Time to sputum culture conversion and its predictors among patients with multidrug resistant tuberculosis in Hangzhou, China: a retrospective cohort study

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Abstract

Background To investigate the time to initial sputum culture conversion (SCC) and its predictors among multidrug-resistant tuberculosis (MDR-TB) patients in Hangzhou, China.

Methods A retrospective cohort study was conducted among patients initiating treatment for MDR-TB from 2011-2015 in Hangzhou, China. Time to initial SCC was analyzed using the Kaplan-Meier method, and Cox proportional hazards regression was used to identify predictors of SCC.

Results Among 384 patients enrolled with MDR-TB, 359 (93.5%) successfully achieved initial SCC after a median of 85 days (inter-quartile range, 40-112 days). A higher rate of SCC was observed in participants with successful treatment outcomes than those with poor treatment outcomes (P<0.01). Multivariate analysis showed that age 25-64 years (adjusted odds ratio [AOR], 0.7; 95% confidence interval [CI], 0.5-0.9; P<0.01), age ≥65 years (AOR, 0.5; 95%CI, 0.3-0.8; P<0.01) and household registration in Hangzhou (AOR, 1.3; 95%CI, 1.0-1.5; P<0.05) were found to be associated with SCC.

Conclusions Although high SCC and treatment success rates were observed among MDR-TB patients in Hangzhou, the prolonged duration to initial SCC underscores the importance of emphasizing measures for infection control. A new policy of shifting outpatient treatment to inpatient treatment in China may reduce the risk of transmission from patients in the time window prior to SCC.

Background

The World Health Organization (WHO) estimated that tuberculosis (TB) caused 1.6 million deaths in 2017, exceeding HIV globally as the infectious disease leading to the greatest number of deaths (1). In that same year, 10 million people developed TB disease with 9% of those cases occurring in China. Furthermore, 460 000 people worldwide were diagnosed with multidrug-resistant tuberculosis (MDR-TB), which is defined as resistance to at least two most common anti-TB drugs isoniazid and rifampin, and 13% of cases were in China (1). TB has been a major public health challenge in China, calling for the development of both broad coverage and high-quality programs for TB screening, diagnosis, treatment and care, especially for individuals with MDR-TB.

Treatment of MDR-TB typically involves prolonged (2) and expensive therapeutic regimens (1), with patients enduring at least 6 months of injections as well as side effects. The average cure rate of MDR-TB is only about 50% globally (1). Studies have shown that primary resistance, resulting from transmission of resistant TB strains, is more common than newly acquired drug-resistance (3, 4), and successful treatment can rapidly reduce the risk of transmission of MDR-TB to others (5). Therefore, effectively identifying and treating existing cases through high quality diagnosis and treatment services is a crucial step in preventing the spread of MDR-TB.

Sputum culture conversion (SCC) is a prognostic marker of therapeutic efficacy in patients with MDR-TB (6–8). Additionally, better clinical outcomes have been observed among MDR-TB patients who achieve

culture conversion (9, 10). Based upon these findings, the WHO highly recommends routine SCC monitoring to assess treatment response and enable early detection of therapeutic failure (2). Elucidating potential predictors of SCC in MDR-TB could help identify patients who are likely to develop poor outcomes and prompt clinical intervention to improve treatment outcomes for these individuals. Numerous studies have been conducted to investigate the predictors for MDR-TB treatment outcomes (11–13), but few have been carried out in China. We therefore designed a retrospective cohort study to evaluate the SCC and identify its predictors among MDR-TB patients in Hangzhou in eastern China.

Methods

Study Overview

Hangzhou is the capital city of Zhejiang Province in eastern China. It comprises 13 districts, one county-level city and two counties, and has 7.2 million local residents and over 2 million migrant inhabitants. There are 13 TB specialty hospitals, with two designated for treating drug-resistant TB patients.

A retrospective cohort was designed among patients who were diagnosed with MDR-TB and initiated on treatment in one of the TB specialty hospitals in Hangzhou from 2011–2015. The eligibility criteria included: patients diagnosed with MDR-TB in one of the TB specialty hospitals in Hangzhou; initiated treatment after diagnosis; had demographic and clinical data, e.g., gender, age, occupation, residence, ethnicity, year of starting TB treatment, sputum microscopy testing, culture and drug sensitivity testing, duration of therapy, and treatment outcome. All patients meeting these inclusion criteria were consecutively included in the cohort. The bacteriology examinations including sputum sample collection, smear, culture and drug sensitivity tests (DST) have been reported elsewhere (14). De-identified demographic, clinical and sputum culture data, which were examined at a monthly interval, were extracted from the online Tuberculosis Information Management System (TBIMS) (15). Because TB is a notifiable disease in China, all diagnosed cases are reported to TBIMS, and this database serves as a central repository for TB diagnosis, treatment, and monitoring data. All diagnosed MDR-TB patients who started treatment from 2011–2015 in Hangzhou, China were included in this analysis.

Sputum Culture Conversion and Treatment Outcome

The outcome event was SCC, which was defined as two consecutive negative cultures taken at least 30 days apart following an initial positive culture. According to the WHO guidelines(16), treatment outcomes were defined as follows: (1) A patient was considered cured if he/she completed treatment and had at least five consecutively negative sputum cultures during the final 12 months of treatment; or if one of those culture was positive, then at least three subsequent consecutive cultures should have been negative. (2) Treatment completion was defined as completion of MDR-TB treatments without evidence of failure, but with inadequate bacteriological records for classification as cure. (3) Treatment failure was defined when two or more of the five final sputum cultures were positive, or one positive culture of the final three cultures during the final 12 months of treatment. (4) Death was defined when a patient died due to any cause during treatment. (5) A patient was considered lost to follow-up if treatment was

interrupted for two or more consecutive months against his/her clinicians' advice. These treatment outcomes were subsequently categorized into two groups: The *treatment success group* included patients who met criteria for cure or treatment completion, whereas the *poor treatment outcome group* included patients who were classified into the treatment failure, lost to follow-up or death categories.

Statistical Analysis

Statistical analyses were conducted with SPSS software (IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, NY, USA)). Proportions were computed for categorical variables and expressed as percentages. Means with standard deviations and medians with inter-quartile ranges (IQRs) were calculated for normally distributed and non-parametric continuous data, respectively. The Pearson chi-square test or fisher's exact test were used to compare the differences in treatment outcomes between groups. Time to SCC was analyzed using the Kaplan-Meier method, and differences in survival times were assessed with the log-rank test. Bivariate and multivariable Cox proportional hazards regression analyses were used to identify predictors of SCC. Time of entry into cohort was the date of initiating treatment within the study period, and exit time was date of collecting the first negative sputum specimen for diagnosing SCC. Study participants were censored from the analysis at the time of death, last follow-up date, or December 31, 2015, depending on which came first.

All variables with $P < 0.1$ in univariate analysis were included in multivariable analysis. Statistical significance was defined as a two-sided P value < 0.05.

Results

Demographic and Clinical Characteristics of the Participants

Between 2011–2015, a total of 25081 cases of pulmonary tuberculosis were diagnosed in Hangzhou, and 8806 were sputum smear positive and screened for drug resistance. Among 527 patients diagnosed with MDR-TB, 394 (74.8%) started treatment during the study period. Patients who did not start treatment during the study period were excluded from this study. Of the 394 patients, 5 patients who were still on treatment at the end of study, and 5 patients who had incomplete information on treatment and treatment outcome were excluded from the study, resulting in a total of 384 patients with MDR-TB included in the analysis.

Of the 384 participants, 296 (77.1%) met criteria for successful treatment outcomes and 88 (22.9%) had poor treatment outcomes. The mean age of participants was 41.7 year (standard error [SD], 15.4). The median duration of follow up was 86.5 days (range, 13–1281; interquartile range [IQR], 44.5–117.5). *Table 1* displays demographic and clinical characteristics of the participants.

Sputum Culture Conversion and Treatment Outcomes

In all, 359 (93.5%) patients achieved SCC in a median of 85 days (range, 13–541; IQR, 40–112), and 25 (6.5%) failed to achieve SCC. *Fig. 1* shows the survival curve during the first 12 months of treatment, and

there is little change thereafter.

The observed rate of SCC was markedly higher among participants with successful treatment outcomes compared to those with poor treatment outcomes (OR,110.6; 95%CI, 14.7–832.7; *P*<0.01) (*Table 2)*.. The time to initial SCC also differed significantly between those with successful treatment outcomes and those with poor treatment outcomes (^{2} = 35.5, *P*<0.01; *Fig. 2)*..

Predictors of Time to Initial Sputum Culture Conversion

All variables with *P* <0.1 in univariate analysis (*Table 3)*,, including age ≥65 years (OR, 0.5; 95%CI, 0.3~0.8; *P*<0.01), age 25–64 years (OR, 0.7; 95%CI, 0.5–0.9; *P*<0.01), occupation (OR, 0.8; 95%CI, 0.6–1.0; *P*<0.05) and household registration in Hangzhou (OR, 1.2; 95%CI, 1.0–1.5; *P* = 0.09), were entered in multivariable analysis. Variables that remained in the final model included: age 25–64 years (adjusted OR [AOR], 0.7; 95%CI, 0.5–0.9; *P*<0.01), age ≥65 years (AOR, 0.5; 95%CI, 0.3–0.8; *P*<0.01) and household registration in Hangzhou (AOR, 1.3; 95%CI, 1.0–1.5; *P*<0.05) (*Table 4)*..

Discussion

Routine sputum culture monitoring during clinical treatment is a critical component of successful MDR-TB management (2, 12), as SCC has been demonstrated consistently to predict the therapeutic efficacy of treatment, and time to SCC has been shown to be early predictor of treatment outcomes (8, 17). Few studies have evaluated these issues in China, and this study evaluated time to SCC and predictors of initial SCC among patients with MDR-TB in Hangzhou and has several important findings.

First, the present study revealed that 93.5% participants achieved SCC in their treatment course. To the best of our knowledge, this is the highest SCC rate reported in the past five years. The SCC rates reported by studies from Pakistan (7), Ethiopia (11, 12), Peru (18), India (19), Jiangsu province in China (8), and one multi-center study carried out in nine countries (6) varied from 76.3% to 90.0%. The high SCC rate was concordant with the treatment success rate among participants in this study, which was the highest ever reported in a domestic study (20–22) and relatively high globally (6, 23–25). This, combined with the declining drug resistance rates among pulmonary tuberculosis patients during 2011–2015 in Hangzhou, e.g. the prevalence of MDR declined from 11.6% to 8.0% and resistance to any first-line drugs declined from 31.3% to 22.3%, confirms the progress achieved by TB treatment and management programs in Hangzhou (14).

Second, a higher SCC rate was observed among participants with successful treatment outcomes compared with those with poor treatment outcomes, which is similar to results reported in previous studies using SCC as a prognostic marker for treatment outcomes in patients with MDR-TB (6–8). However, further research should investigate the validity of SCC at different timepoints as an early predictor of treatment efficacy, as it may differ by regions with different HIV prevalence, capacities for MDR-TB treatment, and drug resistance patterns (12, 13). For example, the 6-month SCC had stronger association with cure than 4-month SCC among Pakistan patients (7), while studies conducted in China

and Ethiopia showed that the optimum time point of achieving SCC for predicting successful treatment outcome was between four to six months (26).

Third, the median time to initial SCC in our study was 85 days, which is relatively high when compared with the median 58–91.5 days reported in earlier studies (7, 8, 11, 12, 18, 19). This may due to multiple reasons, for example unknown second-line drug (SLD) susceptibility, treatment regimens, lost to follow-up rates and laboratory tests. This is to be further studied.

MDR-TB patients with positive sputum cultures are infectious and could potentially act as a source of transmission of disease in the community (12). This has been reported as the main driver of MDR-TB in China, as opposed to *de novo* acquisition of drug resistance (4). The rates of SCC and treatment success were high, but the median time from starting treatment to initial SCC was almost two months, and these mixed results indicated that further efforts should be made to reduce the time to SCC for the purpose of effective infection control. Most Chinese MDR-TB patients receive outpatient treatment without isolation from their families and communities, except for those with severe side effects or comorbidities who receive inpatient treatment, so few measures have been taken for infection control in routine treatment and management of MDR-TB patients, this consequently increases the risk of transmission. Hangzhou health department is planning to provide free inpatient treatment for MDR-TB patients until they achieve SCC. This new policy could help reduce the likelihood of MDR-TB transmission to their contacts.

Older patients were less likely to achieve SCC, and this finding is in line with previous studies reporting older age as a risk factor for poor treatment outcomes among patients with MDR-TB (27, 28). Furthermore, patients with household registration in Hangzhou were more like achieve SCC. One reason for this may be that migrant patients without household registration were more likely to have treatment interruption due to limited insurance coverage and unstable living place, and financial resources have been reported to be strongly associated with treatment outcomes (29).

This study has several limitations. First, certain important clinical variables such as body mass index, HIV infection status, smoking and alcohol use, which have been reported to be related to initial SCC (12, 22), were not investigated in this study. These data were not collected or uploaded to TBIMS by hospitals. Second, patients were asked to undergo sputum examinations once a month according to the guidelines for treatment of drug-resistant tuberculosis in China (30), but most patients have missed one or more examination, which may affect the accuracy of the observed time to initial SCC in this study. Third, this study was carried out in a single, therefore the findings are not necessarily generalizable to other cities.

However, this retrospective study is among few studies evaluating the rate and predictors of initial SCC among MDR-TB patients in China and provides valuable data on high rate of initial SCC and its correlation with successful treatment outcome. This study also highlights the need for revising the current policy of outpatient treatment to reduce the risk of transmission during the window from initiating treatment to achieving SCC.

Abbreviations

SCC: sputum culture conversion; MDR-TB: multidrug-resistant tuberculosis; AOR: adjusted odds ratio; CI: confidence interval; WHO: World Health Organization; TB: tuberculosis; DST: drug sensitivity tests; TBIMS: Tuberculosis Information Management System; IQRs: inter-quartile ranges; SD: standard error; OR: odds ratio; SLD: second-line drug

Declarations

- Ethics approval and consent to participate

The study was approved by the ethics committee of Hangzhou City Center for Disease Control and Prevention.

- Consent for publication

All authors have reviewed and approved the manuscript for publication.

- Availability of data and materials

According to Chinese law, the public health data are not publicly available, but are available on reasonable requests from the corresponding author.

- Competing interests

The authors declared no conflicts of interest.

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- Authors’ contributions

LQC participated in study design, data collection, analysis, manuscript writing and funding support; LM, WLM, WM, WL, WK, ZG and XL participated in study design and data collection; HE participated in study design and revised the manuscript; WYF conducted laboratory testing; HZQ participated in study design and revised the manuscript. All the authors have read the manuscript and have approved it.

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None.

- Authors’ information (optional)

None.

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Tables

Table 1. Demographic and clinical characteristics of study participants

Variables	N (%)	Treatment Outcomes		χ2	*P*-value
		Successful, N (%)	Poor, N (%)		
Total	384	296(77.1)	88(22.9)		
Gender				5.36	<0.05
Male	272(70.8)	201(67.9)	71(80.7)		
Female	112(29.2)	95(32.1)	17(19.3)		
Age, year				14.4	<0.05
<25	58(15.1)	55(18.6)	3(3.4)		
25≤age□65	293(76.3)	220(74.3)	73(83.0)		
Age>65	33(8.6)	21(7.1)	12(13.6)		
Ethnic				0.14	0.99
Han	378(98.4)	291(98.3)	87(98.9)		
Other	6(1.6)	5(1.7)	1(1.1)		
Occupation				7.83	<0.05
Other	101(26.3)	88(29.7)	13(14.8)		
Farmer/worker/migrant worker	283(73.7)	208(70.3)	75(85.2)		
Residence				6.48	<0.05
Rural	160(41.7)	113(38.2)	47(53.4)		
Urban	224(58.3)	183(61.8)	41(46.6)		
Household registration in Hangzhou				0.52	0.47
No	214(55.7)	162(54.7)	52(59.1)		
Yes	170(44.3)	134(45.3)	36(40.9)		
Resistance to ethambutol				0.29	0.59
No	219(57)	171(57.8)	48(54.6)		
Yes	165(43)	125(42.2)	40(45.5)		
Resistance to streptomycin				0.11	0.74
No	147(38.3)	112(37.8)	35(39.8)		
Yes	237(61.7)	184(62.2)	53(60.2)		
Resistance to ofloxacin				0.16	0.69
No	354(92.2)	272(91.9)	82(93.2)		
Yes	30(7.8)	24(8.1)	6(6.8)		
Resistance to kanamycin				0.01	0.99
No	375(97.7)	289(97.6)	86(97.7)		
Yes	9(2.3)	7(2.4)	2(2.3)		
Number of resistant drugs				0.18	0.67
2	98(25.5)	74(25.0)	24(27.3)		
>2	286(74.5)	222(75.0)	64(72.7)		
Previous TB treatment history				2.81	0.09
No	29(7.6)	26(8.8)	3(3.4)		
Yes	355(92.4)	270(91.2)	85(96.6)		

Table 2. SCC and treatment outcomes

SCC	Successful, N (%)	Poor, N (%)	c^2	*P* value
Yes	295(99.7)	64(72.7)	80.9	<0.001
No	1(0.3)	24(27.3)		

Table 3. Univariate analysis of predictors of SCC among MDR-TB patients in Hangzhou, China

Variable	N	Sputum culture conversion (%)	HR (95% CI)	*P*-value
Residence				
Rural	160	143(89.4)		
Urban	224	216(96.4)	1.0(0.8,1.2)	0.97
Household registration in Hangzhou				
No	214	199(93.0)		
Yes	170	160(94.1)	1.2(1.0,1.5)	0.09
Gender				
Male	272	252(92.6)		
Female	112	107(95.5)	1.0(0.8,1.3)	0.71
Age, years				
<25	58	58(100.0)		
25-64	293	273(93.2)	0.7(0.5,0.9)	<0.01
≥65	33	28(84.8)	0.5(0.3,0.8)	<0.01
Ethnicity				
Han	378	354(93.7)		
Other	6	5(83.3)	1.1(0.5,2.7)	0.83
Occupation				
Other	101	100(99.0)		
Farmer/worker/migrant worker	283	259(91.5)	0.8(0.6,1.0)	0.03
Previous TB treatment				
No	29	27(93.1)		
Yes	355	332(93.5)	1.0(0.7,1.5)	0.85
Number of resistant drugs				
2	98	95(96.9)		
>2	286	264(92.3)	0.9(0.7,1.2)	0.44
Resistance to ethambutol				
No	219	209(95.4)		
Yes	165	150(90.9)	0.9(0.7,1.1)	0.29
Resistance to streptomycin				
No	147	139(94.6)		
Yes	237	220(92.8)	0.9(0.8,1.2)	0.51
Resistance to ofloxacin				
No	354	332(93.8)		
Yes	30	27(90.0)	0.8(0.5,1.2)	0.32
Resistance to kanamycin				
No	375	350(93.3)		
Yes	9	9(100.0)	1.1(0.6,2.1)	0.85

Note: HR, hazard ratio; CI, confidence interval

Table 4. Multivariate analysis of predictors of SCC among MDR-TB patients in Hangzhou, China

Variable	AHR (95% CI)	*P* value
Household registration in Hangzhou		
No	1.0	
Yes	1.3(1.0,1.5)	<0.05
Age, years		
<25	1.0	
25-64	0.7(0.5,0.9)	<0.01
≥65	0.5(0.3,0.8)	<0.01

Note: AHR-adjusted hazard ratio; CI-confidence interval

Figures

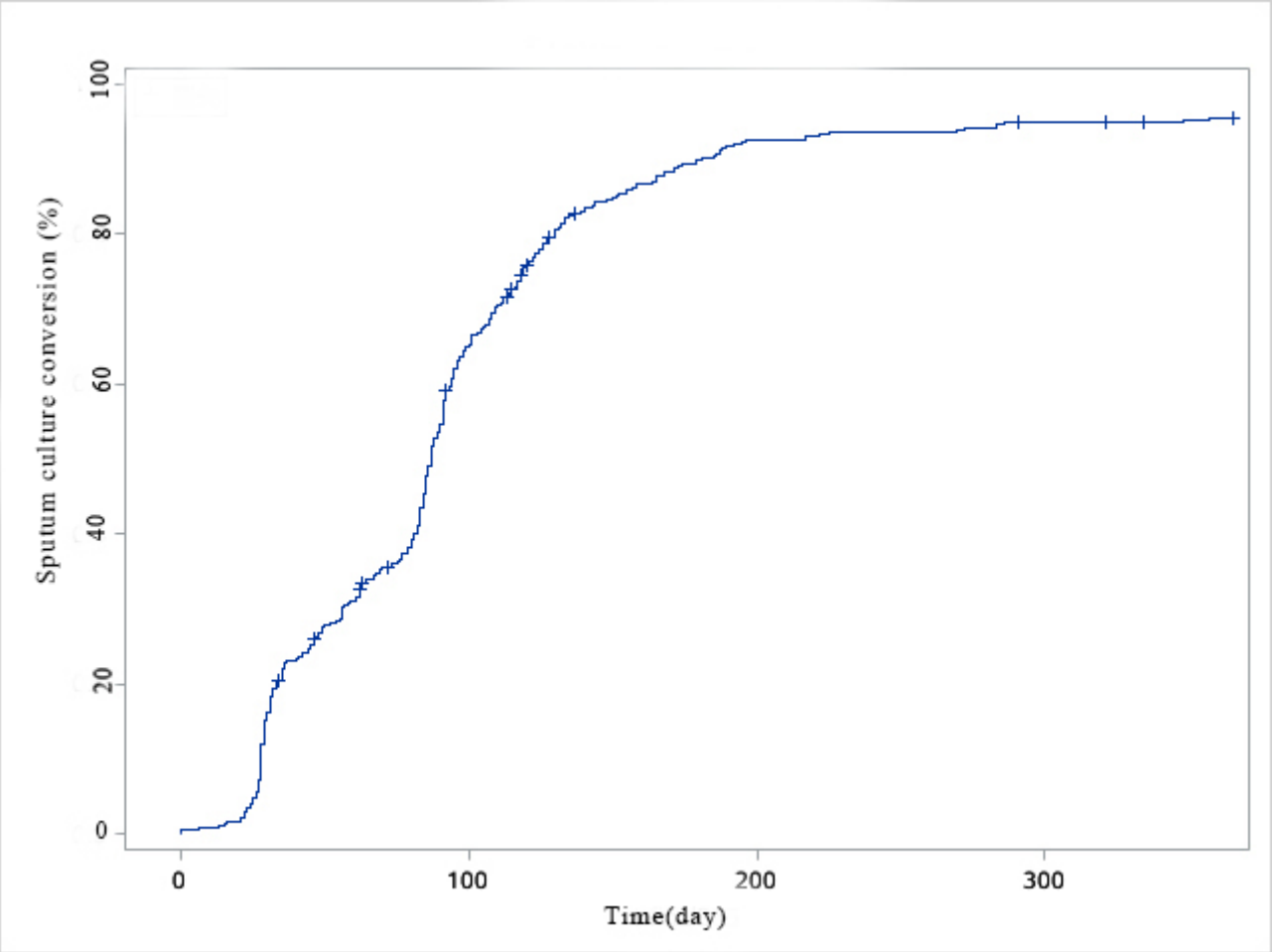

Figure 1

The survival curve during the first 12 months of treatment

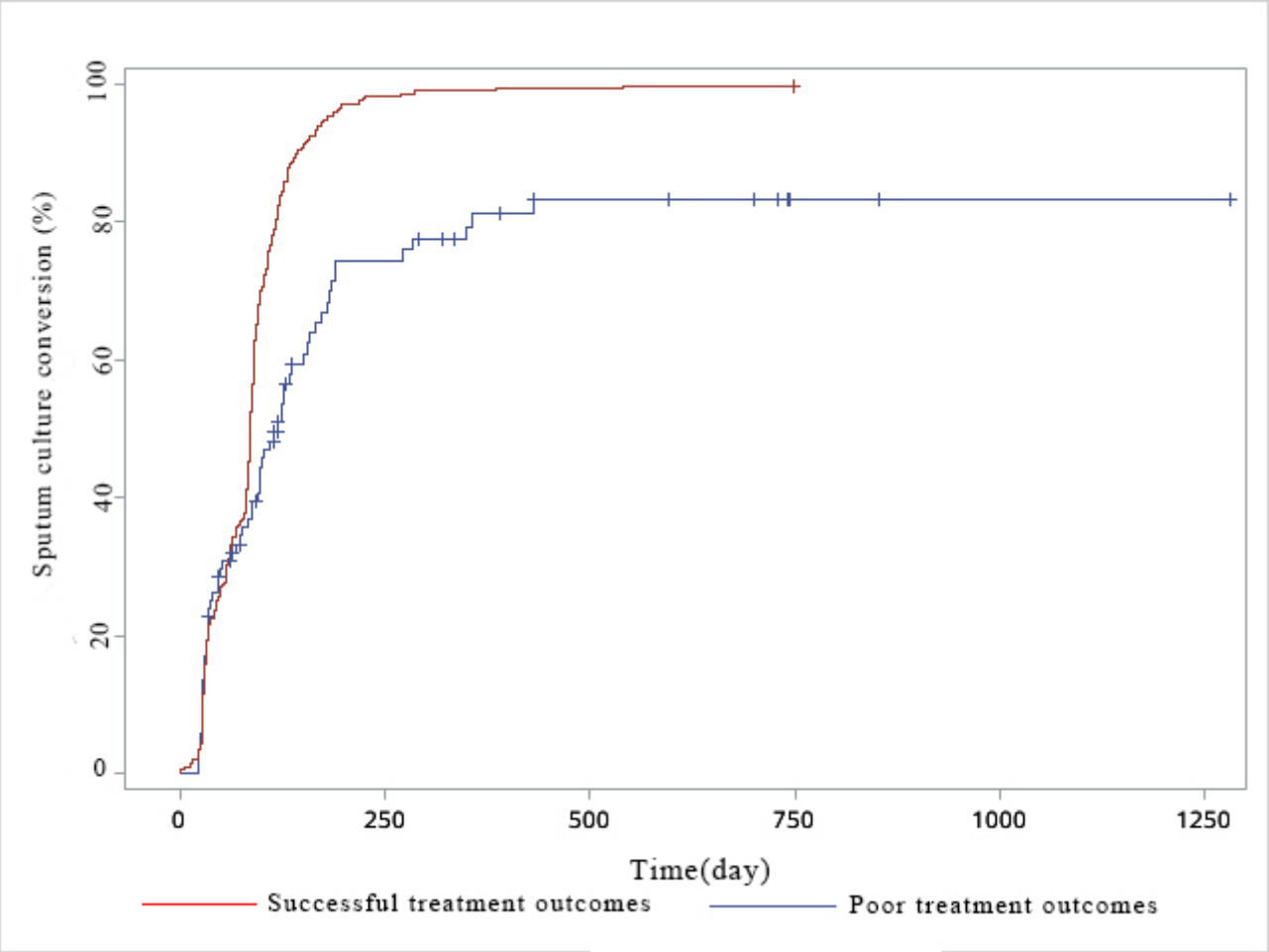
Sputum culture conversion (%)
100
80
60
40
20
0
0
250
500
750
1000
1250
Time(day)
Successful treatment outcomes
Poor treatment outcomes

Figure 2