------|--------------|-------|
|                          | OR (95% CI)| value | OR (95% CI)  | value |
| Total lymphocyte count   | 0.26(0.10–0.66) | **0.005** | 0.43(0.11–1.64) | 0.216 |
| Neutrophils-lymphocytes ratio | 1.11(1.00-1.24) | **0.046** | 0.99(0.86–1.13) | 0.828 |
| Serum albumin            | 0.90(0.83–0.97) | **0.006** | 0.96(0.87–1.05) | 0.356 |
| Immunosuppressive agents | 12.50(1.53-102.26) | **0.019** | 13.90(1.48-130.75) | **0.021** |
| Dialysis therapy         | 3.79(1.52–9.24) | **0.003** | 3.33(1.13–9.78) | **0.029** |

### Declarations

#### Conflict of Interest

The authors declare that this research was conducted in the absence of commercial or financial relationships that could be construed as a potential conflict of interest.

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#### Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Third Xiangya Hospital of Central South University (NO.2050-s388).

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