Non-tuberculous mycobacterial infections in patients with end-stage renal disease: prevalence, risk factors, and mortality

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ABSTRACT

Non-tuberculous mycobacterial (NTM) disease has increased in prevalence in the USA, however, little is known on NTM in the population with end-stage renal disease (ESRD). Thus, we investigated patients with ESRD to determine risk factors for NTM disease and mortality. We queried the United States Renal Data System from 2005 to 2015 using International Classification of Diseases (ICD)-9/ICD-10 codes to identify NTM and risk factors. Logistic regression was used to examine the association of risk factors with NTM and Cox proportional hazards modeling was used to assess the association of NTM with mortality. Of 1,068,634 included subjects, 3232 (0.3%) individuals were identified with any NTM diagnosis. Hemodialysis versus peritoneal dialysis (OR=0.10, 95% CI=0.08 to 0.13) was protective for NTM, whereas black (OR=1.27, 95% CI=1.18 to 1.37) or other race compared with white race (OR=1.39, 95% CI=1.21 to 1.59) increased the risk of NTM. HIV (OR=15.71, 95% CI=14.24 to 17.33), history of any transplant (OR=4.25, 95% CI=3.93 to 4.60), kidney transplant (OR=3.00, 95% CI=2.75 to 3.27), diabetes (OR=1.32, 95% CI=1.23 to 1.43), rheumatologic disease (OR=1.92, 95% CI=1.77 to 2.08), and liver disease (OR=2.09, 95% CI=1.91 to 2.30) were associated with increased risk for NTM diagnosis. In multivariable analysis, there was a significant increase in mortality with any NTM diagnosis (HR=1.83, 95% CI=1.76 to 1.91, p≤0.0001). Controlling for relevant demographic and clinical risk factors, there was an increased risk of mortality associated with any diagnosis of NTM. Early diagnosis and treatment of NTM infection may improve survival in patients with ESRD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have demonstrated that patients with end-stage renal disease (ESRD) have impaired host defenses and have higher risks of serious infections.
⇒ Chronic renal failure has been identified as a possible risk factor for non-tuberculous mycobacterial (NTM) disease.
⇒ NTM infections are on the rise in the USA.

WHAT THIS STUDY ADDS

⇒ Of 1,068,634 included subjects, 3232 (0.3%) individuals were identified with any NTM diagnosis.
⇒ Increased age, black and other race, hemodialysis (vs peritoneal dialysis), access type other than an arteriovenous fistula, HIV, chronic lung disease, liver disease, and cardiovascular disease were associated with increased mortality.
⇒ The presence of any NTM diagnosis was independently associated with increased mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings highlight the need for clinicians to remain vigilant for NTM infection in ESRD, as it is independently associated with increased mortality.
⇒ Early diagnosis and treatment may potentially decrease mortality in patients with ESRD.

INTRODUCTION

Non-tuberculous mycobacteria (NTM) are members of the *Mycobacterium* genus that are not part of the *M. tuberculosis* complex or *M. leprae*.[1] They are commonly found in the environment and are enveloped in a thick triple-layered cell wall which allows them to be resistant to many disinfectants and antibiotics.[1 2] These bacteria are frequent human pathogens, with the most common manifestation being chronic pulmonary disease in people without HIV.[3] In patients with advanced HIV infection, disseminated disease due to NTM is most common.[4] Other disease manifestations include lymphadenitis, cutaneous, gastrointestinal, and ophthalmic disease.[4] Many patients with NTM lung disease have other immunocompromising factors, such as defects in the interleukin (IL)-12/interferon-gamma axis.[5 6]

The estimated incidence of NTM disease varies from 1.0 to 1.8 cases per 100,000 with the most common species in the USA being *M.*

avium complex (MAC).[4] NTM is not a reportable condition in the USA, so no central database of cases exists, which is generally associated with an underestimation of prevalence. However, an estimated adjusted prevalence of pulmonary NTM disease for 2010 in the USA was 27.9 cases per 100,000 annually.[7] NTM infections are rising in the USA, potentially due to improved detection and the increased use of immunosuppressive drugs to treat conditions such as rheumatoid arthritis, other connective tissue disorders, and transplantation.[1]

Pulmonary NTM is the most common form of NTM disease.[8] Classic risk factors for pulmonary NTM infection include female sex, age, and the presence of chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, bronchiectasis, cystic fibrosis, and lung cancer.[5 8] The incidence of chronic lung diseases, such as COPD and bronchiectasis, and the number of patients with pulmonary NTM disease have increased in recent years, with one recent report estimating that the number of pulmonary NTM cases in the USA increased by at least twofold between 2010 and 2014.[3] This recent increase in the diagnosis of NTM may be related to the greater incidence of COPD in the aging population and associated immunocompromise, which results in an increased number of individuals at risk for NTM lung disease.[9]

Overall, MAC infections are rare. Pulmonary MAC infection is the overwhelming majority of NTM disease, and those with chronic lung disease and immunosuppression are at higher risk.[7 8] MAC lung disease may also present with nodular bronchiectasis infiltrates in postmenopausal, non-smoking, white females, sometimes labeled 'Lady Windermere syndrome'.[4 10] Disseminated MAC disease has primarily been associated with advanced HIV/AIDS, but given the advancements made in the treatment and management of HIV with antiretroviral therapy, the rate of disseminated MAC in people living with HIV has fallen drastically.[8]

As NTM are widespread in the environment, person-to-person transmission is an unlikely source of respiratory disease for most patients, unlike pulmonary tuberculosis.[1] Due to the presence of NTM in the water supply, the organisms are also present in the hospital environment and present an ongoing potential for nosocomial infection, including dialysis-associated infections.[5 8 11] However, there is little known about NTM in the population with end-stage renal disease (ESRD).

Patients with ESRD also have impaired host defenses and are prone to infections in part due to the immunosuppressive effects of uremia.[12 13] Patients with impaired kidney function have higher risks of serious infections, estimated at rates 3–4 times of the general population.[14] Prior studies have identified chronic renal failure as a possible risk factor for NTM disease.[6] Patients on dialysis may also be predisposed to cutaneous NTM from catheter exit site infections or peritonitis in patients on peritoneal dialysis (PD) due to NTM-contaminated water sources.[6 15]

Furthermore, patients who have undergone kidney transplant have the additional issue of immunosuppressive medications and as a result, their most common manifestation of NTM disease is disseminated disease, with the most common pathogen being *M. chelonae*.[16 17] One review found that during anti-NTM treatment, 30.2% of patients lost kidney graft function and 20.9% of patients died from NTM infection or related complications.[17] NTM disease is a severe and often overlooked condition in these patients.

With the rising prevalence of NTM in the USA and the theoretical risk for NTM infection in patients with ESRD, this study seeks to define the prevalence of NTM diagnosis, risk factors for NTM infection, and the risk for mortality among patients with ESRD, including patients who have undergone renal transplantation, with NTM disease compared with those without NTM disease.

MATERIALS AND METHODS

Study cohort

The population comprises all patients with ESRD in the United States Renal Data System (USRDS) between the ages of 18 and 100 years at the time of the start of dialysis, who began therapy between January 1, 2005 and December 31, 2015. Subjects with missing age, race, sex, ethnicity, or missing or unknown incident dialysis modality or access type were excluded from the study cohort. Patients who had undergone renal transplantation were included in the cohort.

Main independent variables

The diagnosis of NTM following initiation of dialysis was determined using International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes in the USRDS dataset. ICD-9/ICD-10 codes used to identify a NTM diagnosis included: pulmonary (031.0/A31.0), cutaneous (031.1/A31.1), disseminated (031.2/A31.2), other specified (031.8/A31.8), or unspecified (031.9/A31.9). Additional ICD-9/ICD-10 codes used are shown in online supplemental table 1. Subjects had to have at least one diagnosis of NTM to be included in the NTM-infected group. Subjects with no NTM diagnosis were considered controls.

Outcome variable

The primary outcome variable was time to death in years. For those with an NTM diagnosis who died, the time to death was the number of years from the first NTM diagnosis to the date of death or to December 31, 2015 for those who did not die. For subjects without an NTM diagnosis, time to death was the number of years after the start of dialysis until death or to December 31, 2015 for those who did not die. Those who did not die were considered censored observations.

Other demographic and clinical risk factors

Demographic variables including age at NTM diagnosis or start of dialysis, race, sex, ethnicity, incident dialysis type, access type, and kidney transplant were determined from the Centers for Medicare & Medicaid Services Medical Evidence Form 2728. Other clinical risk factors were identified using ICD-9 or ICD-10 codes from hospital, detailed inpatient, or physician/supplier claims in the USRDS datasets. Clinical risk factors included HIV, chronic lung disease, cancer, diabetes, rheumatologic disease, a history of transplant of any kind, liver disease, and cardiovascular disease.

Statistical analysis

All statistical analysis was performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA), and statistical

significance was assessed using a significance level of 0.05. Descriptive statistics were determined overall, by NTM status and by mortality. The prevalence of NTM overall and for each type of NTM was determined.

To examine potential confounders, simple logistic regression models were used with an outcome of any type of NTM diagnosis for each demographic or clinical risk factor. A Kaplan-Meier survival curve was determined for NTM overall and for each NTM type on time to death and a log rank test was used to examine preliminary differences in survival between those who had or did not have an NTM. Cox proportional hazards (CPH) models were used to examine the relationship between NTM overall and for each NTM type with mortality controlling for demographic and clinical risk factors. Each variable was first examined in a simple CPH model on time to death and the assumption of proportional hazards was assessed using the -log(log(Survival)) plot due to the large sample size. Then two different multivariable CPH models on time to death using NTM overall or using the five types of NTM as the main independent variables and all other demographic and clinical risk factors were constructed. Any demographic or clinical risk factor was then removed one at a time from the model and tested to see if it was required for statistical significance and did not change the model fit. Model fit was examined using the Akaike information criterion and the Bayesian information criterion. The final CPH models on time to death consisted of an NTM diagnosis (overall or the five different types), any statistically significant demographic or clinical risk factor, or any demographic or clinical risk factor that was not statistically significant but needed in the model to improve model fit.

RESULTS

Prevalence of NTM and non-NTM groups

For the 10-year study period, 3232 out of 1,068,634 (0.3%) eligible patients were identified with an NTM diagnosis (table 1). The prevalence of each type of NTM was as follows: pulmonary 0.1%, cutaneous 0.02%, disseminated

Table 1 Descriptive statistics for demographic and other clinical risk factors for NTM infection in patients with ESRD

	With NTM diagnosis	Without NTM diagnosis	OR	95% CI	P value
Demographics					
Age at NTM, years (SD)	62.0 (15.6)	63.6 (14.9)	0.99	0.99 to 1.00	<0.0001
Race, n (%)					
Black	1056 (32.7)	300 613 (28.2)	1.27	1.18 to 1.37	<0.0001
Other	228 (7.1)	59 591 (5.6)	1.39	1.21 to 1.59	<0.0001
White	1948 (60.3)	705 198 (66.2)	1.00		<0.0001
Sex, n (%)					
Female	1280 (39.6)	458 374 (43.0)	0.87	0.81 to 0.93	<0.0001
Male	1952 (60.4)	607 028 (57.0)	1.00		<0.0001
Ethnicity, n (%)					
Hispanic	435 (13.5)	156 277 (14.7)	0.91	0.82 to 1.00	0.0525
Non-Hispanic	2797 (86.5)	909 125 (85.3)	1.00		0.0525
First dialysis modality, n (%)					
Hemodialysis	3178 (98.3)	1 063 593 (99.8)	0.10	0.08 to 0.13	<0.0001
Peritoneal	54 (1.7)	1809 (0.2)	1.00		<0.0001
Access type, n (%)					
Catheter	2609 (80.7)	863 913 (81.1)	0.97	0.87 to 1.07	0.8506
Graft	108 (3.3)	35 535 (3.3)	0.98	0.80 to 1.21	0.8506
AV fistula	515 (15.9)	165 954 (15.6)	1.00		0.8506
Clinical risk factors					
Kidney transplant, n (%)	656 (20.3)	83 468 (7.8)	3.00	2.75 to 3.27	<0.0001
HIV, n (%)	484 (15.0)	11 815 (1.1)	15.71	14.24 to 17.33	<0.0001
Chronic lung disease, n (%)	1667 (51.6)	334 809 (31.4)	2.32	2.17 to 2.49	<0.0001
Cancer, n (%)	715 (22.1)	147 232 (13.8)	1.77	1.63 to 1.93	<0.0001
Diabetes, n (%)	2205 (68.2)	658 932 (61.9)	1.32	1.23 to 1.43	<0.0001
Rheumatologic disease, n (%)	780 (24.1)	151 616 (14.2)	1.92	1.77 to 2.08	<0.0001
Any transplant, n (%)	877 (27.1)	85 849 (8.1)	4.25	3.93 to 4.60	<0.0001
Liver disease, n (%)	515 (15.9)	88 468 (8.3)	2.09	1.91 to 2.30	<0.0001
Cardiovascular disease, n (%)	2784 (86.1)	738 163 (69.3)	2.75	2.49 to 3.04	<0.0001
Mortality					
Died, n (%)	2314 (71.6)	684 225 (64.2)			
Alive, n (%)	918 (28.4)	381 177 (35.8)			
Time to death/Follow up, years (SD)	2.2 (2.3)	3 (2.6)			

AV, arteriovenous; ESRD, end-stage renal disease; NTM, non-tuberculous mycobacteria.

Table 2 Prevalence of NTM types

Diagnosis	Overall, n (%)*
Any NTM	3232 (0.3)
Pulmonary NTM	1488 (0.1)
Cutaneous NTM	213 (0.02)
Disseminated NTM	995 (0.1)
Other specified NTM	560 (0.1)
Unspecified NTM	1242 (0.1)

*The n and percentages for each NTM infection do not add to the total for any NTM because some patients were diagnosed with more than one NTM infection.
NTM, non-tuberculous mycobacteria.

0.1%, other specified 0.1%, and unspecified 0.1% (table 2). Demographic characteristics associated with decreased incidence of NTM included using hemodialysis (HD) versus PD (OR=0.10, 95% CI=0.08 to 0.13).

When compared with the white reference group, black (OR=1.27, 95% CI=1.18 to 1.37) or other race (OR=1.39, 95% CI=1.21 to 1.59) was associated with increased risk of NTM diagnosis. Clinical variables associated with increased risk for NTM diagnosis included HIV (OR=15.71, 95% CI=14.24 to 17.33), history of any transplant (OR=4.25, 95% CI=3.93 to 4.60), kidney transplant (OR=3.00, 95% CI=2.75 to 3.27), diabetes (OR=1.32, 95% CI=1.23 to 1.43), rheumatologic disease (OR=1.92, 95% CI=1.77 to 2.08), and liver disease (OR=2.09, 95% CI=1.91 to 2.30) (table 1).

Clinical risk factors for mortality

The presence of any NTM diagnosis was independently associated with increased mortality (adjusted HR (aHR)=1.83, 95% CI=1.76 to 1.91) (table 3). Diagnoses of pulmonary (aHR=1.33, 95% CI=1.24 to 1.43), cutaneous (aHR=1.24, 95% CI=1.04 to 1.48), disseminated (aHR=1.34, 95% CI=1.23 to 1.45), other specified (aHR=1.20, 95% CI=1.08 to 1.34), and unspecified NTM (aHR=1.44, 95% CI=1.33 to 1.55) were also associated with increased mortality, controlling for demographic and other clinical risk factors (as shown in table 3).

The Kaplan-Meier curves for any NTM and for pulmonary, disseminated, and other specified NTM are shown in figure 1. These figures show that survival was significantly worse for all non-cutaneous NTM groups when compared with the non-NTM group. The average time to death (or the study's end date) was 2.2 years in individuals with NTM diagnosis vs 3 years in those without an NTM diagnosis (table 1). Overall, even after controlling for the demographic and clinical risk factors, the final model showed a significant increase in mortality with any NTM diagnosis (HR=1.83, 95% CI=1.76 to 1.91, p≤0.0001).

Figure 2 gives the forest plot of the aHRs and 95% CI for the final CPH model.

DISCUSSION

While other studies have evaluated the epidemiology of NTM infections in the general population, to our knowledge this is the first study to investigate the prevalence of

Table 3 Final CPH model on mortality with any NTM diagnosis as the main independent variable

	Final model		
	aHR	95% CI	P value
Any NTM diagnosis	1.83	1.76 to 1.91	<0.0001
No NTM diagnosis	1.00		<0.0001
Demographics			
Age (1-year increase)	1.03	1.03 to 1.03	<0.0001
Race, n (%)			
Black	1.13	1.12 to 1.14	<0.0001
Other	1.51	1.50 to 1.53	<0.0001
White	1.00		<0.0001
Sex, n (%)			
Female	0.99	0.98 to 0.99	<0.0001
Male	1.00		<0.0001
Ethnicity, n (%)			
Hispanic	0.69	0.69 to 0.70	<0.0001
Non-Hispanic	1.00		<0.0001
First dialysis modality, n (%)			
Hemodialysis	1.30	1.21 to 1.40	<0.0001
Peritoneal	1.00		<0.0001
Access type, n (%)			
Catheter	1.49	1.48 to 1.50	<0.0001
Graft	1.19	1.17 to 1.20	<0.0001
AV fistula	1.00		<0.0001
Clinical risk factors			
Kidney transplant	0.15	0.15 to 0.16	<0.0001
HIV	1.11	1.08 to 1.13	<0.0001
Chronic lung disease	1.03	1.03 to 1.04	<0.0001
Cancer	0.99	0.98 to 0.99	<0.0001
Diabetes	0.92	0.92 to 0.93	<0.0001
Rheumatologic disease	0.70	0.69 to 0.70	<0.0001
Any transplant	0.92	0.91 to 0.93	<0.0001
Liver disease	1.19	1.18 to 1.20	<0.0001
Cardiovascular disease	1.02	1.01 to 1.03	<0.0001

aHR, adjusted HR; CPH, Cox proportional hazards; NTM, non-tuberculous mycobacteria.

NTM and the mortality associated with NTM infection in a large population with ESRD from the USA.

Similar to other studies, we found that chronic lung disease was a clinical variable that statistically significantly increased the risk for NTM diagnosis. A Danish population-based study found an increased susceptibility to NTM disease in patients with chronic respiratory disease, as well as a dose-risk response with increasing doses of inhaled corticosteroids.[18] Structural lung disease, such as bronchiectasis and emphysema, likely plays a role in infection in immunocompetent persons and puts them at increased risk for NTM infection.[1 6] Granulomatous inflammation of the airways, which is a hallmark of NTM disease, may lead to worsening bronchiectasis and cavitary lung disease.[19]

Additionally, while prior literature has not directly established diabetes as a risk factor for NTM infection,[20] our study shows that there is an increased risk for NTM in patients with ESRD with diabetes. Diabetes may be associated with increased risk of NTM due to its activation of pro-inflammatory mediators, which can cause reduced

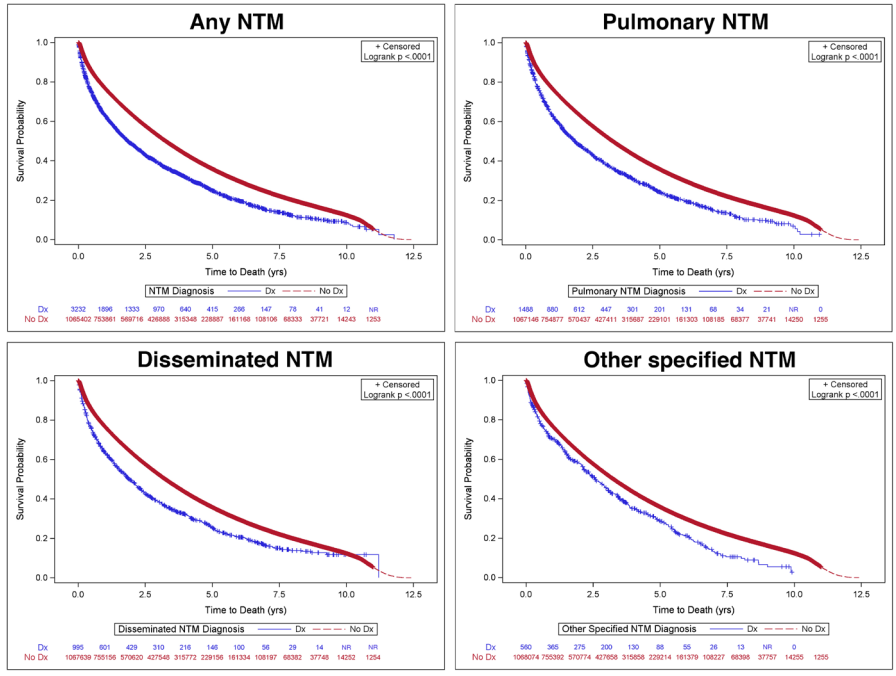

Figure 1 NTM (any as well as pulmonary, disseminated, and other specified) decreases survival of patients with ESRD. Shown are Kaplan-Meier survival curves comparing patients with ESRD with the indicated diagnosis of NTM versus those without the diagnosis. NR, not reported, per United States Renal Data System regulations that observations of 10 or less must be suppressed. Dx, diagnosis; ESRD, end-stage renal disease; NTM, non-tuberculous mycobacteria. Additional curves for cutaneous and unspecified NTM infection are included in supplemental material.

phagocytic and antibacterial activity of neutrophils and macrophages. This environment can provide a niche for intracellular pathogens such as NTM to replicate.[21]

We found that there was an increased OR of NTM infection in patients on PD compared with patients on HD. Prior studies have addressed the increased risk of NTM infection related to contaminated water sources, which results in a predisposition for PD-related peritonitis for patients who are on continuous ambulatory PD.[15] However, a different study design would be necessary to further assess for this connection due to the nature of the USRDS database, as there is a lack of ICD-9/ICD-10 codes for NTM peritonitis, and no lab or culture data are available for this study. Additionally, there was a probable underestimation of the true number of patients receiving regular PD to be at risk for NTM-related peritonitis, as patients may be transitioned between HD and PD for varying durations which we were unable to quantify here.

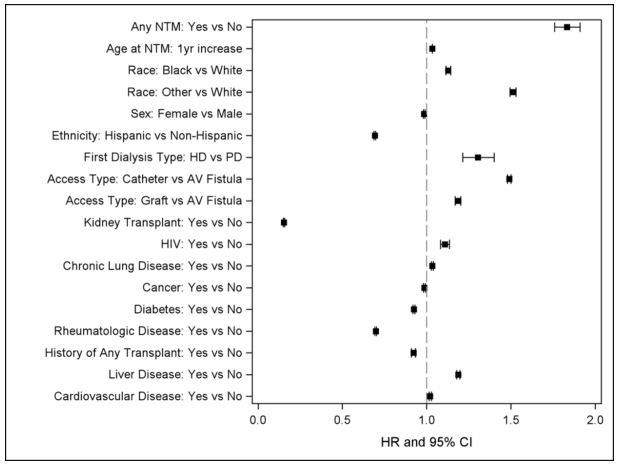

Figure 2 NTM is a risk factor for mortality in patients with ESRD. The forest plot of risk factors for mortality in patients with ESRD illustrates the adjusted HR with the 95% CI. Those parameters that fall to the right of the dotted line at 1.0 (with a non-overlapping 95% CI) are factors that increase the risk of mortality whereas those to the left are protective. AV, arteriovenous; ESRD, end-stage renal disease; NTM, non-tuberculous mycobacteria.

Rheumatologic disease was also associated with an increased risk for NTM diagnosis, which is consistent with prior studies.[22] In particular, previous studies have found that patients with rheumatoid arthritis who use immunosuppressive therapy are at increased risk of NTM infection.[23 24] Key immune pathways involving interferon-gamma and IL-12 are involved in the host response to NTM, so immunosuppression could predispose patients with rheumatologic disease to added risk by interfering with these pathways.[25] Along these lines, we found that a history of solid organ transplant and renal transplantation also increased the risk for NTM in our study population. Similar to patients with rheumatologic disease, these transplant patients may also be more vulnerable to NTM due to their immunosuppressed state, and it is important to monitor for the development of NTM in these patients, especially in those with added risk factors.[26 27] Additionally, despite our findings demonstrating an increased risk of NTM disease in patients who had undergone renal transplantation, there was a significantly decreased mortality

seen in this population. This result supports the transplant of allograft kidneys as an overall benefit to patients with ESRD despite the risks associated with immunosuppression. A study from Finland found that after kidney transplantation, common bacterial infections were the most frequent cause of infection-related mortality, whereas unconventional and opportunistic bacterial infections rarely caused death.[28] However, the risk of death from infections has declined overall in renal transplant recipients, which may be partially due to restored kidney function, regular follow-up with healthcare professionals and infection prophylaxis, as well as potential selection bias for healthier patients to be selected for kidney transplant.[28]

Prior studies have shown a clear relationship between risk for disseminated NTM infection and HIV-1 seropositivity, especially when the $CD4^+$ T cell count falls below 50 cells/mm^3.[25] However, due to modern antiretroviral therapy, HIV was not associated with increased mortality in our study. Recent prophylaxis guidelines no longer recommend universal MAC prophylaxis for patients receiving antiretroviral therapy, in keeping with this lack of mortality risk.[8 29]

In the present study, the diagnosis of any NTM in patients with ESRD was associated with increased mortality in our multivariable analysis. One large population-based study from Korea found that patients with NTM had a significantly higher mortality rate than those with tuberculosis or in the control group.[30] Following mycobacterial infections, complications such as postinfectious bronchiectasis or persistent cavitation are more likely to occur, and these factors may provide a pulmonary environment that is more prone to further infections.[30 31]

Limitations

A major limitation of this study is the nature of the USRDS dataset and our reliance on accurate recording and reporting of ICD-9 and ICD-10 codes.[32] The USRDS does not contain laboratory data to provide additional confirmation of the diagnosis of NTM infection. Cases in this study were selected based on the presence of a single diagnostic code for NTM. Prior studies attempting to validate the use of diagnostic codes in identifying NTM cases have demonstrated that the presence of a diagnostic code for NTM has moderate sensitivity but a very high positive predictive value (PPV) for identifying a true case.[33] Attempts to add further qualifiers to the search such as the use of fluoroquinolones within a specific time range of the diagnosis code served to improve PPV only somewhat but further decreased sensitivity.[34] When the literature review is expanded to include those studies assessing pulmonary NTM disease alone, the use of a single diagnosis code to identify cases becomes more commonplace.[35 36] Undercoding for pulmonary NTM is well-established, with an estimated 73% of microbiologically confirmed cases missed by ICD-9 coding alone.[7] While this could theoretically skew results if too many cases were included as part of the non-NTM group, the prevalence of NTM is incredibly rare within the general population. As the population within the USRDS database could be expected to have a higher prevalence, the difference would be minimal given the large total number of patients within the USRDS database. As such, it was deemed appropriate to use a single diagnosis code for identification of cases within this study in order to maximize sensitivity.

There are other potentially confounding conditions associated with ESRD that were not specifically monitored in this study as the USRDS database does not have access to certain clinical data, such as patient's body mass index, C reactive peptide levels, other laboratory data, or medication usage.[37–39] The ICD-9/ICD-10 codes were only able to show presence or absence of a diagnosis. This limits data on disease severity and makes it difficult to ascertain whether findings are related to pursuing treatment for the comorbid conditions or NTM disease versus an inherent risk from the disease processes themselves. Additionally, we understand that dialysis access types vary over the course of treatment and that access type on initiation, as used here, is not always reflective of the access type a patient primarily uses for dialysis. However, while we can obtain the dialysis access type at the time of the NTM diagnosis for the case group, there is no associated time point for the control population to determine the primary dialysis access type. Finally, our study was not able to distinguish between different mycobacterial species due to coding limitations, although it should be assumed that most diagnoses are related to MAC. Despite these limitations, this study design uses the largest available database of patients with ESRD in the USA, thereby providing a large cohort of patients and increasing the power of the study.

Summary

In summary, this is the first large-scale study of the prevalence, risk factors, and mortality associated with NTM disease in the population with ESRD in the USA. This work showed that the diagnosis of NTM in patients with ESRD was associated in multivariable analysis with increased mortality. It is important for clinicians to remain vigilant for NTM in patients with ESRD to facilitate early diagnosis and treatment to potentially decrease mortality in these patients. Future studies should be pursued to identify the causes for the increase in mortality that is specific to patients with ESRD with a diagnosis of NTM disease.

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Contributors ET, JLW, WBB, BS, AM, MK, SP, LY, SLB, and ST conceptualized the project. JLW created the analysis dataset and curated and created the models to analyze the data. ET, JLW, and ST obtained and interpreted the data. ET, JLW, and ST wrote the original draft. ET, JLW, WBB, BS, AM, MK, SP, LY, SLB, and ST reviewed and edited the manuscript. ET, JLW, and ST visualized the data. JLW, SLB, and ST supervised the project. JLW, SLB, and ST administered the project and AM and MK acquired funding to support the study. All authors contributed to critical revision and have approved the manuscript, contributed significantly to the work, and approved its submission to the *Journal of Investigative Medicine*. All authors agree to be accountable for all aspects of the work ensuring questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SLB is the guarantor.

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