Title:

Risk factors for death among hospitalized tuberculosis patients in poor urban areas in Manila, the Philippines

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SUMMARY

OBJECTIVE: To determine the mortality rate and risk factors for in-hospital death among hospitalized HIV-negative tuberculosis (TB) patients in poor urban areas in the Philippines.

DESIGN: A cross-sectional study was conducted at a national infectious disease hospital in Manila City. The target population was all forms of HIV-negative TB patients aged ≥13 years who were admitted from October through December 2009. Demographic and clinical information was collected from medical charts, and the risk of in-hospital death was measured.

RESULTS: Among a total of 407 HIV-negative TB patients, four were excluded due to missing records, and 403 were included in the analysis. The majority were poor urban residents (90%), and 66% were males. Overall, 37.5% of hospitalized patients died in the hospital (n=151/403), and 30% of these patients died before the third day of hospitalization. The risk factor analysis demonstrated that complications of bacterial pneumonia had the greatest effect on in-hospital death (adjusted odds ratio [AOR]: 4.53; 95% confidence interval [CI]: 2.65 to 7.72), followed by anorexia (AOR: 3.01; 95% CI: 1.55 to 5.84), anemia (hemoglobin <10 g/dL, AOR: 2.35; 95% CI: 1.34 to 4.13), and older age (aged

≥50 years, AOR: 1.85; 95% CI: 1.08 to 3.17). The presence of hemoptysis (AOR: 0.44; 95% CI: 0.25 to 0.80) was associated with improved survival.

CONCLUSION: The mortality rate of hospitalized HIV-negative TB patients was extremely high in poor urban areas in the Philippines.

INTRODUCTION

The Philippines has the ninth highest rate of endemic tuberculosis (TB) in the world. The annual estimated incidence rate of newly diagnosed TB was 275 per 100,000 population, and the TB-related mortality rate was 33 per 100,000 population in 2010[1], while the prevalence of human immunodeficiency virus (HIV) infection among the adult population remains very low (<0.1% in 2009)[2]. As is the case in other TB-endemic countries, delays in seeking health care are common among Filipino TB patients. According to a nationwide survey, 43% of residents with TB symptoms took no action, 31.6% self-medicated, and only 25.4% consulted a health care provider[3]. Many TB patients thus remain untreated, and only those with serious disease are expected to be hospitalized, especially in poor urban areas such as Manila City.

In TB-endemic countries, the mortality rate of hospitalized TB patients is considerably high. Studies have shown that the mortality rate of hospitalized TB patients is 26.5% in South Africa and 16.1% in Brazil; in these populations, acquired immune-deficiency syndrome (AIDS), respiratory failure requiring mechanical ventilation, and malnutrition were associated with in-hospital death[4, 5]. However, these studies were conducted in African and South American

79 countries, and no data regarding the in-hospital TB mortality are available for
80 Southeast Asian countries, including the Philippines.
81 We therefore conducted this hospital-based study 1) to describe the
82 clinical characteristics of HIV-negative TB patients hospitalized at a national
83 infectious disease hospital in poor urban areas of Manila, the Philippines; 2) to
84 calculate the in-hospital mortality rate; and 3) to elucidate the factors associated
85 with death.
86

MATERIALS AND METHODS

Setting and study population

Metro Manila is the national capital region and comprises 16 cities, including Manila City. According to the United Nations Human Settlements Program, the population in the Philippines was 11 million in 2008, and 44% of Manila City residents lived in urban slum areas[6]. The San Lazaro Hospital (SLH) is a national infectious disease referral center for Metro Manila and neighboring provinces. The hospital has a 500-bed capacity and provides free medical care, particularly for poor inhabitants. According to the hospital admission database, 1,884 patients were hospitalized with a diagnosis of pulmonary TB (PTB) in 2009.

We conducted a retrospective hospital-based cross-sectional study in November 2010. Our target patients were adolescents and adults aged ≥13 years who were admitted to the SLH's TB ward with a diagnosis of PTB or extra-pulmonary TB (EPTB) from October 1st 2009 through December 31st 2009. Patients younger than 13 years old were excluded from the study because they were generally hospitalized in different wards. Patients with suspected immunodeficiency were routinely screened for HIV and excluded from the study.

Although cultures for *Mycobacterium tuberculosis* were not performed in the SLH, patients who failed two courses of the standard treatment regimen were considered as multidrug-resistant TB (MDR-TB) cases and usually referred to other institutions, and therefore MDR-TB cases were not likely included in our study. Eligible patients were identified from a hospital admission database using ICD-10 coding[7].

Case definitions

A patient was diagnosed with smear-positive PTB if s/he fulfilled at least one of the following criteria: 1) acid-fast bacilli (AFB) was positive for at least two sputum samples, 2) AFB was positive for one sputum sample and radiographic findings were consistent with active PTB, or 3) AFB was positive for one sputum sample and sputum culture was positive for MTB. A patient was diagnosed with smear-negative PTB if s/he fulfilled the following criteria: 1) AFB was negative for three sputum samples, 2) radiographic findings were consistent with active PTB, 3) antibiotic treatment was not effective, and 4) physicians or TB diagnosed committee (TBDC) decided to treat the patient as PTB. A patient was diagnosed with EPTB if smear or culture was positive for at least one clinical sample from

an extra-pulmonary site, or there was a clinical and/or histopathological evidence consistent with active EPTB[8]. We also included the patients who could not provide appropriate sputum samples but whose signs and clinical history were consistent with active TB. Patients with PTB plus EPTB were classified as PTB patients based on the WHO definition[1].

Data collection and analysis

Demographic and clinical information were collected from medical charts using a standardized data collection form. The data were subsequently entered into an electronic database programmed by EpiData Version 3.1 (the EpiData Association, Denmark). We measured the risk of death during the hospitalization as an outcome. Patient characteristics were summarized using descriptive statistics. To investigate the risk factors for in-hospital death, unadjusted and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were generated using logistic regression models. Variables were included in the multiple logistic regression model if their p values were less than 0.2 by using a backward stepwise selection method; body mass index (BMI) was excluded from the final model as the data was available only for a limited number of patients.

The statistically significant level was taken to be 5%. All statistical analyses were performed using STATA Version 10.0 (STATA Corp., USA).

This study was approved by the Institutional Review Board (IRB) of the SLH and the IRB of the Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.

RESULTS

Baseline characteristics

During the target period, a total of 422 patients were hospitalized with a diagnosis of TB. Of these patients, 19 (4.5%) were excluded because of missing medical records (N=4), non-TB diagnosis (N=1), HIV positivity (N=11), and suspected history of HIV (N=3). Therefore, 403 (95.5%) HIV-negative TB patients were included in our analysis. Among these patients, 35 were discharged against medical advice. We included these patients as surviving patients.

The demographic and clinical characteristics of the 403 included patients are shown in Table 1. The median age of the patients was 41 years (13 to 86 years), and more than 60% were male. The majority of our patients were poor urban residents; more than three-quarters were residents of the National Capital Region, and 88.6% were living below the national poverty line[9]. A total of 332 (82.4%) patients were diagnosed with isolated PTB, 50 (12.4%) patients were diagnosed with PTB plus EPTB (pleural, n=38; meningeal, n=7; hepatic, n=2; bone, n=1; pleural+hepatic+bone, n=1; lymphatic+hepatic+bone, n=1), and 21 (5.2%) patients were diagnosed with isolated EPTB (meningeal, n=19;

pleural, n=2). Half of the patients had a previous history of TB treatment. Although the data of BMI, past medical history, and social history were available only for a limited number of patients, a low BMI (median 16.8; range 8.5-32) and a high rate of comorbidities (10.7%) were observed in our patients.

Among all hospitalized TB patients, cough was the most common symptom, followed by dyspnea. The median duration of symptoms from onset to admission was 30 days (range: a few hours to four years), but the data was not available for six patients. 26.2% of our patients had experienced chronic symptoms for more than three months. A total of 183 (45.2%) patients submitted at least one sputum sample, and among them, 60 were AFB smear positive for two specimens. Most patients who failed to submit sputum did so due to the severity of their conditions, and 118 (29.3%) patients died before submitting sputum samples. Chest radiography findings were available only for 221 (54.8%) patients because many patients kept their chest X-ray films after discharge. A total of 50 (12.5%) patients had already received anti-TB treatment before coming to our hospital, but 28 of these patients were receiving inadequate regimens (ie. only one or two anti-TB drugs were prescribed) and their treatment was suspended after the hospitalization: 19 were prescribed from private

practitioners, and 9 were from health centers. Anti-TB treatment was initiated in 76 (18.9%) patients during their hospitalization at our institution, and thus a total of 98 patients (ie. 22 continued and 76 newly initiated) received anti-TB treatment before their discharge. 34.5% of TB patients had bacterial pneumonia at the time of admission or developed pneumonia after admission; amoxicillin, cephalosporins, and azithromycin were mainly used for treatment of bacterial pneumonia.

Risk factors for in-hospital mortality

Among all 403 patients evaluated, 151 died during hospitalization, resulting in an in-hospital mortality rate of 37.5% (Table 1). Of these patients, 101 (66.9%) died within the first week of hospitalization; 21 (13.9%) died on the day of admission, and another 24 (15.9%) died on the second day of hospitalization (Figure 1). The causes of death were recorded only in 29 patients, and among them, massive hemoptysis was the leading cause (n=11) followed by heart failure (n=4). The factors associated with in-hospital mortality are shown in Table 2. Univariate analysis showed that older age (patients aged $\geq$50 years), referrals, dyspnea, anorexia, absence of hemoptysis, neutrophilia (white blood cell count $\geq 12 \times$

10^9/L), anemia (hemoglobin <10 g/L), not receiving anti-TB treatment, and the presence of bacterial pneumonia were associated with higher mortality. Lower BMI was also likely to be associated with death, but the statistical evidence was weak due to the limited number of patients for whom BMI data were available. We excluded BMI from the multivariate analysis due to the deficiency of sample size. Multivariate analysis revealed that the presence of bacterial pneumonia was most strongly associated with in-hospital death. Absence of hemoptysis, anorexia, anemia, and older age also remained associated with higher rates of death. To control for the potential change in patients' characteristics throughout the duration of hospitalization, we stratified our patients into two groups: patients who stayed in the hospital for <7 days (N=137) and those stayed for $\geq$7 days (N=266). The magnitude of the effect of each risk factor was almost identical between these two groups (data not shown).

DISCUSSION

The in-hospital mortality rate among HIV-negative TB patients in poor urban areas in the Philippines was as high as 37.5%; this figure was substantially higher than the mortality among PTB patients at local health centers in Manila city (7.7% in 2009, according to the local health authority). The in-hospital mortality shown in our study was higher than those previously reported in other TB-endemic countries (4.9 to 26.5%)[4,5,10,11]. Several studies have reported higher mortality rates (25.9 to 67.8%)[12-15], but these studies included only patients requiring intensive care.

We demonstrated that 34.5% of HIV-negative TB patients had complications from bacterial pneumonia, and bacterial pneumonia co-infection substantially increased the risk of in-hospital TB death. Studies have shown that TB/pneumonia co-infection is not uncommon in TB-endemic countries[16-18]. Nyamande et al showed that TB co-infection increased the mortality rate of bacterial pneumonia[17]. Among the TB patients requiring intensive care, hospital-acquired pneumonia was associated with in-hospital death[12, 14]. These findings may indicate that severe PTB causes serious lung damage and/or reduces the effectiveness of the immune response, thus increasing the risk of

233 secondary bacterial infection[14]. However, our study lacked sufficient
234 microbiological/immunological data to provide a causal explanation for the
235 observed phenomenon. Some of community-acquired bacterial pneumonia
236 cases may have been misclassified as PTB in our cases. Furthermore, the data
237 on antimicrobial therapy for pneumonia were not recorded systematically.
238 Further investigations are warranted.

239 We found that anorexia and anemia were correlated with mortality. Many
240 of our patients had a low BMI. Studies have suggested that lower BMI, a lower
241 serum albumin concentration, and a lower hemoglobin level are important risk
242 factors for mortality among TB patients[19,20]. The high in-hospital mortality
243 observed in this study is likely at least partly explained by the poor nutritional
244 status of our study population. Older age was also associated with in-hospital TB
245 death. Many elderly individuals have comorbidities, and the presence of
246 comorbidities is known to be associated with a lower diagnostic yield for TB[10,21].
247 Although the available data on underlying conditions were limited, our findings
248 were compatible with previous reports. Unexpectedly, the presence of
249 hemoptysis was associated with improved survival. According to a
250 healthcare-seeking behavior survey conducted in the Philippines, residents with

hemoptysis were more likely to consult healthcare providers[3]. Together, these data suggest that a frightening symptom, such as hemoptysis, may drive patients to consult a doctor earlier than they would otherwise.

In our study, 25.1% of hospitalized patients died within a week of admission. Similar findings were reported in other countries with high TB endemicity. In South Africa, the in-hospital mortality was highest during the first week of hospitalization, and late presentation was associated with mortality[22]. In Serbia, 34% of hospitalized TB patients died within four days of admission due to the delay in diagnosis[23]. The delay in healthcare seeking determines the outcome of TB patients[24]. In the Philippines, only 25% of patients with TB symptoms consult a health care provider[3]. In the current study, a quarter of our patients were not hospitalized until three months or more after disease onset and we believe that the late visit to the hospital should be attributed to the high mortality. In our setting, we could not show the significant association between the duration from onset to admission and mortality. This may be due to recall bias; recalling exact point of chronic disease onset is difficult. Furthermore the associations with anolexia, anemia, low BMI indicate that the poor health state in the population should also be a determinant of the high TB mortality in the

Philippines. In addition, the quality of care offered by private practitioners is often questionable in TB-endemic countries[25-27]. A systematic review suggested that consulting a private practitioner is one risk factor associated with diagnostic delay[28]. In Metro Manila, 53% of TB patients initially consulted a private physician[29]. In fact, among 28 of our patients who had been receiving inadequate anti-TB treatment prior to admission, 19 (68%) had consulted private practitioners. Improvements in access to high-quality care are critical to the success of TB programs in slum settings, such as those studied here. We noted that almost half of our patients had a previous history of TB treatment. But the history of TB treatment was not associated with the mortality.

Even after hospitalization, the delay between admission and the initiation of anti-TB treatment—i.e., the in-hospital delay—remains problematic[30, 31]. In our setting, of the 252 patients who survived to discharge, 71% were discharged without anti-TB treatment. According to our hospital guideline, patients need to submit three sputum samples for AFB screening prior to initiating the treatment, but only a half of them completed the screening before discharge. In addition, it requires additional time for smear-negative PTB patients to have the treatment recommendation by the TBDC. Although their

287 treatments were intended to be initiated at the hospital outpatient department or
288 at community clinics, a high follow-up rate cannot be expected in our poor urban
289 setting. The delayed treatment of TB is a crucial problem not only with respect to
290 curing patients but also with respect to protecting the wider community from the
291 spread of *Mycobacterium tuberculosis*[32]. The recent national clinical guidelines
292 recommend that anti-TB treatment be initiated for any patient whose symptoms
293 or chest radiographs are highly suggestive of TB before final culture results are
294 received[33]. The initiation of anti-TB treatment during the hospitalization must be
295 considered for newly diagnosed TB patients in high endemic areas. The
296 introduction of early TB detection systems, such as Xpert MTB/RIF, may shorten
297 the in-hospital delay[34].

298 Our study has several limitations due to its retrospective nature. Some
299 potential risk factors for mortality, including comorbidities, social histories, and
300 contact histories, were not sufficiently recorded in the medical charts. Chest
301 radiographs were available only for 55% of our patients. The TB diagnosis was
302 largely based on clinical assessments, and only a limited number of cases were
303 confirmed microbiologically. Also many of EPTB cases may have been
304 undetected in our resource limited setting. Bacterial pneumonia was also

305 diagnosed clinically, and the timing of disease onset was not recorded. However,
306 all of our doctors are experienced infectious disease experts, and their clinical
307 diagnoses were expected to be sufficiently accurate[35]. We are now conducting a
308 prospective study to identify aetilogy of co-existing bacterial pneumonia.
309

CONCLUSION

The in-hospital mortality among HIV-negative TB patients was high in poor urban areas in Manila, the Philippines. Bacterial co-infection and poor nutritional status were strongly associated with TB-related death, reflecting these poor living conditions. The expansion of case detection and the early initiation of treatment are important strategies for reducing the in-hospital TB mortality rate in countered with high TB endemicity such as the Philippines. Early antibiotic therapy for bacterial co-infection may also improve outcomes of patients with severe TB; however, further investigations are warranted.

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Conflicts of interest

None declared.

Author Contributions

TS, SDM, EMD, EPS, KA, JBV, and MS were responsible for the study conception and design. TS, SDM, NRDS, and EPS acquired the data. TS, SDM, EPS, KA, JBV, and MS analyzed and interpreted the data. TS, EMD, EPS, KA,

and MS drafted the manuscript. All authors commented on and approved the final draft.

References

1. World Health Organization. Global tuberculosis control: WHO Report 2011. WHO/HTM/TB/2011.16.
2. The Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDSinfo. Available at: http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/ Accessed 24 Oct 2012.
3. Tupasi TE, Radhakrishna S, Co VM, et al. Bacillary disease and health seeking behavior among Filipinos with symptoms of tuberculosis: implications for control. Int J Tuberc Lung Dis 2000; 4: 1126-1132.
4. Alvarez GG, Thembela BL, Muller FJ, Clinch J, Singhal N, Cameron DW. Tuberculosis at Edendale Hospital in Pietermaritzburg, Kwazulu Natal, South Africa. Int J Tuberc Lung Dis 2004; 8: 1472-1478.
5. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin Pde T. Factors associated with mortality in hospitalized patients with newly diagnosed tuberculosis. Lung 2010; 188: 33-41.
6. United Nations Human Settlements Programme (UN-HABITAT) Regional Office for Asia and the Pacific. COUNTRY PROGRAMME DOCUMENT 2008-2009 PHILIPPINES. .
7. ICD-10 Version:2008. Available at: http://apps.who.int/classifications/icd10/browse/2008/en Accessed 13 Jan 2013.
8. Department of Health Republic of the Philippines. Manual of Procedures for the NATIONAL TUBERCULOSIS CONTROL PROGRAM. Philippines, 4th Edition, 2005. In: Case Holding. Department of Health Republic of the Philippines, December 2005
9. Department of Health Republic of the Philippines. Implementing Guidelines on Classification of Patients and on Availment of Medical Social Services in Government Hospital. Available at: http://portal1.doh.gov.ph/files/ao51A-01.pdf Accessed 19 Sep 2012.
10. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest 1998; 114: 1244-1252.
11. Greenaway C, Menzies D, Fanning A, Grewal R, Yuan L, FitzGerald JM. Delay in

370 diagnosis among hospitalized patients with active tuberculosis--predictors and
371 outcomes. Am J Respir Crit Care Med 2002; 165: 927-933.
372 12. Erbes R, Oettel K, Raffenberg M, Mauch H, Schmidt-Ioanas M, Lode H.
373 Characteristics and outcome of patients with active pulmonary tuberculosis
374 requiring intensive care. Eur Respir J 2006; 27: 1223-1228.
375 13. Ryu YJ, Koh WJ, Kang EH, et al. Prognostic factors in pulmonary tuberculosis
376 requiring mechanical ventilation for acute respiratory failure. Respirology 2007; 12:
377 406-411.
378 14. Lin SM, Wang TY, Liu WT, et al. Predictive factors for mortality among
379 non-HIV-infected patients with pulmonary tuberculosis and respiratory failure. Int
380 J Tuberc Lung Dis 2009; 13: 335-340.
381 15. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT. Mortality among
382 patients with tuberculosis requiring intensive care: a retrospective cohort study.
383 BMC Infect Dis 2010; 10: 54.
384 16. Lockman S, Hone N, Kenyon TA, et al. Etiology of pulmonary infections in
385 predominantly HIV-infected adults with suspected tuberculosis, Botswana. Int J
386 Tuberc Lung Dis 2003; 7: 714-723.
387 17. Nyamande K, Lalloo UG, John M. TB presenting as community-acquired pneumonia
388 in a setting of high TB incidence and high HIV prevalence. Int J Tuberc Lung Dis
389 2007; 11: 1308-1313.
390 18. Feng JY, Fang WF, Wu CL, et al. Concomitant pulmonary tuberculosis in
391 hospitalized healthcare-associated pneumonia in a tuberculosis endemic area: a
392 multi-center retrospective study. PLoS One 2012; 7: e36832.
393 19. Hanrahan CF, Golub JE, Mohapi L, et al. Body mass index and risk of tuberculosis
394 and death. AIDS 2010; 24: 1501-1508.
395 20. Kim HJ, Lee CH, Shin S, et al. The impact of nutritional deficit on mortality of
396 in-patients with pulmonary tuberculosis. Int J Tuberc Lung Dis 2010; 14: 79-85.
397 21. Schaaf HS, Collins A, Bekker A, Davies PD. Tuberculosis at extremes of age.
398 Respirology 2010; 15: 747-763.
399 22. Sacks LV, Pendle S. Factors related to in-hospital deaths in patients with
400 tuberculosis. Arch Intern Med 1998; 158: 1916-1922.
401 23. Zafran N, Heldal E, Pavlovic S, Vuckovic D, Boe J. Why do our patients die of active
402 tuberculosis in the era of effective therapy? Tuber Lung Dis 1994; 75: 329-333.
403 24. Pablos-Mendez A, Sterling TR, Frieden TR. The relationship between delayed or
404 incomplete treatment and all-cause mortality in patients with tuberculosis. JAMA
405 1996; 276: 1223-1228.

406 25. Pirkis JE, Speed BR, Yung AP, Dunt DR, MacIntyre CR, Plant AJ. Time to initiation
407 of anti-tuberculosis treatment. Tuber Lung Dis 1996; 77: 401-406.
408 26. Auer C, Lagahid JY, Tanner M, Weiss MG. Diagnosis and management of
409 tuberculosis by private practitioners in Manila, Philippines. Health Policy 2006; 77:
410 172-181.
411 27. Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC. International standards
412 for tuberculosis care. Lancet Infect Dis 2006; 6: 710-725.
413 28. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and
414 treatment of tuberculosis. BMC Public Health 2008; 8: 15.
415 29. Auer C, Sarol J, Jr., Tanner M, Weiss M. Health seeking and perceived causes of
416 tuberculosis among patients in Manila, Philippines. Trop Med Int Health 2000; 5:
417 648-656.
418 30. Lin CY, Lin WR, Chen TC, et al. Why is in-hospital diagnosis of pulmonary
419 tuberculosis delayed in southern Taiwan? J Formos Med Assoc 2010; 109: 269-277.
420 31. Whitehorn J, Ayles H, Godfrey-Faussett P. Extra-pulmonary and smear-negative
421 forms of tuberculosis are associated with treatment delay and hospitalisation. Int J
422 Tuberc Lung Dis 2010; 14: 741-744.
423 32. Squire SB, Belaye AK, Kashoti A, et al. 'Lost' smear-positive pulmonary tuberculosis
424 cases: where are they and why did we lose them? Int J Tuberc Lung Dis 2005; 9:
425 25-31.
426 33. Philippine Society for Microbiology and Infectious Disease. Clinical Practice
427 Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in
428 Adult Filippinos: 2006 UPDATE.
429 34. Parsons LM, Somoskovi A, Gutierrez C, et al. Laboratory diagnosis of tuberculosis in
430 resource-poor countries: challenges and opportunities. Clin Microbiol Rev 2011; 24:
431 314-350.
432 35. Chen TC, Lu PL, Lin WR, et al. Diagnosis and treatment of pulmonary tuberculosis
433 in hospitalized patients are affected by physician specialty and experience. Am J
434 Med Sci 2010; 340: 367-372.
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438 **Table 1** Characteristics of hospitalized TB patients at the San Lazaro Hospital, Manila, the Philippines.

	Total N	N (%) or Median (range)		Total N	N (%) or Median (range)
Age (years)	403	41 (13-86)	Duration of symptoms[Д]	397	
13 – 30 yrs		118 (29.3)	< 1 months		178 (44.8)
31 – 50 yrs		145 (36)	>=1 months - <3 months		115 (29.0)
> 50 yrs		140 (34.7)	>=3 months		104 (26.2)
Sex	403		Sputum status	403	
Male		266 (66)	Smear positive		
Female		137 (34)	>= 2 sputum		60 (14.9)
Body mass index (kg/m^2)	149	16.8 (8.5-32.0)	1 sputum		5 (1.2)
Address	403		Negative		118 (29.1)
Metro Manila		313 (77.7)	No sputum		220 (54.6)
Other region		90 (22.3)	WBC (x 10^9 /L)	358	10.7 (1.4-44.0)
Income level*	378		Hemoglobin (g/L)	358	11.4 (3.0-17.3)
Non-poor		21 (5.2)	CXR findings[Ф]	221	
Poor		357 (88.6)	Normal		10 (2.5)
			Abnormal		211 (52.4)
Referrals[†]	403		Minimal		22 (10)
Yes		128 (32)	Extensive		183 (82.8)
No		275 (68)	Form of TB	403	
Any comorbidities[‡]	149		Isolated PTB		332 (82.4)
Yes		43 (10.7)	PTB + Extra PTB		50 (12.4)
No		106 (26.3)	Extra PTB		21 (5.2)
Past TB treatment[¶]	403		Anti-TB drug	403	
Yes		205 (50.9)	Started		98 (24.3)
No		198 (49.1)	not started		305 (75.7)
Symptoms at admission	403		Complication	403	
Cough		276 (68.5)	bacterial pneumonia		139 (34.5)
Dyspnea		259 (64.3)	Pneumothorax		40 (9.9)
Fever		170 (44.7)	Length of hospital stay[§]	403	
Sputum production		178 (44.2)	<= 7 days		175 (43.4)
Hemoptysis		134 (33.3)	> 7days		228 (56.6)
Anorexia		85 (21.1)	Status at discharge	403	
Weight loss		73 (18.1)	Alive		252 (62.5)

Body malaise	68 (16.9)	Death	151 (37.5)

TB = tuberculosis; SD = standard deviation; BMI = Body mass index; mo = month; WBC = White blood cell count; CXR = Chest X ray; PTB = pulmonary tuberculosis.

The number of missing data for BMI, income level, comorbidities, duration of symptoms, WBC count, hemoglobin, and CXR findings were 254, 35, 254, 6, 45, 45, and 182, respectively.

* Income level was classified according to the per capita poverty threshold (PCPT) defined by the government[9]. PCPT indicated the annual per capita income required to satisfy essential nutritional requirements (2,000 calories) and other basic needs. The annual income of non-poor people was above the PCPT and that of poor people was below the PCPT.

† Cases referred from other hospitals, health centers, or private clinics.

‡ Past medical history included asthma, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, heart diseases, and renal diseases.

¶ A history of past TB treatment regardless of treatment completion status.

Д median; 30 days, range; few hours to 4 years

Ф The terminology of CXR findings is according to the national TB guideline[8].

§ median; 9 days, range; few hours to 241 days

456 **Table 2** Univariate and multivariate analysis of risk factors for in-hospital TB mortality.

	Discharged N (%)	Deceased N (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Age (years)				
>= 50	77 (51.7)	72 (48.3)	2.07 (1.37-3.14)	1.85 (1.08-3.17)
< 50	175 (68.9)	79 (31.1)	Ref.	Ref.
Sex				
Male	164 (61.6)	102 (38.4)	1.11 (0.73-1.71)	0.77 (0.43-1.37)
Female	88 (64.2)	49 (35.8)	Ref.	Ref.
Body mass index (kg/m^2)				
< 17	50 (64.9)	27 (35.1)	1.89 (0.91-3.91)	
>= 17	56 (77.8)	16 (22.2)	Ref.	
Place of residence				
Other region	59 (65.6)	31 (34.4)	0.85 (0.52-1.38)	
Metro Manila	193 (61.7)	120 (38.3)	Ref.	
Income level				
Poor	228 (63.9)	129 (36.1)	3.4 (0.98-11.7)	1.17 (0.62-2.22)
Non-poor	18 (85.7)	3 (14.3)	Ref.	Ref.
Referrals				
No	163 (59.3)	112 (40.7)	1.57 (1.00-2.45)	
Yes	89 (69.5)	39 (30.5)	Ref.	
Any comorbidities				
Yes	24 (55.8)	19 (44.2)	1.26 (0.66-2.42)	
No	72 (67.9)	34 (32.1)	Ref.	
Past TB treatment				
Yes	124 (60.5)	81 (39.5)	1.2 (0.80-1.79)	
No	128 (64.6)	70 (35.4)	Ref.	
Symptom at admission				
Cough				
Yes	175 (63.4)	101 (36.6)	0.89 (0.58-1.37)	
No	77 (60.6)	50 (39.4)	Ref.	
Dyspnea				
Yes	145 (56.0)	114 (44.0)	2.27 (1.45-3.55)	
No	107 (74.3)	37 (25.7)	Ref.	
Fever				

Yes	104 (61.2)	66 (38.8)	0.94 (0.63-1.41)	
No	138 (61.9)	85 (38.1)	Ref.	
Sputum production				
Yes	116 (65.2)	62 (34.8)	0.82 (0.54-1.23)	
No	136 (60.4)	89 (39.6)	Ref.	
Hemoptysis				
Yes	103 (76.9)	31 (23.1)	0.37 (0.23-0.60)	0.44 (0.25-0.80)
No	149 (55.4)	120 (44.6)	Ref.	Ref.
Anorexia				
Yes	36 (42.4)	49 (57.7)	2.88 (1.76-4.71)	3.01 (1.55-5.84)
No	216 (67.9)	102 (32.1)	Ref.	Ref.
Weight loss				
Yes	45 (61.6)	28 (38.4)	1.05 (0.62-1.76)	0.57 (0.27-1.19)
No	107 (46.5)	123 (53.5)	Ref.	Ref.
Duration of symptoms				
>= 3 months	62 (60.0)	42 (40.0)	1.20 (0.76-1.89)	
< 3 months	187 (63.8)	106 (36.2)	Ref.	
WBC (x 10^9 /L)				
>= 12	84 (60.0)	56 (40.0)	1.64 (1.05-2.57)	
< 12	155 (71.1)	63 (28.9)	Ref.	
Hemoglobin (g/L)				
< 10	65 (56.0)	51 (44.0)	2.01 (1.27-3.19)	2.35 (1.34-4.13)
>= 10	174 (71.9)	68 (28.1)	Ref.	Ref.
CXR findings				
Abnormal	163 (77.3)	48 (22.7)		
Minimal				
Yes	20 (91.0)	2 (9.0)	0.30 (0.07-1.32)	
No	149 (74.9)	50 (25.1)	Ref.	
Extensive				
Yes	138 (75.4)	45 (24.6)	1.44 (0.60-3.50)	
No	31 (81.6)	7 (18.4)	Ref.	
Form of TB				
Extra PTB	15 (71.4)	6 (18.6)	0.61 (0.23-1.62)	
PTB + Extra PTB	36 (72.0)	14 (28.0)	0.60 (0.31-1.15)	
Isolated PTB	201 (60.5)	131 (39.5)	Ref.	
Anti-TB drug				

not started	180 (59.0)	125 (41.0)	1.92 (1.16-3.18)	
Started	72 (74.5)	26 (26.5)	Ref.	
Bacterial pneumonia				
Yes	58 (41.7)	81 (58.3)	3.87 (2.51-5.97)	4.53 (2.65-7.72)
No	194 (73.5)	70 (26.5)	Ref.	Ref.

457

458 *Variables were included in the multiple logistic regression model if their p values were less than 0.2 by

459 using a backward stepwise selection method; BMI was excluded from the final model as the data was

460 available only for a limited number of patients. *Definition of abbreviations:* SD = standard deviation, CI =

461 Confidence interval, TB = tuberculosis, WBC = White blood cell count, PTB = pulmonary tuberculosis

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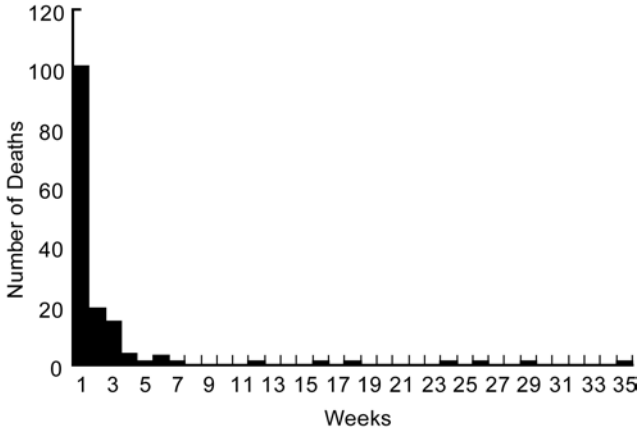

464

465 **Figure 1** Number of in-hospital TB deaths by week after admission to the San Lazaro Hospital,

466 Manila, the Philippines