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ORIGINAL RESEARCH

Chronic dialysis patients with infectious spondylodiscitis have poorer outcomes than non-dialysis populations

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Purpose: Infectious spondylodiscitis is a serious disease that can lead to permanent neurological deficit. Because there were only a few case reports or series featuring infectious spondylodiscitis in chronic dialysis patients, we investigated the epidemiology and outcome in the chronic dialysis patients versus general population.

Materials and methods: We retrospectively identified chronic dialysis patients admitted for infectious spondylodiscitis between January 2002 and December 2015. A total of 105 chronic dialysis patients were included, and we performed a 1:2 case–control match on propensity score in non-dialysis patients with infectious spondylodiscitis. The demographic features, clinical manifestation, infection focus, and disease outcome were recorded.

Results: A total of 302 patients entered the final analysis. Chronic dialysis patients less frequently had fever (34.3%), and in the majority, bacterial entry was through dialysis vascular access (30.5%). Methicillin-resistant *Staphylococcus aureus* (MRSA) comprised the majority of causative pathogen. The chronic dialysis group had longer hospital stay, higher in-hospital mortality, and higher 1-year mortality. The odds ratio of in-hospital mortality was 2.20 compared with the non-dialysis group.

Conclusions: The study highlighted poorer outcome and high frequency of resistant Staphylococcus of infectious spondylodiscitis in chronic dialysis patients. Therefore, high vigilance, prompt recognition, and empiric coverage of MRSA will be important in the management of infectious spondylodiscitis in chronic dialysis patients.

Keywords: end stage renal disease, pyogenic spondylodiscitis, infectious spondylodiscitis, methicillin-resistant *Staphylococcus aureus*, mortality

Introduction

Infectious spondylodiscitis is a relatively uncommon but serious disease that can lead to permanent neurological deficit or chronic pain. It may be diagnosed late because of relative insidious onset, and non-specific symptoms. In recent years, the incidence of infectious spondylodiscitis seems to have increased with the development of advanced radiographic diagnosis, increased spinal intervention, and increased life expectancy.[1] The microorganisms inoculate vertebra via several pathways. The hematogenous spread of pathogen from another primary focus remains the major mechanism. Retrograde, ascending infection from the urinary tract, direct invasion from surrounding tissues, or contamination during an invasive or surgical procedure are also possible contributing mechanisms.[2–6]

The patients with end-stage renal disease (ESRD), especially those on chronic maintenance hemodialysis, are susceptible to bloodstream infection because of infected

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vascular access, repetitive vascular puncture, or dialysis water purification system. The immune dysfunction under uremia milieu may also contribute to the inability to defend against microorganism invasion.[7–10] With these additional risk factors of infection, the clinical presentation, microbiology characteristics, and the outcome may be different in the chronic dialysis population compared with the non-dialysis counterpart. To date, there are only a few case reports and small series discussing infectious spondylodiscitis in the dialysis population.[11–18] This study aims to elucidate the epidemiology, risk factors, and outcome in infectious spondylodiscitis in a larger chronic dialysis population.

Materials and methods

Patient selection and data collection

The study was carried out at a tertiary referral center with about 3,700 beds and an average of 10,700 episodes of in-patient service annually. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No 201600819B0C101). The need for written informed consent was waived by the IRB because this study was retrospective, non-interventional design, and patient data confidentiality and privacy was maintained.

We searched the discharge diagnosis from the health information system in the study hospital by International Classification of Disease-9 (ICD-9) code (720.9: unspecified inflammatory spondylopathy) between January 2002 and August 2015. Patients discharged with ICD-9 720.9 and ESRD were included. We excluded patients who were aged <20 years, started dialysis therapy during the index hospitalization, underwent dialysis <14 days, received solid organ or hematopoietic stem cell transplantation, had recurrent infectious spondylodiscitis, or those treated incompletely owing to personal reasons. We performed a 1:2 case-control match on propensity score depending on age, sex, and the presence of diabetes mellitus (DM) from the non-dialysis group.

The patients' demographic information, clinical presentations, laboratory data, and survival were recorded by chart review. The serum C-reactive protein (CRP) level at baseline and 1 week after treatment were documented. The causative pathogens were determined if the microorganism grew from the blood, abscess, and/or tissue culture. The numbers and levels of the involved vertebrae were documented from image study, including CT, MRI, and/or the inflammatory scan with Gallium radio-isotope or ^{18}F-fluorodeoxyglucose (FDG).

Statistical analysis

The categorical variables are presented with proportion and compared by Chi-square test. The continuous variables are presented with mean and SD, and these variables are tested by independent *t*-test. Patient survival between groups was compared with Kaplan–Meier analysis. A 2-sided *p*-value <0.05 was considered to be statistically significant. The statistical analysis was done with SPSS version 17.

Results

Figure 1 illustrates the patient selection procedure. Between January 2002 and August 2015, we found 1,402 hospitalized patients discharged with the ICD-9 diagnosis code 720.9. Among them, 106 patients were identified with a diagnosis of ESRD undergoing chronic dialysis. We performed a 1:2 case–control match on propensity score depending on age, sex, and the presence of DM. After thorough chart review, we excluded 7 cases admitted for recurrent infectious spondylodiscitis and 9 cases discharged against medical advice before completing treatment. A total of 302 patients entered the final analysis, with 105 patients in the chronic dialysis group and 197 patients in the non-dialysis control.

The demographics are shown in Table 1. The chronic dialysis group had significantly more hypertension, coronary artery disease, and congestive heart failure. The prevalence of degenerative spinal disease was lower in the chronic dialysis group. No statistic differences were found in the co-morbidities, including cirrhosis, active malignancy, use of immunosuppressive agents, or vertebral trauma.

Table 2 summarizes the clinical characteristics of infectious spondylodiscitis. Back pain was the major symptom in both groups, while fever occurred in less than half of both groups. The chronic dialysis patients had fever less frequently compared with non-dialysis patients (34.3% vs 46.7%, p=0.038). Dialysis vascular access infection was shown to be a major focus (30.5%) of bacterial entry in the chronic dialysis group. The initial laboratory data demonstrated higher blood urea nitrogen, creatinine, and lower hemoglobin in the chronic dialysis group. Both the baseline erythrocyte sedimentation rate and the 1-week post-treatment CRP were higher in the chronic dialysis group. No differences were found in the level of infected vertebrae and the frequency of skipped lesions, but the chronic dialysis patients had less abscess formation (48.6% vs 60.7%, p=0.039).

Table 3 summarizes the pathogen spectrum in both groups. The Gram-positive cocci (GPC) were isolated more frequently in the chronic dialysis group (59.1% vs 42.6%, p=0.0064). Methicillin-resistant *Staphylococcus aureus* (MRSA) comprised the majority of GPC isolates from dialysis patients (28.6% vs 11.2%, p<0.0001). The Gram-negative bacilli (GNB) were rare in the chronic dialysis group (0.95% vs 14.7%, p=0.0001). The frequency of fungal,

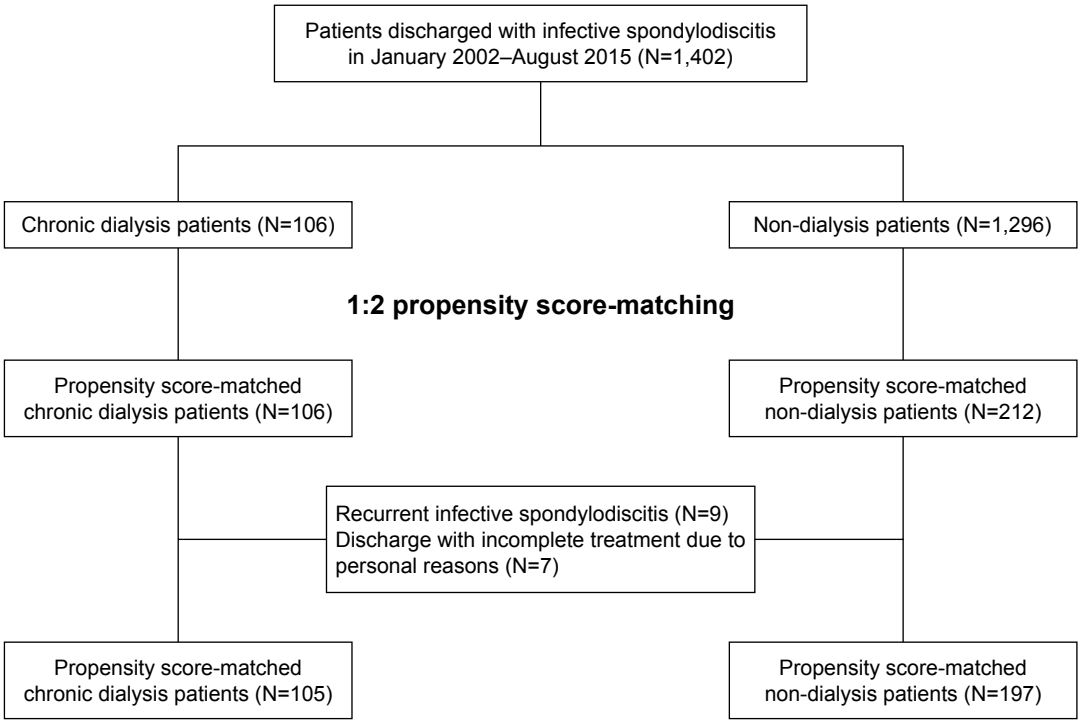

Figure 1 The flowchart of study patient enrollment.

mycobacterial, or polymicrobial infectious spondylodiscitis were similarly rare in both groups.

Out of the total number of patients, 37 died in the hospital, only 2 died of causes other than sepsis (one from acute myocardial infarction and the other one from massive gastrointestinal [GI] bleeding). Another 9 patients who survived at discharge, died within 1 year. The causes of death included 1 GI bleeding, 1 severe aortic stenosis with refractory heart failure, 2 with recurrent spondylodiscitis, and 5 due to pneumonia. With respect to outcome, the chronic dialysis group had longer hospital stay and worse in-hospital survival (Table 4). The Kaplan–Meier survival analysis also demonstrated worse 1-year survival in the chronic dialysis group (Figure 2, Log-rank p=0.004). The odds ratio of hospital death in chronic dialysis group was 2.20 (95% CI: 1.10–4.40, p=0.026) compared with the non-dialysis control. The 1-year recurrence rates were the same in both groups.

Table 1 Demographics of chronic dialysis vs non-dialysis group

Patient characteristics	Chronic dialysis (N=105) (%)	Non-dialysis (N=197) (%)	*p*-value
Age (years), mean ± SD	66.7±10.8	63.2±9.4	0.977
Male gender	51 (48.6)	96 (48.7)	0.979
Diabetes mellitus	51 (48.6)	89 (45.2)	0.573
Hypertension	67 (63.8)	55 (27.9)	<0.001
Coronary artery disease	23 (21.9)	11 (5.6)	<0.001
Congestive heart failure	17 (16.2)	15 (7.6)	0.021
Cerebrovascular accident	12 (11.4)	14 (7.1)	0.202
Cirrhosis	10 (9.5)	20 (10.2)	0.862
Active malignancy	6 (5.7)	14 (7.1)	0.643
Immunosuppression	3 (2.9)	14 (7.1)	0.127
Degenerative spinal disease	89 (84.8)	186 (94.4)	0.005
Vertebral trauma	3 (2.9)	15 (7.6)	0.094

Discussion

Infectious spondylodiscitis is an uncommon but devastating disease that can lead to permanent neurological deficit, chronic pain, and even mortality. Risk factors for infectious spondylodiscitis include diabetes, endocarditis, degenerative spine disease, prior spinal surgery, corticosteroid therapy, or other immunocompromised states. Its incidence has been increasing in the recent years, likely due to the following reasons: increasing rates of bacteremia due to intravascular devices and other forms of instrumentation; increasing age of the population; and increasing number of patients on renal replacement therapy.[19]

Till now, there have been no randomized trials evaluating outcome of infectious spondylodiscitis in ESRD patients with chronic dialysis, which is the most common type of renal replacement therapy. In this study, we performed a 1:2 case-control match on propensity score depending on age, sex, and the presence of DM to compare the epidemiology, risk factors, and outcome of infectious spondylodiscitis in chronic dialysis patients with the non-dialysis patients.

Table 2 Clinical characteristics of infectious spondylodiscitis in chronic dialysis vs non-dialysis group

Clinical features	Chronic dialysis (N=105) (%)	Non-dialysis (N=197) (%)	*p*-value
Disease manifestations			
Fever	36 (34.3)	92 (46.7)	0.038
Back pain	80 (76.2)	164 (83.2)	0.138
Shock	24 (22.9)	33 (16.8)	0.197
Concurrent infective endocarditis	2 (1.9)	4 (2.0)	0.941
Possible primary focus			
Spine surgery	9 (8.6)	26 (13.2)	<0.001
Soft tissue infection	5 (4.8)	13 (6.6)	
Vascular access	32 (30.5)	0 (0)	
Pneumonia	0 (0)	5 (2.5)	
Urinary tract infection	2 (1.9)	17 (8.6)	
Peritonitis	0 (0)	1 (0.5)	
Unknown	57 (54.3)	135 (68.5)	
Positive tissue culture	39 (37.1)	84 (42.6)	0.238
Positive blood culture	60 (57.1)	85 (43.1)	0.387
Laboratory data			
Hemoglobin (g/dL)	9.4±1.6	10.7±2.1	<0.001
Albumin (g/dL)	3.0±0.5	2.9±0.7	0.384
Blood urea nitrogen (mg/dL)	48.7±23.6	26.3±21.9	<0.001
Creatinine (mg/dL)	6.2±2.3	1.3±1.2	<0.001
Alkaline phosphatase (U/L)	164.5±143.50	142.6±93.2	0.182
CRP (baseline) (mg/L)	123.7±91.5	122.9±113.9	0.951
CRP (1 week after treatment) (mg/L)	85.1±71.8	68.4±61.8	0.046
WBC (baseline) (1,000/μL)	11.8±5.8	11.8±6.6	0.997
WBC (1 week after treatment) (1,000/uL)	10.1±4.4	10.1±12.7	0.140
ESR (mm/hr)	86.6±33.6	70.0±31.7	0.001
Features of the involved vertebral lesions			
Cervical spine	11 (10.5)	21 (10.7)	0.961
Thoracic spine	14 (13.3)	39 (19.8)	0.160
Lumbar spine	89 (84.8)	150 (76.1)	0.079
Sacral spine	10 (9.5)	27 (13.7)	0.291
Skipping lesions	5 (4.8)	5 (2.5)	0.304
Abscess formation	51 (48.6)	120 (60.9)	0.039
Invasive interventions			
CT-guided drainage	14 (13.3)	19 (9.6)	0.328
Surgery	56 (53.3)	124 (62.9)	0.105

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.

Our study found the higher in-hospital and 1-year mortality rate in ESRD patients with infectious spondylodiscitis compared with non-dialysis population. This is in concordance with previous studies that have examined the outcome of other infections in chronic dialysis patients. Sarnak et al reported higher mortality in patients with ESRD who were hospitalized for sepsis or pneumonia.[20,21] In ESRD patients diagnosed with infective endocarditis, smaller studies did not find differences in mortality;[22,23] however, a larger nationwide study involving ~250,000 patients in the USA found a significantly higher in-hospital mortality in ESRD populations.[24]

Higher prevalence of hypertensive cardiovascular disease, coronary artery disease, and congestive heart failure among the ESRD patients may partly explain the increasing mortality in this population. Tonelli et al reported that patients with chronic kidney disease have a higher cardiovascular risk and as much as 58% of mortality may be attributed to cardiovascular events.[25] In patients hospitalized for sepsis and septic shock, pre-existing cardiac diseases, including impaired systolic or diastolic left ventricular function were associated with higher mortality.[26,27] In our study, the dialysis group had more pre-existing hypertension, coronary artery disease, and congestive heart failure. These co-morbidities, which impair cardiovascular adaptations in facing septic status, may contribute to the higher mortality observed in our chronic dialysis patients than the non-dialysis patients. Degenerative spine disease is less common in the chronic dialysis group. This may be contrary to the usual belief that degenerative spine disease and subsequent surgery increase the risk of infectious spondylodiscitis.[19] A possible explanation of this difference may be that it resulted from the fact that some of the dialysis patients acquired spine infection from other sources, for example, repetitive bacteremia from vascular access.

Another significant difference highlighted by our study is the higher proportion of MRSA in the chronic dialysis group. Previous studies in infectious spondylodiscitis of general population demonstrated that GPC is the most common pathogen and followed by GNB. Methicillin-susceptible *S. aureus* (MSSA) remained the most common bacteria among GPC, while *Escherichia coli* accounts for up to one-third of the GNB group.[1,6,28]

Patients on chronic hemodialysis are associated with increased risk of Staphylococcal infection. Two nationwide studies from Denmark reported a high incidence of overall bloodstream infection (137 per 1,000 person-year vs 5.3 per 1,000 person-year) and Staphylococcal bacteremia (35.7 per 1,000 person-year vs 0.5 per 1,000 person-year) in dialysis group compared with general population.[29,30] *S. aureus* bacteremia accounts for up to 30%–40% of bloodstream infection in the hemodialysis group.[31,32] The hemodialysis vascular access is one of the most important route for bacterial entry. Zhang et al reported organism-specific rate of bloodstream infection in patients using different dialysis vascular access. The study demonstrated lowest *S. aureus* bacteremia in those using native arterio-venous fistula. However, the rate is still higher than in general population.[29,33]

Table 3 Microbiologic data of the chronic dialysis vs non-dialysis group

Microorganism species	Chronic dialysis (N=105) (%)	Non-dialysis (N=197) (%)	*p*-value
Gram-positive cocci	62 (59.1)	84 (42.6)	0.0064
Methicillin-susceptible *Staphylococcus aureus*	9 (8.6)	38 (19.2)	
Methicillin-resistant *S. aureus*	30 (28.6)	22 (11.2)	
Coagulase-negative staphylococci	14 (13.3)	8 (4.1)	
Streptococcus spp.	2 (1.9)	12 (6.1)	
Enterococcus	7 (6.6)	4 (2.0)	
Gram-negative bacilli	1 (0.95)	29 (14.7)	0.0001
Escherichia coli	0 (0)	14 (7.1)	
Klebsiella pneumoniae	1 (0.95)	8 (4.1)	
Pseudomonas aeruginosa	0 (0)	4 (2.0)	
Salmonella enterica	0 (0)	3 (1.5)	
Fungus	1 (0.95)	4 (2.0)	0.4939
Candida parapsilosis	1 (0.95)	1 (0.5)	
Candida glabrata	0 (0)	1 (0.5)	
Candida albicans	0 (0)	1 (0.5)	
Yeast-like	0 (0)	1 (0.5)	
Mycobacterium	2 (1.9)	6 (3.1)	0.5395
Mycobacterium tuberculosis	1 (0.95)	4 (2.0)	
Mycobacterium chelonae	1 (0.95)	1 (0.5)	
Mycobacterium abscessus	0 (0)	1 (0.5)	
Polymicrobial isolates	4 (3.8)	7 (3.6)	0.9300
Others	1 (0.95)	5 (2.5)	
Unknown	34 (32.4)	62 (31.5)	0.8731

Patients with MRSA bacteremia had higher mortality compared with those with MSSA bacteremia.[34] Despite the use of appropriate antibiotic, a significantly high mortality was found in the MRSA compared with MSSA infections.[35]

There is no literature directly indicating a low frequency of GNB infectious spondylodiscitis in the dialysis group. Kang et al reported that GNB accounted for 18% of the pathogen in a 344-patients' series. Multivariate analysis showed that female gender, co-existing urinary tract or intra-abdominal infection were strongly associated with the development of GNB infectious spondylodiscitis.[2] From this point of view, the extremely low rate of co-existing urinary tract or intra-abdominal infection may indirectly explain the low occurrence of GNB in the dialysis group.

Uremia has been linked to immune dysfunction. The most important first-line defense toward bacterial infection, that is, the neutrophil and macrophage, is dysregulated. Both neutrophil and macrophage have higher baseline expression of Toll-like receptors and synthesis of reactive oxygen species, but these cells present with impaired phagocytosis while encountering the pathogen.[7,9,10] The adaptive immune cells are also quantitatively and qualitatively impaired in

Table 4 Outcomes of the chronic dialysis vs non-dialysis group

Outcomes	Chronic dialysis (N=105) (%)	Non-dialysis (N=197) (%)	*p*-value
Length of hospital stay (days), mean ± SD	62.78±39.30	51.65±30.43	0.012
In-hospital survival	86 (81.9)	179 (90.9)	0.024
1-year survival	80 (76.2)	176 (89.3)	0.002
1-year recurrence	17 (16.2)	39 (19.8)	0.722

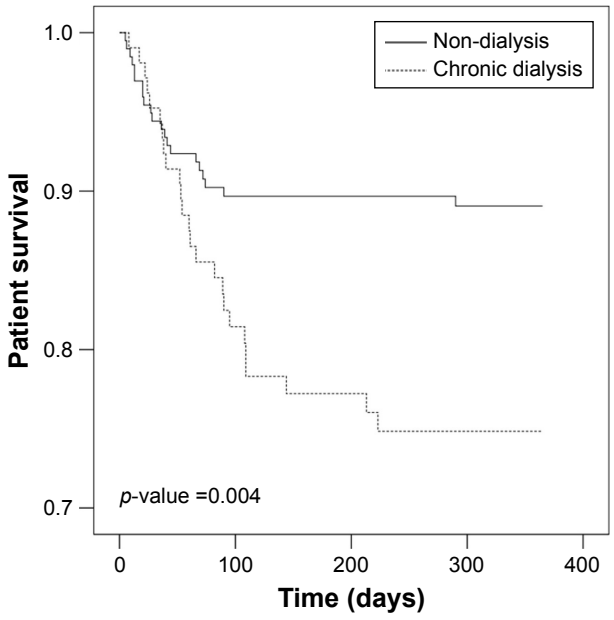

Figure 2 Kaplan–Meier survival curves of 1-year survival between chronic dialysis and non-dialysis patients with infectious spondylodiscitis.

the uremia milieu.[7,8] However, these phenomena are mostly observed in vitro or ex vivo. There is lack of direct evidence of the aforementioned immune dysfunction on patient outcome. In our study, the dialysis group presented with less fever compared with non-dialysis control. A recent study in Korea found afebrile status during bacteremia was associated with mortality in chronic dialysis patients. Elevated CRP, on the other hand, remained a good indicator of bacterial infection.[36] Although the direct link between immune dysfunction and less presentation with fever is not clear, this phenomenon reminds the clinician to be alert.

There are still limitations in this study. The study enrolled patients from single medical center and did not include patients with less severe disease. This may limit generalization of our results to a larger population. Second, the attribution of infectious spondylodiscitis to permanent neurologic outcome was not clear. Patients documented to be bedridden or wheelchair-bound were possibly affected by severe physical de-conditioning during hospitalization rather than a true, significant nerve injury. We could not distinguish these 2 important factors apart. Finally, despite some significant findings, the retrospective study only provides association but not causal relationship.

Conclusion

This propensity score matched case–control study demonstrated a higher in-hospital and 1-year mortality rate of infectious spondylodiscitis in chronic dialysis patients compared with the non-dialysis control. MRSA comprised the majority of bacterial isolates from the chronic dialysis patients, and the vascular access for hemodialysis contributed to the major focus of bacterial entry. Because of the poorer outcome and high frequency of resistant Staphylococcus, high vigilance, prompt recognition and empiric coverage of MRSA will be important in the management of infectious spondylodiscitis in chronic dialysis patients.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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