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MAJOR ARTICLE

Tuberculosis Among Patients With Systemic Lupus Erythematosus in Indonesia: A Cohort Study

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Background. In previous studies, researchers have identified systemic lupus erythematosus (SLE) as a risk factor for tuberculosis (TB), but data from TB-endemic countries are still relatively scarce. We examined TB in a large cohort of SLE patients in Indonesia.

Methods. All patients registered in a lupus registry of the top referral hospital for West Java between 2008 and 2020 were included. Data on SLE characteristics and treatment were retrieved from the registry, and data on TB diagnosis, localization, and outcome were extracted from medical records. Cox-proportional hazard model was used to examine risk factors for development of TB.

Results. Among 1278 SLE patients observed over a total of 4804 patient-years, 131 patients experienced 138 episodes of TB, a median of 2 years (interquartile range, 0.6–5.4) after diagnosis of SLE. A total of 113 patients (81.9%) had pulmonary involvement and 61 (44.2%) had extrapulmonary involvement, with disseminated disease in 26 of 138 episodes (18.8%), and 13 of 131 patients (9.9%) died from TB. The estimated TB incidence was 2873 cases per 100 000 person years. In multivariate cox regression analysis, development of TB was associated with household TB contact (hazard ratio [HR], 7.20; 95% confidence interval [CI], 4.05–12.80), pulse methylprednisolone therapy (HR, 1.64; 95% CI, 1.01–2.67), and age ≤25 years old at SLE diagnosis (HR, 1.54; 95% CI, 1.00–2.35).

Conclusions. There is a high burden of TB in SLE patients in this TB-endemic setting, underlining the need for evaluation or implementation of TB preventive strategies.

Keywords. Indonesia; risk factors; systemic lupus erythematosus; tuberculosis.

Infections are a leading cause of morbidity and mortality among patients treated with immunosuppressive agents. An infectious complication of particular interest is tuberculosis (TB), which is reported to be more frequent in patients with rheumatic diseases including systemic lupus erythematosus (SLE), especially for those living in TB-endemic settings [1,2].

Development of TB may either be a result of *Mycobacterium tuberculosis* infection earlier in life, with reactivation of latent TB infection under immunosuppressive therapy, or newly acquired infection with primary progression to active TB [3]. Moreover, due to immunosuppressive therapy, extrapulmonary or disseminated TB may be more common, diagnosis of TB may be more challenging, and treatment outcomes might be worse in patients with SLE [4,5].

Indonesia has the second highest number of TB cases globally [6], but little is known about the TB burden among SLE patients in Indonesia. Therefore, in this study, we evaluated incidence, clinical characteristics, and risk factors for TB in SLE patients in an urban setting in Indonesia.

METHODS

Study Design and Settings

This was a retrospective cohort study involving all SLE patients who were registered from 2008 to 2020 in the Lupus Registry at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, the largest referral hospital for West Java, a province with 41 million inhabitant. In brief, the Lupus Registry is a database relating to SLE patients from the time they were first diagnosed

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onwards. Included are data on clinical manifestations, laboratory test results, treatment, and clinical outcome [7]. Comorbidities are recorded both at onset (entry in the registry) and during follow-up. However, details of TB (such as specific TB manifestations, microbiological testing etc) were retrieved from patients' medical records).

Data Collection

Patients were included if they fulfilled American College of Rheumatology 1997 and/or Systemic Lupus International Collaborating Clinics 2012 Classification Criteria for SLE. They were excluded if there was no date of SLE diagnosis or date of birth. History of Bacille Calmette-Guerin (BCG) vaccination, smoking, and close contact to an infectious TB patient were retrieved by interview when patients entered the SLE registry. The SLE starting date was recorded as the first time an individual was diagnosed with SLE. Most of our patients visit the outpatient clinic monthly initially, then every 3 months when SLE is in remission. Recorded visits of each patient were collected from the registry until their last visit in December 2020. Patients were considered lost to follow-up if they did not have any visit from December 2018 to the end of the study date and were not known to have died. Medications used for SLE were extracted from the registry and included corticosteroids as well as complications and their treatment, such as vasculitis, nephritis, and hemodialysis. Recorded information on other comorbidities, such as diabetes, was limited and not included in the analysis.

Histopathology, sputum smear microscopy for acid-fast bacilli, and sputum molecular TB diagnostic testing by Xpert MTB/Rif (which was introduced in approximately 2012) were used to define a diagnosis of definite TB; sputum *M tuberculosis* culture is not routinely performed in Indonesian hospitals. Clinical TB (without microbiological confirmation) was defined as TB diagnosed or anti-TB treatment started by the attending physician.

Patient Consent Statement

Written consent was obtained from all of patients involved in this study. The registry had received ethical clearance from the Ethic Committee of University of Padjadjaran (number 036/UN6.KEP/EC/2021).

Statistical Analysis

Comparisons between presenting clinical features and the prevalence of various clinical manifestations were made using the χ^2 or Fisher exact tests. The unpaired Students' *t* test was used to compare parametric continuous data between 2 groups. When normal distribution or equal variance could not be assumed, the Mann-Whitney *U* test was used instead. Correlation between various continuous data was evaluated by Spearman's rank correlation test. Estimates of the survival of the patients were studied by life table analysis using the Kaplan-Meier method. Survival curves with the presence and absence of a TB event were compared using the non-parametric log-rank test. Univariate and multivariate analyses of the predictive factors for TB were conducted using a Cox proportional hazard regression model. Statistical significance was defined as a *P* value of less than .05, 2-tailed, without correction for multiple testing.

RESULTS

Among a total of 1293 registered SLE patients, 1278 could be included in the study, most of whom were young females (Table 1). Nephritis was the most commonly reported complication (45.3%). Almost all patients used corticosteroids, and many had previously received pulse methylprednisolone (MP) or other immunosuppressive therapy (Table 1). Regarding possible other risk factors for TB, human immunodeficiency virus (HIV) and diabetes were not systematically screened for, but few reported smoking or a history of TB in the household. There were 130 (10.2%) patients with a history of TB when they were diagnosed with SLE, and 18 of them developed another episode of TB after diagnosed SLE.

Table 1. Baseline Characteristic and Treatment of Systemic Lupus Erythematosus Patients[a]

Characteristics	Total SLE Patients $n = 1278$
Female gender	1123 (95.7)
Median disease duration, years (IQR)	2.3 (0.5–5.8)
Median age diagnosed, years (IQR)	27 (22–35)
Age of SLE diagnosis	
≤25 years old	552 (43.2)
>25 years old	726 (56.8)
BCG scar, n/N (%)	230/388 (59.3)
Household TB contact, n/N (%)	29/711 (4.1)
Smoking (current/ever), n/N (%)	69/756 (9.1)
History of TB before SLE diagnosis	130 (10.2)
Complication	
Nephritis	579 (45.3)
Vasculitis	85 (6.7)
Hemodialysis	18 (1.4)
Medication	
Corticosteroids	1247 (97.6)
Chloroquine/hydroxychloroquine	675 (52.8)
Azathioprine	557 (43.6)
Cyclophosphamide	293 (22.9)
Mycophenolate mofetil/mycophenolate acid	287 (22.5)
Ever methylprednisolone pulse therapy	239 (18.7)
Methotrexate	82 (6.4)
Cyclosporine	84 (6.6)
Rituximab	9 (0.7)

Abbreviations: BCG, Bacille Calmette-Guerin; IQR, interquartile range; SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]Data are presented as percentage unless stated otherwise. Data for BCG scar, household TB contacts, and smoking status were only available for 388, 711, and 756 individuals, respectively.

Table 2. Disease Localization and Diagnosis for 138 TB Episodes Among 131 SLE Patients[a]

Disease Localization	Number (%)	Proportion With Definite TB (n/N, %)
Pulmonary and extrapulmonary	36 (26.1)	
Pulmonary only	77 (55.8)	
Extrapulmonary only	25 (18.1)	
Pulmonary involvement	113 (81.9)	61/85 (71.8)
Extrapulmonary involvement	61 (44.2)	
Meningeal	11 (8.0)	2/3 (66.7)
Pleural	9 (6.5)	
Pericardial	1 (0.7)	
Lymphadenitis	21 (15.2)	11/11(100)
Miliary	15 (10.9)	
Abdominal	6 (4.3)	3/3 (100)
Genitourinary	1 (0.7)	1/1(100)
Mucocutaneous	2 (1.4)	
Musculoskeletal	5 (3.6)	

Abbreviations: SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]Definite TB: positive to at least 1 of histopathology, sputum microscopy, or Xpert MTB/Rif molecular testing. The value is the positive results of the tests that have been done.

Patients were followed for a median of 2.3 years (interquartile range [IQR], 0.5–5.8). During follow-up, 138 episodes of TB were recorded in 131 patients; 7 patients experienced 2 episodes of TB during follow-up. Most patients presented with (1) pulmonary TB or (2) a combination of pulmonary and extrapulmonary disease (Table 2). Microbiological examination could be verified in 85 of 113 (65%) patients with pulmonary disease, 61 of 85 (72%) of whom had confirmed TB by positive sputum smear microscopy (47 or 64 tested) and/or sputum Xpert TB/RIF testing (47 or 64 tested). Three patients who developed pulmonary TB were diagnosed with rifampicin-resistant TB, based on sputum Xpert TB/Rif molecular testing. Among 62 patients with extrapulmonary involvement, most suffered from lymphadenitis ($n = 22$), miliary disease ($n = 15$), or meningitis ($n = 11$); bacteriological or histopathological confirmation of TB was found in 17 of these patients. Thirteen of the 131 diagnosed TB patients (9.9%) died during their episode of active TB.

With 138 episodes of TB disease during 4804 person years of follow-up, the incidence was 2873 (95% confidence interval [CI], 2400–3345) cases per 100 000 person years. The median duration until the diagnosis of TB after SLE diagnosis was 2 years (IQR, 0.6–5.4). There were 6 patients diagnosed with TB within 2 weeks after diagnosis of SLE. The incidence rate of TB was 48.5/1000 patients in the first year after SLE diagnosis, diminishing to 30/1000 patients by year 5, and remaining relatively constant after that (data in the Supplement). The estimated cumulative TB incidence at 15 years was 29.0% (Figure 1).

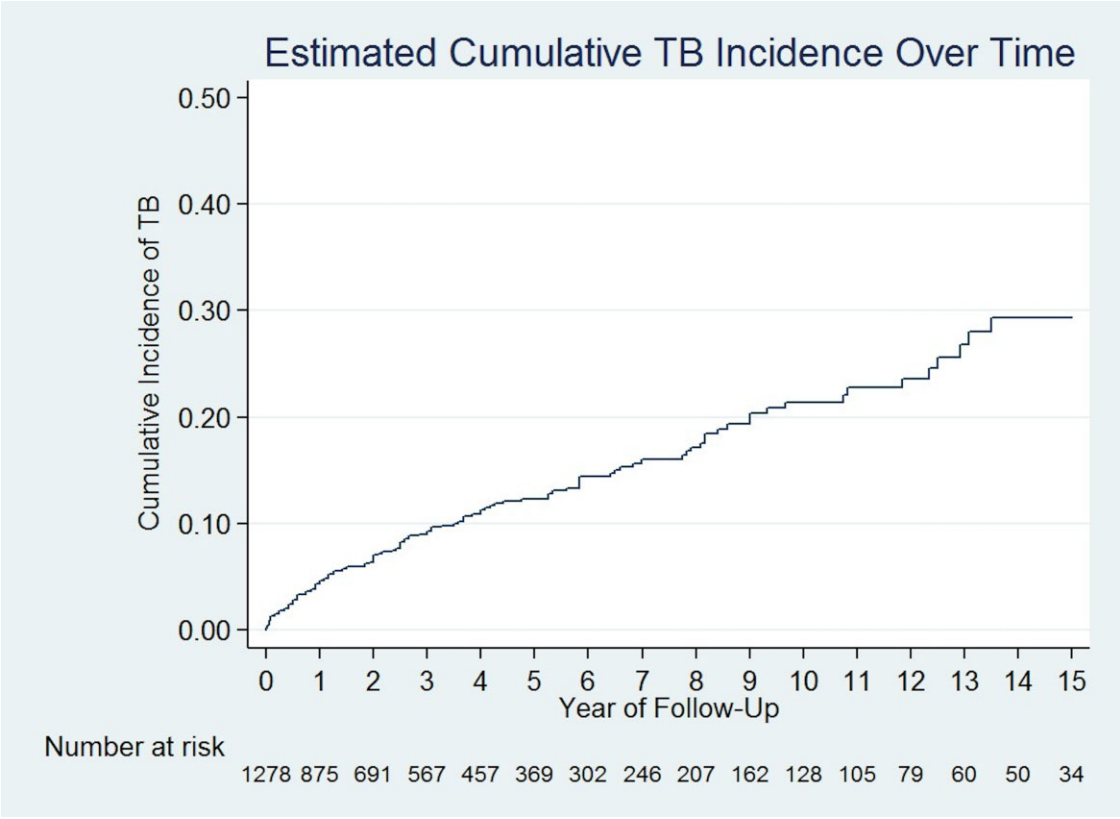

Figure 1. The Kaplan-Meier of estimated cumulative tuberculosis (TB) incidence over time among patients with systemic lupus erythematosus.

Table 3. Factors Associated With Occurrence of Tuberculosis During Follow-up

				Univariate Analysis			Multivariate Analysis					
							Initial Model			Final Model		
Variable	Total	TB ($n=131$) n (%)	Non-TB ($n=1147$) n (%)	Crude HR	95% CI for Crude HR	P Value	Adjusted HR	95% CI for Adjusted HR	P Value	Adjusted HR	95% CI for Adjusted HR	P Value
Gender												
Male	55	7 (12.7)	48 (87.3)	1.47	.69–3.15	.323	1.27	.53–3.02	.595			
Female	1223	124 (10.1)	1099 (89.9)	1 (ref)			1 (ref)					
Age of SLE Diagnosis												
≤25 years old	552	69 (12.5)	483 (87.5)	1.54	1.09–2.17	.014*	1.57	1.02–2.42	.040*	1.54	1.00–2.35	.049*
>25 years old	726	62 (8.5)	664 (91.5)	1 (ref)			1 (ref)					
BCG ($n=388$)												
Yes	230	44 (19.1)	185 (80.9)	0.63	.42–.95	.026*						
No	158	50 (31.6)	108 (68.4)	1 (ref)								
History of TB												
Yes	130	18 (13.8)	112 (86.2)	1.24	.75–2.04	.400	1.14	.59–2.18	.702			
No	1148	113 (9.8)	1035 (90.2)	1 (ref)			1 (ref)					
Household TB Contact ($n=711$)												
Yes	29	15 (51.7)	14 (48.3)	7.17	4.08–12.60	<.001*	6.83	3.64–12.79	<.001*	7.20	4.05–12.80	<.001*
No	682	74 (10.9)	608 (89.1)	1 (ref)			1 (ref)			1 (ref)		
Hemodialysis												
Yes	18	3 (16.7)	15 (83.3)	1.64	.52–5.17	.395	2.92	.88–9.67	.080			
No	1260	128 (10.2)	1132 (89.8)	1 (ref)			1 (ref)					
Nephritis												
Yes	579	53 (9.2)	526 (90.8)	0.91	.64–1.29	.595	1.26	.77–2.05	.356			
No	699	78 (11.2)	621 (88.8)	1 (ref)			1 (ref)					
Vasculitis												
Yes	85	11 (12.9)	74 (87.1)	1.24	.67–2.30	.497	1.21	.59–2.45	.603			
No	1193	120 (10.1)	1073 (89.9)	1 (ref)								
Ever MP Pulse												
Yes	239	28 (11.7)	211 (88.3)	1.62	1.06–2.46	.026*	1.63	.98–2.70	.060	1.64	1.01–2.67	.047*
No	1039	103 (9.9)	936 (90.1)	1 (ref)			1 (ref)			1 (ref)		
Corticosteroid												
Yes	1247	131 (10.5)	1116 (89.5)									
No	31	0 (0)	31 (100)									
Azathioprine												
Yes	557	61 (11)	496 (89)	0.73	.52–1.04	.078	0.88	.56–1.38	.582			
No	721	70 (9.7)	651 (90.3)	1 (ref)			1 (ref)					
Methotrexate												
Yes	82	11 (13.4)	71 (86.6)	0.94	.51–1.76	.856	0.86	.39–1.89	.699			
No	1196	120 (10)	1076 (90)	1 (ref)			1 (ref)					
Cyclosporin												

Table 3. Continued

Variable	Total	TB ($n = 131$) n (%)	Non-TB ($n = 1147$) n (%)	Univariate Analysis			Multivariate Analysis					
							Initial Model			Final Model		
				Crude HR	95% CI for Crude HR	*P* Value	Adjusted HR	95% CI for Adjusted HR	*P* Value	Adjusted HR	95% CI for Adjusted HR	*P* Value
Yes	84	7 (8.3)	77 (91.7)	0.52	.24–1.11	.093	0.84	.37–1.87	.666			
No	1194	124 (10.4)	1070 (89.6)	1 (ref)			1 (ref)					
MMF/MPA												
Yes	287	27 (9.4)	260 (90.6)	0.67	.44–1.02	.062	0.71	.43–1.17	.175			
No	991	104 (10.5)	887 (89.5)	1 (ref)			1 (ref)					
Cyclophosphamide												
Yes	293	27 (9.2)	266 (90.8)	0.78	.51–1.19	.254	0.73	.42–1.26	.260			
No	985	104 (10.6)	881 (89.4)	1 (ref)			1 (ref)					
Rituximab												
Yes	9	1 (11.1)	8 (88.9)	0.82	.12–5.88	.844	1.45	.19–11.11	.723			
No	1269	130 (10.2)	1139 (89.8)	1 (ref)								
Chloroquine/HCQ												
Yes	675	82 (12.1)	593 (87.9)	0.85	.59–1.21	.364	0.69	.44–1.08	.102	0.67	.43–1.04	.074
No	603	49 (8.1)	554 (91.9)	1 (ref)			1 (ref)			1 (ref)		

Abbreviations: CI, confidence interval; HCQ, hydroxychloroquine; HR, hazard ratio; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, mycophenolate acid; ref, referent; SLE, systemic lupus erythematosus; TB, tuberculosis. **P* value <0.05 is considered significant.

Significant differences were found between patients who developed TB and those who did not (Table 3). In multivariate cox regression analysis, household TB contact (hazard ratio [HR], 7.20; 95% CI, 4.05–12.80), a history of methylprednisolone pulse therapy (HR, 1.64; 95% CI, 1.01–2.67), and age ≤25 years old at SLE diagnosis (HR, 1.54; 95% CI, 1.00–2.35) were independently and significantly associated with development of TB, whereas a history of BCG vaccination (HR, 0.63; 95% CI, .42–.95) was associated with a lower risk (HR, 0.67; 95% CI, .43–1.04) (Table 3). The cumulative TB incidence was significantly higher in patients without a BCG scar and those who were under age 25 years at time of diagnosis (Figure 2A and B, increasing steadily over time). Those who had a known TB contact and those who had received MP pulse therapy also showed significant differences in cumulative incidence, which plateaued after the first few years of follow-up (Figure 2C and D), in keeping with MP pulse therapy mostly being used early in SLE treatment, and TB contact history being taken at the time of recruitment. Of the 1278 lupus patients in this cohort, 131 died during the study period. A total of 567 patients did not visit the rheumatology outpatient clinic in the final 2 years of the study period (2018–2020); they most likely continued their care at a lower-level health facility and were considered lost to follow-up.

DISCUSSION

In this cohort of approximately 1300 SLE patients in West Java, Indonesia, TB was a common complication. Although most patients presented with pulmonary disease, almost one fifth of cases presented with disseminated miliary TB or TB meningitis. Younger age (≤25 years) at the time of SLE diagnosis, high-dose pulse corticosteroid therapy, and history of a TB contact were identified as risk factors for development of TB. These data clearly show the burden of TB in SLE patients living in TB-endemic countries and the need for awareness and mitigating measures.

Our study is the largest reported so far from a TB-endemic country, but the incidence of TB in SLE patients in this study was comparable to studies from India (309 SLE patients; TB incidence 2450/100 000 person-years), Malaysia (102 SLE patients; TB incidence 1067/100 000 person-years), and Korea (283 SLE patients; TB incidence 790/100 000 person-years) [1]. The incidence was much higher than the current estimated TB incidence in Indonesia of 312/100 000, or the estimated incidence of 349/100 000 in 2008, when the first patients entered this cohort [6].

The younger age at SLE diagnosis along with the disease itself and additional exposure to immunosuppressive therapy result in an increased susceptibility to TB. Significant findings regarding younger age were noted to increase the risk of TB in this study. Bacille Calmette-Guerin vaccine, which used to be given in newborns, has proved to protect against TB in young

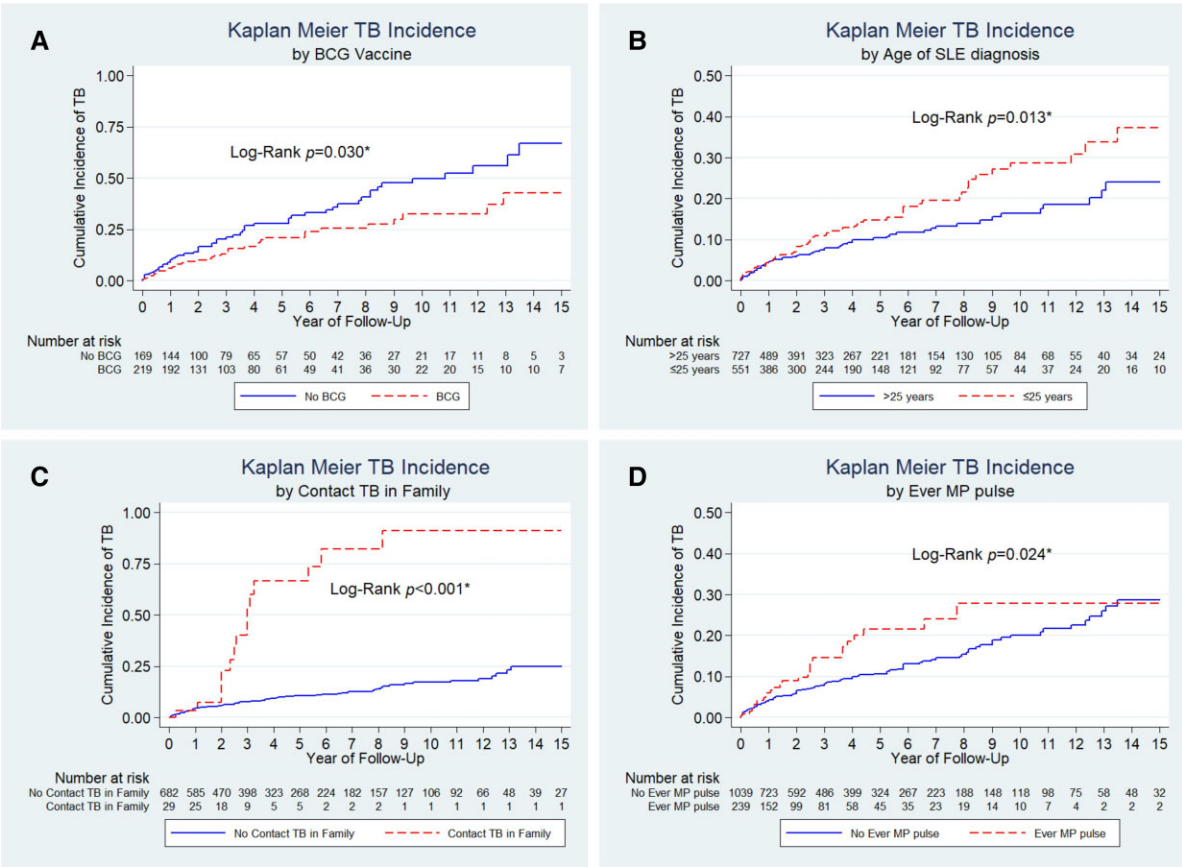

Figure 2. Kaplan-Meyer cumulative tuberculosis (TB) incidence by Bacille Calmette-Guerin (BCG) vaccine (A), age of systemic lupus erythematosus (SLE) diagnosis (B), household contact (C), and ever received methylprednisolone (MP) pulse therapy (D).

children, but its efficacy varies against pulmonary TB in adults [8,9]. In a review of several observational studies, researchers reported that BCG induced trained immunity against TB, which might involve epigenetic and metabolic changes of innate immune cells [10]. Our data demonstrated a significant protective effect of BCG (HR, 0.63; $P = .026$) on TB development among SLE patients, but multivariable analysis could not be performed due to missing data.

Autoimmune diseases including SLE, especially where immunosuppressive medications are needed based on disease activity, may amplify the risk of TB. As shown in previous studies, the use of steroid and or immunosuppressive drugs implies serious potential risk factors for infections [2,11,12]. Active TB was also reported to be more frequent in patients with other rheumatic diseases, including rheumatoid arthritis, Sjogren's syndrome, and systemic vasculitis, especially for those living in TB-endemic settings [2]. Corticosteroid and immunosuppressive agents are the mainstay treatment in SLE. A retrospective case-control study in Colombia showed that 12 months of cumulative steroid dose ≥1830 mg almost tripled the risk of TB [13]. A 13-year cohort study of SLE patients in Taiwan has shown that corticosteroid treatment was associated with a more than 10-fold increased risk of TB [14]. In our study, almost all patients used corticosteroids, but those patients who also received pulse methylprednisolone treatment had an almost 2-fold increased risk of TB, in line with a longitudinal study from China [15].

Evidence of risk of TB associated with the use of other immunosuppressive drugs in patients with SLE is mixed [16,17]. Cyclophosphamide was associated with an almost 3-fold risk of TB in a cohort study in Taiwan [14]. In contrast, consistent with our study, there was no increase in risk in a case-control study in Hong Kong, where azathioprine, cyclophosphamide, and cyclosporin were the immunosuppressive agents used [18]. In univariate analysis, chloroquine or hydroxychloroquine use was associated with a lower risk of developing TB among our SLE patients, but this finding may also be a result of confounding by indication, because these drugs are mostly used for milder disease. We did not specifically measure disease activity as a risk factor, but nephritis, as a marker of higher disease activity, was not significantly associated with the development of TB. Yang et al [14], showed a similar finding in SLE patients with renal complications. In contrast, a study from

Tam et al [18] showed nephritis was associated with over twice the risk of TB.

CONCLUSIONS

Our study has several limitations. First, some relevant clinical data were not recorded in our database, such as average daily and cumulative dose of corticosteroids [18,19]. Second, data on other risk factors for TB such as diabetes and HIV infection were incomplete, noting that diabetes prevalence is likely to be low in this young population (as shown in the low proportion with glycosuria), and that the HIV prevalence in the general population in Indonesia is estimated to be only 0.3%. We did not actively perform TB-case finding for all patients. In addition, bacteriological assessments were incomplete, noting that routine TB diagnosis in Indonesia does not include sputum culture, and that Xpert TB, which was introduced in 2012, is still not widely implemented [20]. Finally, subjects were patients at tertiary referral hospital, limiting the generalizability of the findings of the study and loss to follow-up cases from the registry. However, our study can still conclude that there is a very high burden of TB among SLE patients in this TB-endemic setting. This finding reinforces the need for studies evaluating the benefits or implementation of latent tuberculosis infection screening and TB-preventive therapy in TB-endemic countries.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Authors contributions. L. H. contributed to conception, design, data collection, and interpretation and drafted and revised the manuscript. E. Sa., R. v. C., P. C. H., and B. A. contributed to conception, design, and data interpretation and drafted and revised the manuscript. G. D. drafted and revised manuscript. N. G. G. contributed to data collections and interpretation and revised the manuscript. E. Su. contributed to data analysis and revised the manuscript.

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