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ORIGINAL ARTICLE

Mortality risk after herpes zoster infection in end-stage renal disease patients

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ABSTRACT

Background. End-stage renal disease (ESRD) patients have increased risk of developing herpes zoster (zoster) compared with the general population, but mortality risk is unknown. We assessed the risk of mortality in hospitalized ESRD patients with a diagnosis of zoster from the inpatient hospital files (as opposed to outpatient records) of the United States Renal Data System.

Methods. This study analyzed incident ESRD patients from 2006 to 2009. Based on an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code of zoster infection, we determined 2-year mortality following an inpatient diagnosis. Cox proportional hazards models were used to examine the association of mortality and zoster, when controlling for demographic and other clinical risk factors.

Results. Zoster was diagnosed in 2784 patients, 51% of whom died within 2 years, with a mean time to death of 8.1 months. Patients who died were more likely to be white and older, score higher on the Charlson Comorbidity Index (CCI) and have other clinical diagnoses besides CCI. Increased risk of death within 2 years was associated with older age (adjusted hazard ratio 1.03), malnutrition (1.31), bacteremia/septicemia (1.16) and increasing CCI (1.10). Zoster vaccine was administered to 27 patients, but the small number precluded analysis of its impact.

Conclusions. Mortality in ESRD patients with an inpatient zoster diagnosis is increased with older age and higher severity of clinical comorbidities. The role of zoster vaccination on mortality in this population remains to be defined.

Keywords: dialysis, herpes zoster, mortality, risk factors, United States Renal Data System

INTRODUCTION

Herpes zoster (zoster) is caused by reactivation of latent varicella zoster virus. Zoster, or shingles, typically manifests clinically as a pustular eruption in a dermatomal distribution and lasts ~3 weeks. The disease course may be shortened by glucocorticoids and antiviral therapy with guanosine analogues (e.g. valacyclovir, acyclovir and famciclovir) and prevented with a vaccine [1]. Complications of reactivation include ocular herpes

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with visual loss or blindness, encephalitis, pneumonitis, secondary infection and postherpetic neuralgia [2].

Zoster is of particular concern in end-stage renal disease (ESRD) patients due to their older age (48% are >65 years old) and relatively immunosuppressed state [3, 4]. Although older age is the most important risk factor for development of zoster, an immunosuppressed state in the setting of zoster has been shown to have a significantly higher rate of complications. In ESRD patients, cytokines and uremic toxins accumulate secondary to loss of renal function, and this creates a pro-inflammatory environment that negatively affects both innate and adaptive immunity. Specific examples of these immunological abnormalities related to viral infections include a decreased number and activation of natural killer cells, decreased antigen presentation and circular dichroism 86 (CD86) expression by dendritic cells, increased apoptosis and decreased function of T cells and B cells. Overall, reduced numbers of natural killer cells, dendritic cells, and B and T cell lymphocytes could contribute to the inadequate responses of ESRD patients to viral infections such as zoster [5].

Previous studies have shown that ESRD patients are at increased risk of developing zoster compared with the general population [6]. In this regard, the incidence in the general population is estimated to be 3.9 per 1000 person-years [7], whereas the incidence in ESRD patients is estimated to be nearly 20-fold higher, at 73.3 per 1000 person-years [6].

The increased incidence of zoster infection, and relative level of immunocompromise in ESRD patients, allowed us to theorize that ESRD patients with a zoster diagnosis may be at increased risk for mortality. To test this question, we queried the United States Renal Data System (USRDS), an administrative federal dataset containing all diagnostic and procedural codes submitted to Medicare on every ESRD patient in the USA, for the risk of mortality in hospitalized ESRD patients with a diagnosis of zoster.

MATERIALS AND METHODS

Study cohort

The population comprises incident hemodialysis patients, ages 18–100 years at the time of the start of dialysis, who initiated therapy between 1 January 2006 and 31 December 2009 ($n = 446\,465$). Hospital claims data from the USRDS standard analysis files were used. All patients were covered by Medicare parts A and B as primary payer at initiation of dialysis. Exclusion criteria included no hospital claims; missing or unknown age, sex, race or ethnicity; or death on or before the start of dialysis. The study cohort was defined as patients with a diagnosis of zoster following initiation of dialysis based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) diagnosis code 053 from inpatient hospital claims data.

Outcome variable

The primary outcome variable was mortality within 2 years following a diagnosis of zoster and after the initiation of dialysis. The start date was the date of zoster diagnosis. Time to death within 2 years was determined as the time from the diagnosis of zoster to death for those who died. For those who did not die within 2 years, time to death was defined as the time from the diagnosis of zoster to the last claim date, or 2 years, whichever came first. A 2-year follow-up was chosen to capture any long-term complications that could have been attributed to the infection.

Risk factors for mortality

Potential risk factors for mortality within 2 years of a zoster diagnosis included demographic variables (age, race, sex and ethnicity), dialysis type and clinical diagnoses occurring before the diagnosis of zoster diagnosis. The Charlson Comorbidity Index (CCI) was used to assess not only the number, but also the severity of comorbid diagnoses. Other clinical diagnoses not a part of the CCI were examined as risk factors and include bacteremia/septicemia, candidemia, *Clostridium difficile* infection (CDI), hepatitis B, hepatitis C, methicillin-resistant *Staphylococcus aureus* (MRSA) infection, pancytopenia, kidney transplant, coronary artery disease (CAD), hypertension, malnutrition and total parenteral nutrition (TPN). All clinical risk factors were determined using ICD-9 codes from hospital claims data or Current Procedural Terminology codes in provider claims. Demographic data were determined from the ESRD Medical Evidence form [Centers for Medicare & Medicaid Services (CMS) 2728].

Statistical analysis

All statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics (frequencies and percentages or means and standard deviations, where appropriate) by mortality status were determined. Chi-square tests and *t*-tests were used to examine preliminary differences by mortality.

To examine risk factors for mortality, a Cox proportional hazards (CPH) model building strategy was used. Time to death was the outcome. Each potential independent risk factor was first examined in simple bivariate CPH models and the hazard ratio (HR) and corresponding 95% confidence interval (CI) was estimated. All variables were then entered into a comprehensive full model and a backward model-building strategy was used to arrive at the final model. Variables that had the least significant P-value in the full model were eliminated one by one. The final model consisted of those variables that were statistically significant at the 0.05 significance level or needed in the model using Akaike's information criterion (AIC) and Bayesian information criterion (BIC) model fit criteria. The AIC and BIC were examined after each nonsignificant variable was removed from the model. The final model contained all risk factors that were statistically significant or needed in the model to improve model fit. The adjusted hazard ratio (aHR) and corresponding 95% CI were estimated for each variable in the final model. Note that the aHR is interpreted as the HR for that specific variable adjusting for all other variables in the final model.

RESULTS

Characteristics of the study cohort

For the 3-year study period, there were 446 465 incident dialysis patients. After applying the exclusion criteria, the sample consisted of 221 546 individuals. From this group, 2784 patients had a zoster diagnosis and 51% died ($n = 1420/2784$).

Table 1 summarizes descriptive statistics by mortality status. Patients who died were older, white and non-Hispanic when compared with those who were alive at 2 years. The time

Table 1. Descriptive statistics for mortality within each risk factor and chi-square or t-test results among ESRD zoster patients

Variable	Level	Died [n = 1420 (51.0%)]	Alive [n = 1364 (49.0%)]	P-value
Demographics				
Age at first dialysis (years), mean (SD)		70.7 (12.8)	62.4 (14.8)	<0.0001
Sex, *n* (%)	Female	744 (51.0)	716 (49.0)	0.9586
	Male	676 (51.1)	648 (48.9)	
Race, *n* (%)	Black	249 (40.8)	361 (59.2)	<0.0001
	Other	55 (37.7)	91 (62.3)	
	White	1116 (55.0)	912 (45.0)	
Ethnicity, *n* (%)	Hispanic	165 (45.7)	196 (54.3)	0.0308
	Non-Hispanic	1255 (51.8)	1168 (48.2)	
Dialysis type, *n* (%)	HD	1323 (52.5)	1196 (47.5)	<0.0001
	Missing/unknown	24 (22.4)	83 (77.6)	
	PD	73 (46.2)	85 (53.8)	
Clinical diagnoses				
CCI, mean (SD)		5.7 (2.4)	4.8 (2.3)	<0.0001
Bacteremia/septicemia, *n* (%)	Present	517 (56.3)	402 (43.7)	<0.0001
Candidemia, *n* (%)	Present	6 (100.0)	0 (0.0)	0.0162
C. difficile, *n* (%)	Present	137 (57.3)	102 (42.7)	0.0410
Hepatitis B, *n* (%)	Present	10 (40.0)	15 (600)	0.2688
Hepatitis C, *n* (%)	Present	38 (45.8)	45 (54.2)	0.3339
MRSA infection, *n* (%)	Present	33 (49.3)	34 (50.8)	0.7715
Pancytopenia, *n* (%)	Present	30 (50.0)	30 (50.0)	0.8748
Kidney transplant, *n* (%)	Present	25 (13.4)	162 (86.6)	<0.0001
CAD, *n* (%)	Present	76 (47.5)	84 (52.5)	0.3609
Hypertension, *n* (%)	Present	1371 (51.2)	1308 (48.8)	0.3646
Malnutrition, *n* (%)	Present	299 (61.8)	185 (38.2)	<0.0001
TPN, *n* (%)	Present	39 (56.5)	30 (43.5)	0.3533
Cause of death among those who died				
Primary cause, *n* (%)	Cardiac	476 (33.5)		
	Endocrine	1 (0.1)		
	Gastrointestinal	6 (0.4)		
	Infection	128 (9)		
	Liver disease	9 (0.6)		
	Metabolic	9 (0.6)		
	Other	720 (50.7)		
	Vascular	71 (5)		
Time to death/follow-up (months)		8.1 (7)	16.7 (9.4)	<0.0001

HD, hemodialysis; PD, peritoneal dialysis.

to death or follow-up was 8.1 and 16.7 months in nonsurvivors versus survivors, respectively ($P < 0.0001$).

Zoster patients who died had a higher CCI [5.7 ± 2.4 versus 4.8 ± 2.3 ($P < 0.0001$) for non-survivors versus survivors, respectively] and a greater incidence of bacteremia/septicemia, CDI and malnutrition. Patients with a history of kidney transplant ($n = 62$) had a significantly lower incidence of mortality. The most common primary causes of death were cardiac (33.5%) and unclassified 'other' (50.7%). A total of 27 patients received the zoster vaccination. Ten patients developed zoster and 17 did not ($P = 0.029$).

Risk factors for mortality

Table 2 gives the crude and final multivariable CPH model for mortality for these patients and contains only those variables that were statistically significant or needed in the final model after performing the backward model building. There was a significant increase in mortality in patients who were older (aHR 1.03), with a higher CCI (aHR 1.10), bacteremia or septicemia (aHR 1.16) or with malnutrition (aHR 1.31). Factors that showed a decreased risk of mortality included black (aHR 0.70) or other race (aHR 0.67) when compared with whites, history of kidney transplant (aHR 0.40) and CAD (aHR 0.70). The observed increased aHR (2.07) in patients with a diagnosis of candidemia was not statistically significant due to the small number of patients ($n = 6$).

DISCUSSION

In this population-based cohort study, we found that hospitalized dialysis patients with a diagnosis of zoster who died were older and white. Significant clinical comorbidities that also increased the risk of mortality included malnutrition, bacteremia/septicemia and an increased CCI. To our knowledge, this study is the first to investigate the risk of mortality in ESRD patients diagnosed with zoster during a hospitalization.

In this study we showed that mortality following zoster was associated with increasing age. This is in agreement with what has been reported for the general population [8, 9].

Table 2. Crude and final CPH models on 2-year mortality for demographic and clinical risk factors among zoster patients only

		Crude HR from simple models				Adjusted HR from final model			
			95% CI				95% CI		
Variable	Level	HR	Lower	Upper	P-value	HR	Lower	Upper	P-value
Demographic risk factors									
Age at first dialysis		1.03	1.02	1.03	<0.0001	1.03	1.02	1.03	<0.0001
Sex	Female versus male[a]	0.95	0.86	1.06	0.3575				
Race	Black versus white[a]	0.65	0.56	0.74	<0.0001	0.70	0.61	0.81	<0.0001
	Other versus white[a]	0.64	0.49	0.84		0.67	0.51	0.88	
Ethnicity	Hispanic versus non-Hispanic[a]	0.90	0.77	1.06	0.2038				
Dialysis type, *n* (%)	HD versus PD	1.06	0.83	1.34	0.0026				
	Missing/unknown versus PD	0.52	0.33	0.83					
Clinical diagnosis risk factors									
CCI		1.08	1.06	1.10	<0.0001	1.10	1.07	1.12	<0.0001
Bacteremia/septicemia	Dx versus no Dx[a]	1.23	1.10	1.37	0.0002	1.16	1.04	1.29	0.0106
Candidemia	Dx versus no Dx[a]	2.33	1.04	5.19	0.0389	2.07	0.92	4.64	0.0773
C.difficile	Dx versus no Dx[a]	1.14	0.96	1.36	0.1451				
Hepatitis B	Dx versus no Dx[a]	0.66	0.35	1.23	0.1882				
Hepatitis C	Dx versus no Dx[a]	0.78	0.56	1.07	0.1267				
MRSA infection	Dx versus no Dx[a]	0.82	0.58	1.16	0.2608				
Pancytopenia	Dx versus no Dx[a]	1.08	0.76	1.56	0.6634				
Kidney transplant	Dx versus no Dx[a]	0.31	0.21	0.46	<0.0001	0.40	0.27	0.60	<0.0001
CAD	Dx versus no Dx[a]	0.82	0.65	1.03	0.0823	0.70	0.55	0.88	0.0025
Hypertension	Dx versus no Dx[a]	0.90	0.68	1.20	0.4820				
Malnutrition	Dx versus no Dx[a]	1.38	1.21	1.56	<0.0001	1.31	1.15	1.49	<0.0001
TPN	Dx versus no Dx[a]	1.17	0.85	1.61	0.3270				

[a]Indicates referent group. Dx, diagnosis; HD, hemodialysis; PD, peritoneal dialysis.

The results of this study indicate that in zoster patients, the greater the number of serious comorbidities, the greater the risk of death. In this regard, we showed that an increase in the CCI was associated with an increased risk of mortality. The CCI represents a validated scoring system for predicting mortality by classifying or weighting comorbidities and is an accepted approach for quantitating the burden of disease and case mix [10]. Our data indicate that those who died exhibited a higher disease burden than patients without the zoster diagnosis.

This study demonstrates that malnutrition and bacteremia/septicemia are risk factors for mortality in ESRD patients with a zoster diagnosis during hospitalization. Inflammation and malnutrition have been previously recognized as important contributors to an adverse prognosis in dialysis patients [11, 12], likely associated with blunted or impaired immune responses [6]. Our findings support these contentions and suggest that zoster patients may be particularly susceptible to 2-year mortality from these complications.

The aHR for death was decreased in non-white patients versus white patients, implying that non-white race was protective for mortality. In this regard, a previous study demonstrated that black dialysis patients >50 years of age had a lower risk of death compared with their white counterparts [13]. The reasons for this racial discrepancy are not known. In addition, patients with a failed transplant exhibited a decreased risk for mortality. We would speculate that the decreased mortality may have been the result of these patients being healthier by virtue of the fact they were stable enough for the procedure. In addition, they may have possibly been exposed to long-term antiviral prophylaxis; however, this could not be determined in this study.

The results of the current study indicate that CAD, presumably in association with hypercholesterolemia, is associated with a decreased risk of death in zoster patients. This finding is in direct contrast to prospective studies in the general population in which CAD with hypercholesterolemia is associated with an increased risk of death [12]. However, our data are in agreement with other prospective studies of dialysis patients in which higher cholesterol levels were associated with lower mortality [11, 13].

The current study identified patients with a zoster diagnosis from the USRDS hospital claims data and thus were derivative of diagnoses recorded during a hospitalization. These data did not include patients with a zoster diagnosis recorded from outpatient assessments. On this basis, we would speculate that the zoster patients identified in the present study were sicker than ambulatory dialysis patients with the diagnosis. The presence of several life-threatening comorbidities, as well as the increased risk of death with an increase in the CCI, supports this contention. These studies do not prove causality, but rather demonstrate an association of zoster with significant comorbidities, suggesting it may be a surrogate marker for inpatients at particular risk for 2-year mortality. Further studies are needed to assess this contention.

In the present study, 27 patients received the zoster vaccine and a significant number of these 27 did not acquire the diagnosis. Although encouraging, the small number of patients does not allow us to draw further conclusions. In this regard, recent data support the use of the zoster vaccine in ESRD patients ≥60 years of age. To our knowledge, there is no difference in efficacy based on the modality of dialysis. A study that analyzed the Kaiser Permanente Southern California database from 2007 to 2013 found 582 vaccinated and 2910 unvaccinated ESRD patients; analysis showed that zoster vaccination was associated with a 50% lower risk of developing zoster among ESRD patients [1]. In other works analyzing US Medicare from 2007 to 2009, it was reported that effectiveness estimates for the zoster vaccine in chronic kidney disease patients were similar to those

previously reported for the general population [14]. Taken together, use of the zoster vaccine to prevent zoster in ESRD patients appears encouraging. However, it is unclear if zoster vaccination will have a favorable impact on mortality, representing an area for future research.

The present work is based on a query of the USRDS dataset and has several limitations. First, all diagnoses and procedures were inferred from billing codes submitted to Medicare or extracted from the CMS 2728 form and are not the result of actual medical documentation. However, since this database contains patient-specific data on essentially all ESRD patients treated in the USA, the size of the dataset may, in part, offset these limitations. Second, we identified only persons who had an inpatient encounter during which zoster was coded. Therefore the study did not account for inpatients in whom the diagnosis was missed or for whom the diagnosis was miscoded. Third, some patients with the diagnosis may have been misclassified as disease free. The problem of inaccurate diagnosis is impossible to avoid in a retrospective database study of a diagnosis that depends on clinical findings, raising the possibility of some bias in the results. Finally, as with any observational study, residual confounding by unmeasured factors that are different between zoster and control cohorts is also possible.

In summary, irrespective of whether zoster alone worsens mortality, or is simply a marker for decreased survival, its presence in hospitalized dialysis patients portends a poorer prognosis and necessitates clinical awareness of an increased risk for mortality. The impact of zoster vaccination on disease development and mortality rates remain undefined, but early results are encouraging.

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AUTHORS' CONTRIBUTIONS

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.H.A., J.L.W., S.L.B., R.E.C., M.F.K., N.S.N. and J.E.T. contributed to the study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative, technical or material support; and study supervision. J.L.W. contributed to statistical analysis. N.S.N. and M.F.K. contributed to obtained funding.

CONFLICT OF INTEREST STATEMENT

J.H.A. reports grants from the Medical College of Georgia and the Translational Research Program of the Department of Medicine during the conduct of the study. M.F.K. and N.S.N. report grants from Dialysis Clinic, Inc. during the conduct of the study. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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