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MAJOR ARTICLE

Assessing Complexity Among Patients With Tuberculosis in California, 1993–2016

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Background. Although the number of patients with active tuberculosis (TB) has decreased in the last 25 years, anecdotal reports suggest that the complexity of these patients has increased. However, this complexity and its components have never been quantified or defined. We therefore aimed to describe the complexity of patients with active TB in California during 1993–2016.

Methods. We analyzed data on patient comorbidities, clinical features, and demographics from the California Department of Public Health TB Registry. All adult patients who were alive at the time of TB diagnosis in California during 1993–2016 were included in the analyses. Factors deemed by an expert panel to increase complexity (ie, increased resources or expertise requirement for successful management) were analyzed and included the following: age >75 years, HIV infection, multidrug resistance (MDR), and extrapulmonary TB disease. Second, using additional information on other comorbidities available starting in 2010, we performed exploratory factor analysis on 25 variables in order to define the dimensions of complexity.

Results. Among the 67 512 patients analyzed, the proportion of patients with extrapulmonary disease, age >75 years, or MDR-TB each increased over the study period ($P < .001$), while the proportion of patients with HIV decreased. Furthermore, the proportion of patients with at least 1 factor of those increased, rising from 38.8% to 45.3% ($P < .001$) from 1993 to 2016. Dimensions of complexity identified in the exploratory factor analysis included the following: race/immigration, social features, elderly/institutionalized, advanced TB, comorbidity, and drug resistance risk.

Conclusions. In this first description of complexity in the setting of TB, we found that the complexity of patients with active TB has risen over the last 25 years in California. These findings suggest that despite the overall decline in active TB cases, effective management of more complex patients may require additional attention and resource investment.

Keywords. complexity; time trend; tuberculosis.

The number of active tuberculosis (TB) cases has declined over the last 2 decades in the United States [1, 2]. Most cases now occur in persons born outside of the United States [3]. In addition, the majority of cases are now attributed to reactivation of latent tuberculosis rather than recent tuberculosis transmission [4]. Age is thought to be a risk factor for reactivation, with an increasing proportion of cases of tuberculosis found in those aged 60 or older [5]. Advanced age is also associated with medical comorbidities, such as diabetes and end-stage renal disease, that can promote tuberculosis progression. As new medications that suppress or modulate the immune system are increasingly prescribed for various chronic diseases, these medications may also contribute to activation of tuberculosis [6]. Additionally, drug–drug interactions between TB drugs and medications used to treat chronic conditions can make TB management more challenging. Given these changes, active cases of tuberculosis in the United States are now presumed to be more complex, though this increase in complexity has not been documented.

Defining and quantifying the complexity of TB cases may help refine predictions about tuberculous disease outcomes including treatment success and toxicity from treatment. Furthermore, understanding complexity may also assist in the distribution of resources, such that jurisdictions with more complex cases could receive more funding or investment of personnel. Careful and tailored management that addresses complexity may influence whether patients are successfully treated for tuberculosis.

Although previous studies have examined risk factors for death, treatment failure, and duration of therapy for patients with active tuberculosis, these studies did not focus on conceptualizing complexity [7]. We aimed to first describe the trend in patient complexity over time, focusing on demographic factors, social factors, and patient comorbidities in patients with active TB during the years 1993 to 2016 in California. Second, we aimed to concretely define this complexity further by determining its underlying dimensions using factor analysis.

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METHODS

Subjects

We analyzed data on patient demographics, clinical features, and comorbidities from the California Department of Public Health TB Registry. Criteria for inclusion were (1) confirmed culture-positive tuberculosis; (2) age ≥18 years; (3) alive at the time of TB diagnosis; (4) diagnosis occurring during 1993–2016, and (5) complete or near-complete data available regarding comorbidities and demographic data. Starting in 2010, data regarding comorbid conditions were included on the surveillance forms, and therefore these data were analyzed separately. These documented conditions included end-stage renal disease, diabetes, organ transplant, TNF alpha antagonist therapy, and "other immunosuppressed state," which was defined as immunosuppression due to other medical conditions or medications, such as hematologic or reticuloendothelial malignancy, or immunosuppressive therapy, such as prolonged use of high-dose adrenocorticosteroids [8].

Complexity Definition and Factor Analysis

To accomplish our first aim, we focused on factors that directly complicate clinical management among those collected in the surveillance data. We selected 4 factors that were deemed by expert consensus to increase complexity because they increase the need for resources or expertise for successful management. We then combined them into a single "complexity" variable to determine its trend over time. Thus, patients with at least 1 of the following were deemed "complex": age >75 years; HIV infection; multidrug resistance (MDR); or extrapulmonary TB disease. In a second analysis using data collected starting in 2010, we included an additional "comorbidity" variable to the definition of complexity, which was defined as having 1 of either end-stage renal disease, diabetes, organ transplant, or immunosuppression (as defined above). We performed a simple linear regression to examine whether the annual proportion of each feature and overall complex patients increased over the study period.

Our second aim was to identify the key dimensions of complexity using exploratory factor analysis of a broader range of variables. Factor analysis was chosen because it identifies contributions to shared variance by observed variables without a priori hypotheses of whether any relationships existed between these variables. Promax, an oblique rotation, was chosen because it allowed the factors to correlate, which was important for our study because we expected some correlation among the factors in our data. We used principal axis factor as the chosen extraction method, and we included only patients diagnosed in 2010 and afterwards due to the availability of comorbidity data. Twenty-five variables from the TB case report form were included in the analysis. On first inspection, several variables were removed due to insufficient variation in their distributions across the study population. We generated multiple exploratory factor analysis models with the goal of obtaining the number of factors with the most "clean" configuration [9]. We removed variables if they did not load ≥0.3 on any factor or if they had similar loadings on multiple factors. A scree plot was also used to help determine the optimal number of factors to retain. We then created a score for each patient, derived from the factor loadings, and rescaled the scores to have a mean score of 100 and standard deviation of 10. These scores were then trended over the period of observation, and a linear regression was performed to test whether there was a significant increase in the factor during this time.

STATA (version 14.1; College Station, TX, USA) was used for statistical analyses. This analysis was conducted as part of the California Department of Public Health's mandate to routinely collect and analyze surveillance data for public health purposes. It was reviewed and determined to be a nonresearch public health activity by the California Health and Human Services Agency's Committee for the Protection of Human Subjects.

RESULTS

Descriptive Statistics of Complexity

We analyzed data on 55 255 patients with active tuberculosis reported during the study period who met inclusion criteria. Annual cases of active TB declined from 1993 to 2016 (3433 cases to 1570 cases) (Table 1). Notably, the proportion of patients who were female, of Asian race, or of foreign birth increased during this time period. In addition, 2 of the 4 features contributing to our definition of complexity (extrapulmonary disease and age >75 years) significantly increased during the study period, while HIV co-infection significantly declined. As a result, the proportion of patients who were complex significantly increased during this period, rising from 38.8% to 45.3% from 1993 to 2016 (Figure 1).

During the period 2010–2016, 11 698 patients were diagnosed with active tuberculosis (Table 2). The mean age of patients increased, while the percentage of cases with HIV co-infection and extrapulmonary TB decreased. The proportions of patients with diabetes and end-stage renal disease rose, while the number of patients with organ transplant, immunosuppression, and who were on TNF antagonist medication remained stable. After adding "comorbidity" to the definition of complexity starting in 2010, we found the same trend of increased complexity ($P < .001$) during 2010–2016.

Factor Analysis

The variables included in the model are shown in Table 3. The variables that were excluded due to lack of sufficient loading onto a single variable were all the various individual extrapulmonary sites, including, but not limited to, axillary disease, osteomyelitis, and cervical lymph node disease, and

Table 1. Complexity Features of Patients with Tuberculosis, 1993–2016

	1993	2004	2016	
	No. (%)	No. (%)	No. (%)	*P*[a]
Total cases	3433	2230	1570	
Average age ± SD, y	46.7 ± 18.5	50.0 ± 19.3	54.8 ± 20.1	<.001
Age >75 y	345 (10.1)	297 (13.3)	339 (21.6)	<.001
Male sex at birth	2257 (65.7)	1359 (60.6)	997 (63.5)	<.001
Extrapulmonary disease	787 (22.9)	572 (25.7)	382 (24.3)	<.001
MDR TB	51 (1.5)	35 (1.6)	29 (1.9)	.75`
HIV-positive	406 (11.8)	118 (5.3)	55 (3.5)	<.001
Non-US-born	2219 (64.6)	1804 (80.9)	1331 (84.7)	<.001
Ethnicity				
White	549 (16.0)	207 (9.3)	98 (7.5)	<.001
Black	520 (15.12)	163 (7.3)	70 (4.5)	<.001
Hispanic	1154 (33.6)	810 (36.3)	510 (32.5)	<.05
Asian	1160 (33.8)	1029 (46.1)	873 (55.6)	<.001
Native American	31 (0.9)	12 (0.5)	13 (0.8)	<.05
Social factors				
Excess alcohol use	369 (10.8)	237 (10.6)	110 (7.4)	<.001
Homeless	358 (10.5)	140 (6.3)	92 (5.9)	<.001
Intravenous drug use	133 (3.9)	61 (2.7)	16 (1.0)	<.001
Long-term care facility	98 (2.9)	38 (1.7)	35 (2.2)	<.001
Migrant worker	76 (2.2)	38 (1.7)	49 (3.1)	<.05
Complex patients[b]	1333 (38.8)	888 (43.0)	711 (45.3)	<.001

Abbreviations: MDR, multidrug-resistant; TB, tuberculosis.

[a] *P* value associated with the linear regression model.

[b] Complexity was defined as at least 1 of MDR TB, age >75 years, HIV-positive status, and extrapulmonary disease.

whether the patient was a migrant worker. Based on the resulting scree plot, we chose to retain 6 factors on the basis of the apparent inflection point on the plot (plot not shown). The calculated overall Kaiser-Meyer-Olkin (KMO) measure of the model was 0.604, suggesting that a moderate proportion of variance in our variables may be caused by the underlying factors. No single variable had a KMO value <0.5. Furthermore, on examination of the correlation matrix, no 2 factors had an absolute correlation value >0.2, indicating lack of co-linearity among variables.

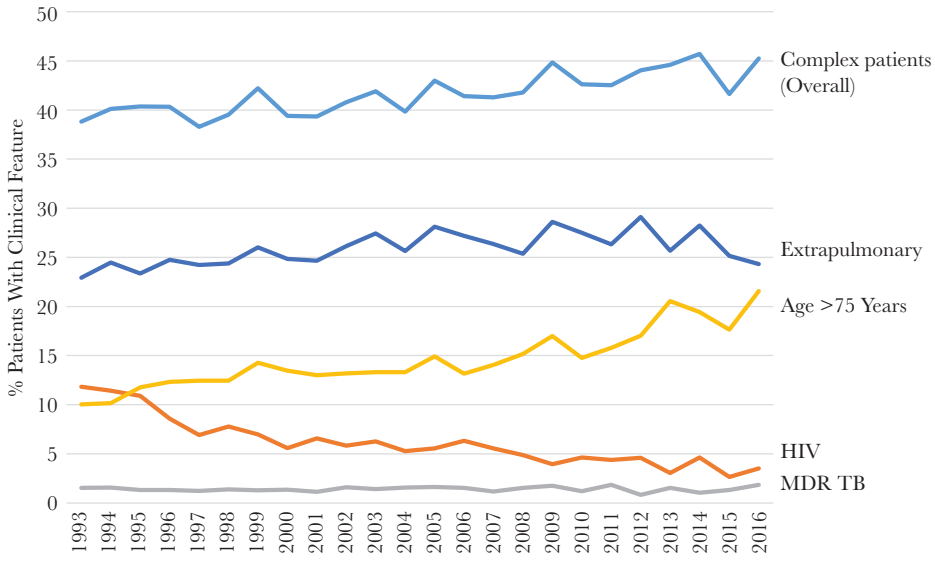

Figure 1. The yearly proportion of complex patients and patients with features associated with complexity increased between 1993 and 2016. Only the proportion of patients who were HIV-positive decreased during the study period, while the features increased in proportion. Abbreviations: MDR, multidrug-resistant; TB, tuberculosis.

Table 2. Complexity Features of Patients With Tuberculosis, 2010–2016

	2010	2013	2016	
	No. (%)	No. (%)	No. (%)	*P*[b]
Total cases	1753	1644	1571	
Average age ± SD, y	51.7 ± 19.1	54.8 ± 19.6	54.0 ± 20.0	<.001
Age >75 y	259 (14.8)	338 (20.6)	339 (21.6)	<.001
Male sex at birth	1042 (60.1)	1036 (63.0)	997 (63.5)	<.05
Extrapulmonary disease	482 (27.5)	422 (25.7)	382 (24.3)	<.05
MDR TB	21 (1.2)	25 (1.5)	29 (1.9)	.534
Comorbidities				
HIV-positive	81 (4.6)	50 (3)	55 (3.5)	<.01
Diabetes	411 (23.5)	452 (27.5)	405 (28.6)	<.001
End-stage renal disease	67 (3.8)	57 (3.5)	63 (4.0)	<.05
Immunosuppression[a]	120 (6.9)	92 (5.6)	94 (6.0)	.093
Organ transplant	12 (0.7)	11 (0.7)	8 (0.5)	.637
TNF antagonist	14 (0.8)	13 (0.8)	11 (0.7)	.986
Non-US-born	1454 (82.9)	1365 (83.0)	1338 (85.2)	.150
Immigration visa	641 (36.6)	617 (37.6)	554 (35.3)	.409
Unknown/other immigration status	617 (35.2)	627 (36.1)	587 (37.4)	.183
Other visa status	145 (6.8)	173 (8.8)	140 (9.3)	.067
Refugee/asylee	68 (3.9)	55 (3.9)	58 (3.5)	.704
Miliary disease	48 (2.7)	60 (3.7)	63 (4.0)	.256
Complex patients[c]	1040 (59.3)	1037 (63.1)	1029 (65.5)	<.001

Abbreviations: MDR, multidrug-resistant; TB, tuberculosis; TNF, tumor necrosis factor.

[a]Defined as features not including HIV/AIDS.

[b]*P* value associated with the linear regression model.

[c]Complexity defined as at least 1 of MDR TB, age >75 years, HIV-positive status, extrapulmonary disease, diabetes, end-stage renal disease, or immunosuppression.

On examination of the factors, we assigned the following names to the corresponding scales on the basis of their similarity to real-life constructs: race/immigration, social features, elderly/institutionalized, advanced TB, comorbidity, and drug resistance risk. Using linear regression, we then trended the 7 (scaled) factors over the period of study and found that race/immigration and elderly/institutionalized significantly increased in value during 2010–2016 ($\beta = 0.042$, $P = .027$; $\beta = 0.046$, $P = .015$), while immunosuppression and resistance declined during this period ($\beta = -0.072$, $P < .001$; $\beta = -0.069$, $P < .001$).

DISCUSSION

Our analysis is the first to attempt to describe complexity among patients with active tuberculosis. Patient complexity, as defined by both the raw data and factor analysis, appears to

Table 3. Factor Analysis Variables

Variable	Race/Immigration	Social Features	Elderly/Institutionalized	Advanced TB	Comorbidity	Drug Resistance Risk
Non-US birth	0.714					
Nonwhite race	0.835					
Homeless within the last 12 mo		0.703				
Alcohol abuse		0.693				
Intravenous drug use		0.474				
Admitted to institution (ICE, LTC, prison)			0.529			
Age >75 y			0.573			
TB care provided only as inpatient			0.650			
Miliary pattern on imaging				0.532		
HIV-positive				0.6055		
Extrapulmonary disease				0.589		
Immunosuppressive state					0.408	
Diabetes					0.470	
ESRD					0.756	
History of incomplete latent TB therapy						0.666
MDR						0.657

Abbreviations: ESRD, end-stage renal disease; ICE, Immigration and Customs Enforcement; LTC, long-term care; MDR, multidrug-resistant; TB, tuberculosis.

have risen over the last 25 years. The trend of rising complexity, a trend that has been noted anecdotally by tuberculosis controllers and a concept found more frequently in the medical literature [10, 11], was confirmed during the analysis period. As no prior study has addressed this issue, it represents only the first step in conceptualizing the complexity of patients with active tuberculosis.

In both of our analyses, we established that an increase occurred in patient complexity during 1993–2016. Several explanations for this trend are possible. First, there was an overall rise in the proportion of elderly individuals in the general population of the United States that was accompanied by an increase in comorbidities such as end-stage renal disease (ESRD) and diabetes [12–14]. Second, improvements in medical and public health interventions have led to fewer cases of tuberculosis from recent transmission and a predominance of re-activation TB cases, which are more likely to occur among older patients who accumulate comorbidities associated with immunosuppression or are more likely to be exposed to immunosuppressive medications [15–17]. The influence of age and comorbidities may be particularly important for many immigrant populations, who now constitute >80% of TB cases [18]. Alternatively, a rise in complexity in recent years may also indicate a failure in screening individuals who should have been treated for latent TB to prevent reactivation. For example, in our data, we continued to see a rise in the proportion of patients with ESRD and diabetes, 2 groups of patients that are indicated to undergo testing for latent TB when these conditions are identified among non-US-born patients. On the other hand, the stability or decline in the proportion of cases who have undergone transplantation or been exposed to TNF antagonists (despite the rising statewide numbers of patients in these risk categories) may be due to a high degree of vigilance among clinicians to screen and therefore prevent reactivation by treating latent TB in this group [19]. These examples demonstrate a way in which clinical management of patients with latent TB can affect the overall complexity of patients with active tuberculosis and suggests that increased awareness among clinicians of evidence-based latent TB treatment guidelines can reduce TB and its associated complexity in the long term.

In an effort to determine a definition of complexity, we used factor analysis to establish a characterization that was as objective as possible. Because patient "complexity" can be a vague concept that may be interchangeably used with the idea of "multimorbiditiy" or "multiple chronic conditions," we aimed to demonstrate its dimensions rather than define an overarching concept [10]. Prior attempts at defining complexity for other conditions have been difficult, with some using in-depth interviews with patients [20] or health care workers [21] to derive a definition. However, 1 advantage of our approach was that the included variables are collected in TB surveillance programs nationwide; therefore, our complexity framework can likely be replicated in other settings. Furthermore, we found that the factors generated in our final model correspond to real-world constructs such as immigration status, sociodemographic features, and medical comorbidity. Although our analysis is limited by the lack of a prior standardized or well-established definition for complexity, our results confirm that our model has reasonable external validity and can provide a basis for future research. While data are sparse in this area, some of the factors we derived were consistent with complexity definitions in the primary care setting, internal medicine wards, long-term care, and mental health care (eg, medical comorbidity and sociodemographic factors) [21–25].

While we did not attempt to determine whether the factors we established are associated with a specific outcome, future research should be directed at testing whether the 7 factors we derived can be used to predict resource utilization or poor outcome. If the factors in our model do in fact correlate tightly with resource utilization, reconsideration should be given to altering current national TB funding formulas to better align with the complexity concept we have formulated. This could be accomplished using regression modeling to generate a scoring system that can be used to evaluate complexity and applied on an individual, county, or state level. Such information is particularly important given that funding for TB management has flattened or declined for certain programs across the country [26]. Alternatively, future study may also find that some of these factors are associated with financial investment, while others are associated with other important outcomes such as time to completion of therapy or mortality. If the factors correlate with poor outcome, they could be used to trigger interventions aimed at improving outcomes. These findings may be useful for key decisions and suggest a potential application of our complexity definition for prognostication or treatment guidance.

An important strength of our study was the use of a large sample size drawn over a long period of observation. Furthermore, we believe that our results can be extrapolated to other jurisdictions in North America and Western Europe (with similar patient populations, immigration, and labor patterns). Future research should study data from other states or national databases to confirm the validity of the underlying complexity dimensions and the hypothesis that complexity has risen over the last 25 years. Another important strength of our study is the use of factor analysis to attempt to establish an objective definition of complexity. Although some degree of unavoidable subjectivity was required in the selection of variables for the model, we minimized this bias by including as broad a range of variables as possible.

An important limitation of our study is the lack of available data on some comorbid and sociodemographic features such as tobacco use, primary language, psychiatric illness, hepatic and cardiovascular disease, insurance status, income, and concurrent medication use. Inclusion of these variables may have

provided a more robust model, particularly in reference to 3 of the factors that had <3 variables with high loadings. Our analysis was also limited by the completeness of data collection in various jurisdictions across the state. All the data included in our analysis were known to clinicians at the time of treatment initiation; however, data on the subsequent course of treatment would also be helpful in understanding patient complexity, including drug regimen changes, incentive and enabler utilization, required legal interventions, adverse events from medication, and hospitalizations during treatment. A second important limitation is the lack of financial and resource investment data for each patient. Such data would be helpful in understanding how complexity is related to the resources needed to successfully treat complex patients and would further validate the use of our factor model. Third, we did not include pediatric cases in our analysis, which, although rare, are inherently more challenging than their adult counterparts. Given the declining rate of pediatric cases, we may have slightly overestimated the rising trend in complexity by not including these patients in our analysis. Lastly, the most recent period of observation, which included additional comorbidity data collected since 2010, indicated leveling off or decline of some of the complexity features. Given this short time frame, future observation over the next several years should be performed to confirm this trend.

CONCLUSIONS

In this first description and analysis of TB complexity in the United States, we found that the complexity of patients with active TB has risen over the last 25 years in California. Second, we have demonstrated the 6 potential dimensions of complexity in 3 composite factors, which include comorbidity, sociodemographic features, and immigration status. These findings suggest that despite the overall decline in active TB cases, effective management of more complex patients may require additional attention and resource investment with specific attention paid to these factors.

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