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 4 to 5). 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.¹ 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.² Infectious disease is the second most common cause of morbidity and mortality in CKD, accounting for 30–36% of death.^{3,4} The mechanism underlying the immune dysfunction of CKD includes poor nutritional condition, immunosuppressive medication and uremic toxins.⁵ Consequently, infectious-related mortality increased significantly in patients with CKD, especially for those have progressed to end-stage renal disease (ESRD).⁶

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.^{7–12} Incidence of postherpetic neuralgia (PHN), the most common complication of HZ, also increases significantly among CKD cohort.¹³ PHN patients often present physical, occupational, social, and psychosocial disabilities as a result of the unremitting pain.¹⁴ Furthermore, the overall risk for developing cardiovascular event also increased after zoster attack.^{15,16}

One effective approach to reduce the morbidity of HZ and postherpetic neuralgia is to apply zoster vaccine.¹⁷ Recent study has demonstrated that zoster vaccine was effective against incident zoster for the elderly with CKD.¹⁸ 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 $\pm$ 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 4 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.¹⁹ Previous study has demonstrated that ESRD as a risk factor for development of HZ infection.¹⁰ 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.²⁰ Despite disease severity, herpes zoster is also of particular concern in the elderly.^{21,22} 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.^{23,24} 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.²⁵ The highest risk of HZ infection was reported in patients underwent renal transplant.²⁵ 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.²⁶ 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.²⁷ 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.²⁶

A plethora of corroborative evidence in CKD population has suggested inverse relationship between serum albumin and poor prognosis.^{28,29} 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.²⁹

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.^{26,30} 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
I	0 (0)	0 (0)	
II	6 (13)	2 (4)	
III	6 (13)	4 (9)	
IV	5 (11)	14 (30)	
V	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

laboratory indicators	HZ	Non-HZ	P value
Urea(mmol/L)	33.04 ± 77.24	21.22 ± 10.03	0.310
Creatinine(umol/L)	623.78 ± 432.07	620.87 ± 345.28	0.970

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).

References

1. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2019. (US Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, 2019).

2. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*.17(7):2034-47 (2006).
3. van Dijk PC, Jager KJ, de Charro F, Collart F, Cornet R, Dekker FW, *et al*. Renal replacement therapy in Europe: The results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant*.16:1120–9 (2001).
4. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int*. 58:1758–64 (2000).
5. Overall immune profile and effect of chronic kidney disease on vaccination schedule. *Indian J Nephrol*.26(Suppl 1):S2-S4 (2016).
6. Kato S, Chmielewski M, Honda H, *et al*. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol*. 3(5):1526-1533 (2008).
7. Kawai K, Yawn BP. Risk Factors for Herpes Zoster: A Systematic Review and Meta-analysis. *Mayo Clin Proc*. 92(12):1806-1821 (2017).
8. Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Langan SM. Quantification of risk factors for herpes zoster: population based case-control study. *BMJ*.348:g2911 (2014).
9. Wu MY, Hsu YH, Su CL, Lin YF, Lin HW. Risk of herpes zoster in CKD: a matched-cohort study based on administrative data. *Am J Kidney Dis*.60(4):548-52 (2012).
10. Kuo CC, Lee CT, Lee IM, Ho SC, Yang CY. Risk of herpes zoster in patients treated with long-term hemodialysis: a matched cohort study. *Am J Kidney Dis*.59(3):428-33 (2012).
11. Sato T, Inoue T, Endo K, *et al*. End-stage renal disease (ESRD) contributes to the increasing prevalence of herpes zoster. *NDT Plus*. 2(3):263-264 (2009).
12. Arness T, Pedersen R, Dierkhising R, Kremers W, Patel R. Varicella zoster virus-associated disease in adult kidney transplant recipients: incidence and risk-factor analysis. *Transpl Infect Dis*. 10(4):260-8 (2008).
13. Forbes HJ, Bhaskaran K, Thomas SL, *et al*. Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study. *Neurology*. 87(1):94-102 (2016).
14. Makharita MY. Prevention of Post-herpetic Neuralgia from Dream to Reality: A Ten-step Model. *Pain Physician*. 20(2):E209-E220 (2017).
15. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. *Stroke*. 40(11):3443-8 (2009).
16. Cheikh Hassan HI, Tang M, Djurdjev O, Langsford D, Sood MM, Levin A. Infection in advanced chronic kidney disease leads to increased risk of cardiovascular events, end-stage kidney disease and mortality. *Kidney Int*. 90(4):897-904 (2016).
17. Oxman MN, Levin MJ, Johnson GR, *et al*. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. J. 352(22):2271-84 (2005).
18. Tseng HF, Luo Y, Shi J, Sy LS, Tartof SY, Sim JJ, Hechter RC, Jacobsen SJ. Effectiveness of Herpes Zoster Vaccine in Patients 60 Years and Older With End-stage Renal Disease. *Clin Infect Dis*.

62(4):462-7 (2016).

19. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 67(6):2089-100 (2005).
20. Prakash S, O'Hare AM. Interaction of aging and chronic kidney disease. *Semin Nephrol.* 29(5):497-503 (2009).
21. John AR, Canaday DH. Herpes Zoster in the Older Adult. *Infect Dis Clin North Am.* 31(4):811-826 (2017).
22. Ahn JH, Waller JL, Baer SL, Colombo RE, Kheda MF, Nahman NS Jr, Turrentine JE. Mortality risk after herpes zoster infection in end-stage renal disease patients. *Clin Kidney J.* 12(1):101-105 (2019).
23. Liao TL, Chen YM, Liu HJ, Chen DY. Risk and severity of herpes zoster in patients with rheumatoid arthritis receiving different immunosuppressive medications: a case-control study in Asia. *BMJ Open.* 7(1):e014032 (2017).
24. Hu SC, Yen FL, Wang TN, Lin YC, Lin CL, Chen GS. Immunosuppressive medication use and risk of herpes zoster (HZ) in patients with systemic lupus erythematosus (SLE): A nationwide case-control study. *J Am Acad Dermatol.* 75(1):49-58 (2016).
25. Lin SY, Liu JH, Lin CL, Tsai IJ, Chen PC, Chung CJ, Liu YL, Wang IK, Lin HH, Huang CC. A comparison of herpes zoster incidence across the spectrum of chronic kidney disease, dialysis and transplantation. *Am J Nephrol.* 36(1):27-33 (2012).
26. Hutchinson P, Chadban SJ, Atkins RC, Holdsworth SR. Laboratory assessment of immune function in renal transplant patients. *Nephrol Dial Transplant.* 18(5):983-9 (2003).
27. Lamarche C, Iliuta IA, Kitzler T. Infectious Disease Risk in Dialysis Patients: A Transdisciplinary Approach. *Can J Kidney Health Dis.* 29;6:2054358119839080 (2019).
28. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. *J Am Soc Nephrol.* 21(2):223-30 (2010).
29. Minatoguchi S, Nomura A, Imaizumi T, *et al.* Low serum albumin as a risk factor for infection-related in-hospital death among hemodialysis patients hospitalized on suspicion of infectious disease: a Japanese multicenter retrospective cohort study. *Ren Replace Ther.* 4, 30 (2018).
30. Weinberg A, Kroehl ME, Johnson MJ, Hammes A, Reinhold D, Lang N, Levin MJ. Comparative Immune Responses to Licensed Herpes Zoster Vaccines. *J Infect Dis.* 218(suppl_2): S81-S87 (2018).