MISSED APPOINTMENTS AT A TUBERCULOSIS CLINIC INCREASED THE RISK OF CLINICAL TREATMENT FAILURE

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Abstract. We investigated the charts of 381 new smear-positive tuberculosis patients at Khon Kaen Medical School during 1997-2001 using World Health Organization definitions to evaluate associations among treatment success or failure (defaulted, failed, died, or not evaluated) and tuberculosis clinic contact, demographics and clinical characteristics of the patients. Multinomial logistic regression was used for three-category outcome analysis: treatment success, transferred-out and clinical treatment failure. The treatment success and clinical treatment failure rates were 34.1% and 34.4%, respectively. About 46.5% and 85.8% of patients missed appointments at the tuberculosis clinic in the treatment success and treatment failure groups, respectively. The results show that patients who were absent from the tuberculosis clinic were 5.95 times more likely to have clinical treatment failure than treatment success, having adjusted for the effect of transfering-out and the effect of the treatment regimen and the sputum conversion status (adjusted odds ratio = 5.95; 95% CI: 2.99 to 11.84). The review showed that absence from the tuberculosis clinic was an independent risk factor for clinical treatment failure. We recommended that all new smear-positive tuberculosis patients should be followed closely at a tuberculosis clinic.

INTRODUCTION

Tuberculosis (TB) kills nearly two million people each year (World Health Organization, 2005a). It is among the top ten causes of death in the world (Beltan *et al*, 2000). This global epidemic is growing larger and more dangerous (World Health Organization, 2002). The breakdown in health services, the spread of HIV/AIDS and the emergence of multidrug-resistant TB (MDR-TB) are contributing to the worsening impact of this disease (World Health Organization, 1994). Systematic management is required to combat this disease. This is accomplished via TB clinics (TBC). However, only some infectious TB patients are managed at TBC in Thailand, which is one of the 22 TB high-burden countries in the world (World Health Organization, 2005b). The purpose of this study was to quantify the effect of absence from a TBC on clinical treatment failure (CTF) in new smear-positive tuberculosis patients at Khon Kaen Medical School (KKMS) during a five-year period.

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MATERIALS AND METHODS

The charts of 381 new smear-positive tuberculosis patients, diagnosed at KKMS from January 1997 through December 2001, were reviewed. These patients came from all patients who had positive results for acid-fast bacilli in AFB registry booklets of the school's central laboratory, one-fourth of a random sampling of patients diagnosed with TB in the OPD computerized database of the school. Regarding the World Health Organization's definitions (World Health Organization, 2005b) of infectious tuberculosis treatment outcomes, we divided them into three groups: treatment success (TS), transferred-out, and CTF. We wanted to quantify the

effect of "absence from a TBC" on "CTF", while adjusting for the effect of transfering-out and adjusting for the effect of other factors. Although the World Health Organization classified "transferred-out" as an unsuccessful category because of its doubtful final outcome, many physicians disagree that being "transferred-out" is unsuccessful management. Remedial actions to solve this problem were quite specific and different from other treatment outcomes, so we decided to separate it as a unique category: "transferred-out" or "possible success".

Definition

The operational definitions used in the study are as follows:

Smear-positive pulmonary case. At least two initial sputum smear examinations (direct smear microscopy) positive for AFB; or one sputum examination positive for AFB and radiographic abnormalities consistent with active pulmonary tuberculosis as determined by the treating medical officer; or one sputum specimen positive for AFB and culture positive for *Mycobacterium tuberculosis*.

New case. A patient who has never had treatment for tuberculosis, or who has taken anti-tuberculosis drugs for less than 1 month.

Cured. Initially smear-positive patient who has a negative sputum smear in the last month of treatment, and on at least one previous occasion.

Completed treatment. A patient who has completed treatment but does not meet the criteria for cure or failure.

Transferred out. A patient who was transferred to another reporting unit and for whom treatment results are not known.

Defaulted. A patient who did not collect drugs for 2 months or more at any time after registration.

Failed. A smear-positive patient who remained smear-positive, or became smear-positive again, at least 5 months after the start of treatment

Died. A patient who died during treatment, irrespective of cause.

Not evaluated. A patient who cannot be classified as cured, completed treatment, defaulted, failed, died or transferred out, *eg* a patient who lost contact before the start of treatment.

Treatment success. The sum of patients who were cured and who completed treatment.

Clinical treatment failure. The sum of patients who defaulted, failed, died, or were not evaluated.

Data analysis

The data collectors were three registered nurses who were not directly involved in the TB service of the school. They were trained to collect data regarding a standard protocol. Data collection was done at the Registration Unit of the school's hospital under the supervision of a medical researcher. Quality control of data collection was done via 10% re-examination of the charts by the medical researcher.

Double entries of the collected data were done using EpiInfo program, version 6.04d (Dean *et al*, 2001). Data analysis was done using STATA 8.2 for Windows (Stata Corp, 2003). Multinomial logistic regression was used for three-category outcome analysis: TS, transferred out, and CTF (defaulted, failed, died, and not evaluated). The modeling was aimed at determining a parsimonious model that gives a valid estimate of the adjusted odds ratio for "absent contact with TBC" on the occurrence of "CTF", using TS as reference group. Extraneous variables in the study were age, gender, marital status, education, occupation, place of residence, cavity lesion, HIV co-infection, other concomitant diseases requiring treatment, anti-TB drug resistance, adverse drug reactions or allergies, admission status, diagnosis, treatment regimen, sputum conversion status at second month, being the place of initial diagnosis, and referable linkage between health facilities.

The modeling strategy consisted of three stages: variable specification, interaction assessment, and confounding assessment, followed by consideration of precision (Kleinbaum and Klein, 2002). The initial model in the variable specification stage, which was hierarchically well-formulated, was composed of the following variables: outcome variable, exposure variable of interest, extraneous variables that had a p-value ≤0.20 on bivariate analysis using simple multi-

nomial logistic regression focusing on comparison of CTF versus TS, and two-factor interaction terms that had a p-value ≤0.20 from stratified analysis focusing on comparison of CTF versus TS. The Mantel-Haenszel test of homogeneity of odds ratio across strata was used in stratified analysis to find out potential effect modifiers. The gold standard model composed of all confounders was constructed. Results are given as odds ratios (OR) with 95% confidence intervals (CI). The gold standard odds ratio for "absent contact with TBC" in the comparison of CTF versus TS was calculated. Assessment of confounders was done by removing candidate confounders from the gold standard model, one at a time. The reduced model was accepted if it gave essentially the same odds ratio of interest as the gold standard odds ratio (10% change or less). The statistical method used in modeling was the likelihood ratio test (for testing the effect of independent variables). Post-estimation analysis was composed of the Hausman test and the Small and Hsiao test (for testing the independence of irrelevant alternatives assumption), Hosmer-Lemeshow together with the Pearson test (for testing the Goodness-of-Fit), and the Index plot and Cook's statistic (for identification of influential observations and poorly fit subjects). The assessment of model adequacy was done separately for the two logistic regression equations, as suggested by Hosmer (2000). A value of p ≤0.05 on the two-sided test was consid-

Table 1
Group statistics and simple multinomial logistic regression results.

				Simple multinomial logistic regression			
				Likelihood ratio test		Crude odds ratio (95% CI)	
	Treatment success (n=127)[a]	Transferred out (n=119)[a]	Clinical treatment failure (n=127)[a]	χ^2 (df=2)	p	Transferred out *vs* Treatment success	Clinical treatment failure *vs* Treatment success
"Absent contact" with TB clinic, %	46.5	76.5	85.8	50.28	<0.001	3.75 (2.16, 6.48)	6.98 (3.80, 12.83)
Median age, year (interquartile range)	42.3 (29.7)	53.7 (28.5)	49.4 (33.8)	10.34	0.006	1.12 (1.04, 1.20)[b]	1.08 (1.00, 1.15)[b]
Male, %	58.3	63.0	70.9	4.51	0.105	1.22 (0.73, 2.04)	1.74 (1.04, 2.93)
Non-couple [c], %	40.2	36.1	38.6	0.43	0.808	0.84 (0.50, 1.41)	0.94 (0.57, 1.55)
Farmer or laborer, %	39.4	55.8	53.3	11.81	0.003	2.36 (1.41, 3.94)	1.83 (1.11, 3.02)
Residence outside MKK, %	66.9	96.7	74.8	42.94	<0.001	14.21 (4.91, 41.14)	1.47 (0.85, 2.53)
Cavity lesion, %	16.5	19.3	18.1	0.33	0.848	1.21 (0.63, 2.32)	1.12 (0.58, 2.14)
HIV+, %	11.0	13.4	23.6	8.10	0.017	1.25 (0.58, 2.70)	2.50 (1.25, 4.98)
Other concomitant diseases, %	42.5	42.9	56.7	6.60	0.037	1.01 (0.61, 1.68)	1.77 (1.08, 2.91)
Adverse drug reactions or allergies, %	5.5	7.6	7.9	0.66	0.718	1.40 (0.51, 3.89)	1.47 (0.54, 3.98)
Admission to the hospital, %	32.3	18.5	39.4	13.58	0.001	0.48 (0.26, 0.86)	1.36 (0.81, 2.28)
Diagnosed by GP or AE, %	32.3	47.1	48.0	8.16	0.017	1.86 (1.11, 3.13)	1.94 (1.16, 3.23)
Non-WHO treatment regimen, %	60.6	87.4	93.7	48.67	<0.001	4.50 (2.36, 8.61)	9.66 (4.34, 21.49)
Absent sputum conversion at 2nd month, %	52.0	95.8	88.2	80.79	<0.001	21.07 (8.06, 55.08)	6.90 (3.63, 13.10)

[a]: n for complete observation only; [b]: age as a five-year unit change; [c]: non-couple = single, widow, divorce, separation, or priest;

AE = accidental and emergency; GP = general practice; HIV = human immunodeficiency virus; IQR = inter-quartile range; MKK = Mueang Khon Kaen district; TB = tuberculosis; WHO = World Health Organization

Table 2
Group statistics and gold standard model with gold standard odds ratio of multiple multinomial logistic regession.

				Multiple multinomial logistic regression			
				Likelihood ratio test		Adjusted odds ratio (95% CI)	
	Treatment success (n=127)[a]	Transferred out (n=119)[a]	Clinical treatment failure (n=127) [a]	χ^2 (df=2)	p	Transferred out *vs* Treatment success	Clinical treatment failure *vs* Treatment success
"Absent contact" with TB clinic, %	46.5	76.5	85.8	24.60	<0.001	2.35 (1.13, 4.90)	6.32 (2.95, 13.52) [b]
Median age, year (interquartile range)	42.3 (29.7)	53.7 (28.5)	49.4 (33.8)	2.81	0.246	1.01 (0.99, 1.03) [c]	1.02 (1.00, 1.04) [c]
Male, %	58.3	63.0	70.9	8.67	0.013	1.95 (0.99, 3.87)	2.72 (1.38, 5.37)
Farmer or laborer, %	39.4	55.8	53.3	7.80	0.020	2.15 (1.10, 4.20)	2.47 (1.26, 4.82)
Residence outside MKK, %	66.9	96.7	74.8	32.12	<0.001	9.02 (2.86, 28.48)	0.73 (0.34, 1.54)
HIV+, %	11.0	13.4	23.6	3.37	0.186	0.41 (0.15, 1.14)	0.74 (0.28, 1.93)
Other concomitant diseases, %	42.5	42.9	56.7	4.23	0.121	1.02 (0.54, 1.93)	1.69 (0.90, 3.18)
Diagnosed by GP or AE, %	32.3	47.1	48.0	4.28	0.118	1.90 (0.98, 3.71)	1.83 (0.95, 3.50)
Non-WHO treatment regimen, %	60.6	87.4	93.7	44.83	<0.001	5.67 (2.51, 12.80)	14.55 (5.81, 36.46)
Absent sputum conversion at 2nd month, %	52.0	95.8	88.2	34.80	<0.001	14.15 (4.93, 40.60)	3.16 (1.42, 7.01)

[a]: n for complete observation only; [b]: gold standard odds ratio of exposure of interest; [c]: age as a five-year unit change; AE = accidental and emergency; GP = general practice; HIV = human immunodeficiency virus; IQR = inter-quartile range; MKK = Mueang Khon Kaen district; TB = tuberculosis; WHO = World Health Organization

ered significant.

The Ethical Review Committee of Khon Kaen University approved this study via document number HE450720.

RESULTS

Of 381 new smear-positive tuberculosis patients detected at KKMS during 1997-2001, there were 130, 120 and 131 patients who were TS, transferred out and CTF, respectively. The TS and CTF rates were 34.1% and 34.4%, respectively.

Table 1 reveals that there was 46.5% and 85.8% of patients who had "absent contact" with a TBC in the TS and CTF groups, respectively. There were ten extraneous variables that had p-values ≤0.20 from bivariate analysis using simple multinomial logistic regression. They were age, gender, occupation, place of residence, HIV status, other concomitant disease, admission status, place of diagnosis, treatment regimen, and sputum conversion status. All variables, except admission status, had p-values ≤0.20 when focusing on the comparison between CTF and TS. Nine extraneous variables were included in the initial model for multiple multinomial logistic regression. Ignoring the effect of other factors, the patients who had "absent contact" with a TBC were 6.98 times more likely to be CTF than TS (crude odds ratio = 6.98; 95% CI: 3.80, 12.83).

From stratified analysis, there were three interaction terms that were put into the initial model. These were "(TBC) x (gender)", "(TBC) x (drug adverse reaction)", and "(TBC) x (sputum conversion status)". All of them were removed from the model at the stage of interaction assessment, since none were statistically significant.

Table 2 shows the gold standard model with

Table 3
Group statistics and parsimonious final model of multiple multinomial logistic regession.

				Multiple multinomial logistic regression			
				Likelihood ratio test		Adjusted odds ratio (95% CI)	
	Treatment success (n=127)[a]	Transferred out (n=119)[a]	Clinical treatment failure (n=127) [a]	χ^2 (df=2)	p	Transferred out *vs* Treatment success	Clinical treatment failure *vs* Treatment success
"Absent contact" with TB clinic, %	46.5	76.5	85.8	27.99	<0.001	2.49 (1.31, 4.73)	5.95 (2.99, 11.84)
Non-WHO treatment regimen, %	60.6	87.4	93.7	40.47	<0.001	4.46 (2.17, 9.20)	10.76 (4.57, 25.31)
Absent sputum conversion at 2nd month, %	52.0	95.8	88.2	42.39	<0.001	14.26 (5.27, 38.58)	3.36 (1.61, 7.02)

[a]: n for complete observation only; TB = tuberculosis; WHO = World Health Organization

the gold standard odds ratio from multiple multinomial logistic regression. The model revealed that the patients who had "absent contact" with a TBC were 6.32 times more likely to be CTF than TS, after adjusting for the effect of transfering-out and other confounders (adjusted odds ratio = 6.32; 95% CI: 2.95, 13.52).

The final model in Table 3 shows that the adjusted odds ratio for "absent contact" with a TBC comparing CTF with TS was 5.95, which was 5.85% different from the gold standard odds ratio. Regarding our pre-defined criteria, they were essentially the same. All variables in the model were independently and highly significant ($p < 0.001$). The patients who had "absent contact" with a TBC were 5.95 times more likely to be CTF than TS, after adjusting for the effect of transfering-out and the effect of the treatment regimen and sputum conversion status (adjusted odds ratio = 5.95; 95% CI: 2.99 to 11.84). The other two independent risk factors for CTF in the model were treatment regimen and sputum conversion status.

Concerning post-estimation analysis, both the Hausman and Small-Hsiao test showed that the assumption of independence of irrelevant alternatives was not violated. Assessing the model fit using the Hosmer-Lemeshow and Pearson Goodness-of-Fit test demonstrated that the relevant equations fit the data. The Index plot and Cook's statistic revealed no influential or poorly fit subject in the final model.

DISCUSSION

The study shows that the patients who had "absent contact" with a TBC were 5.95 times more likely to be CTF than TS, after adjusting for transfering-out and the effect of the treatment regimen and sputum conversion status (adjusted odds ratio = 5.95; 95% CI: 2.99 to 11.84). The review shows that "absent contact" with a TBC was an independent risk factor for CTF. This should be considered by policy makers at KKMS since there was a high percentage of infectious TB patients who had "absent contact" with a TBC. The other two independent risk factors for CTF, a non-WHO treatment regimen and absent sputum conversion at second month, can also be remedied by systematic management through a TBC.

Lonnroth *et al* (2003) showed that systematic management of sputum-positive pulmonary TB patients was needed to achieve a high treatment success rate. The problem was not due to differences in patient characteristics or in provider knowledge. Werhane *et al* (1989) revealed that a tuberculosis clinic managed by nurse spe-

cialists provided much more effective treatment to TB patients than general clinics (86% versus 12% for complete treatment, respectively).

Many public and private health care providers did not use an evidence based approach to TB diagnosis and treatment (World Health Organization, 2006). There were many medical schools and large hospitals in Thailand that had low treatment success rates and independent management of infectious TB patients by several clinics or departments in hospitals (Tuberculosis Division, 1999; Srisaenpang, 2001). This strategy should be reconsidered. We recommended that all new smear-positive tuberculosis patients should be systematically managed through a TB clinic.

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