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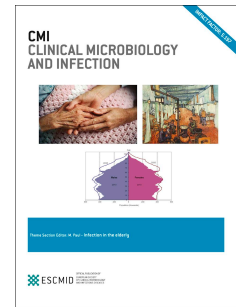
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Predictors for treatment outcomes among patients with drug-susceptible tuberculosis in the Netherlands: a retrospective cohort study

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1 **Predictors for treatment outcomes among patients with drug-susceptible tuberculosis**  
2 **in the Netherlands: a retrospective cohort study**

3  
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66 **ABSTRACT**

67 **Objectives:** We evaluated treatment outcomes and predictors for poor treatment outcomes  
68 for tuberculosis (TB) among native- and foreign-born patients with drug-susceptible TB  
69 (DSTB) in the Netherlands.

70 **Methods:** This retrospective cohort study included adult patients with DSTB treated from  
71 2005 to 2015 from a nationwide exhaustive registry. Predictors for unsuccessful treatment  
72 outcomes (default and failure) and TB-associated mortality were analysed using multivariate  
73 logistic regression.

74 **Results:** Among 5,674 identified cases, the cumulative incidence of unsuccessful treatment  
75 and mortality were 2.6% (n/N = 146/5,674) and 2.0% (112/5,674), respectively. Although  
76 most patients were foreign-born (71%; 4,042/5,674), no significant differences in these  
77 outcomes were observed between native- and foreign-born patients ( $p > 0.05$ ). Significant  
78 predictors for unsuccessful treatment were age of 18–24 years [odds ratio (OR), 2.04; 95%  
79 confidence interval (CI): 1.34–3.10], homelessness (OR, 2.56; 95% CI: 1.16–5.63), prisoner  
80 status (OR, 5.39; 95% CI: 2.90–10.05) and diabetes (OR, 2.02; 95% CI: 1.03–3.97).  
81 Furthermore, predictors for mortality were age of 74–84 (OR, 5.58; 95% CI: 3.10–10.03) or  
82  $\geq 85$  years (OR, 9.35, 95% CI: 4.31–20.30), combined pulmonary and extra-pulmonary TB  
83 (OR, 4.97; 95% CI: 1.42–17.41), central nervous system (OR, 120, 95% CI: 34.43–418.54)  
84 or miliary TB (OR, 10.73, 95% CI: 2.50–46.02), drug addiction (OR, 3.56; 95% CI: 1.34–9.47)  
85 and renal insufficiency/dialysis (OR, 3.23; 95% CI: 1.17–8.96).

86 **Conclusions:** Native- and foreign-born patients exhibited similar TB treatment outcomes. To  
87 further reduce disease transmission and inhibit drug resistance, special attention should be  
88 given to high-risk patients.

89

90 **Keywords:** Risk factors, Treatment outcome, Tuberculosis, The Netherlands, Epidemiology.

## 91 Introduction

92 Although tuberculosis (TB) is a global health problem [1], the associated burden in Europe  
93 has been mainly attributed to the travel and migration of people from high- to low-TB burden  
94 countries [2–4]. Several groups, including immigrants, asylum seekers, prisoners and  
95 homeless individuals, have been identified as high-risk groups [4,5]. Hence, adequate  
96 treatment management is required, especially for high-risk groups.

97 The Netherlands has a low TB incidence, with an estimated incidence of 5.9/100,000  
98 population in 2016 [5]. According to the Netherlands Tuberculosis Registry (NTR), drug-  
99 susceptible TB (DSTB) is the most common form of TB in the Netherlands. From 2005 to  
100 2015, 72% of cases ( $n/N= 7,416/10,303$ ) were identified as using standard treatment for  
101 DSTB. A previous study from the Netherlands (1993–1997) identified a higher probability of  
102 treatment default among asylum seekers, immigrants and illegal immigrants [6]. However,  
103 updated data are needed to determine whether being in a risk group or other factors  
104 contribute to poor outcomes of TB treatment and to evaluate the success of current  
105 treatment programmes in the Netherlands. We therefore aimed to evaluate treatment  
106 outcomes and predictors for poor treatment outcomes for tuberculosis (TB) among native-  
107 and foreign-born patients with drug-susceptible TB (DSTB) in the Netherlands.

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## 119 **Methods**

### 120 *Study design and setting*

121 This retrospective cohort study included patients treated for DSTB between 1 January 2005  
122 and 31 December 2015. Anonymised data were obtained from the NTR database on 23  
123 January 2017 following approval from the NTR committee. The NTR is an exhaustive  
124 national database managed by the Dutch National Institute for Public Health and the  
125 Environment (RIVM). Real-time surveillance data are routinely collected by RIVM in close  
126 collaboration with the TB control department of the Municipal Public Health Services (MPHS)  
127 and Royal Netherlands Tuberculosis Association/ KNCV TB. MPHS are legally required to  
128 record and register all patients with TB in the Netherlands, including those treated in  
129 hospitals. NTR data collection occurs throughout the TB diagnostic and treatment period,  
130 and the information is entered by the physician or nurse into an electronic report via the  
131 Online Registration System for Infectious Diseases in Infectious Diseases Surveillance  
132 Information System (OSIRIS) after the diagnosis is made. KNCV TB and MPHS check the  
133 registrations for completeness and consistency through an interactive process. MPHS  
134 receives reminders when records remain incomplete. The online system enables MPHS to  
135 correct and add information to patient records.

136

### 137 *Study subjects*

138 We included patients with TB aged  $\geq 18$  years who were registered in the NTR database and  
139 classified as being infected with *Mycobacterium tuberculosis* strain that was considered fully  
140 sensitive to first-line anti-TB drugs and treated during the study period. From this cohort of  
141 eligible patients, those with an unknown treatment outcome, i.e. no treatment initiated,  
142 treatment ongoing and treatment continued elsewhere with unknown results during a 1-year  
143 period, were excluded.

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147 *Potential predictors and definitions*

148 Potential predictors for a poor outcome of TB treatment were identified at baseline (before or  
149 during diagnosis) to predict the incidence of the study outcome. We selected a set of  
150 potential predictors based on previously published articles (see **Supplementary 1**), input  
151 from TB practitioners and information from the NTR database. These potential predictors  
152 were classified into five categories: (1) socio-demographic characteristics (age, sex, birth  
153 country, domicile area, insurance coverage for TB), (2) current TB diagnosis (pulmonary TB  
154 type, TB location, place of diagnosis, treatment delay), (3) history of TB disease and  
155 treatment [previously diagnosed TB, treated latent TB infection (LTBI), Bacillus Calmette–  
156 Guérin (BCG) vaccination status] (4) risk groups (those in contact with patients with TB,  
157 immigrants, asylum seekers, illegal immigrants, homeless individuals, healthcare workers,  
158 travellers from/in endemic area, prisoners, alcohol and drug addicts) and (5) high-risk  
159 comorbidities [diabetes, human immunodeficiency virus (HIV), malignancy, renal  
160 insufficiency/dialysis, organ transplantation].

161

162 *Primary outcomes*

163 We retrospectively followed patients from the beginning to the end of DSTB treatment for one  
164 episode of TB during a 1-year period. According to the WHO criteria [7], we categorised the  
165 study outcomes into unsuccessful treatment and TB-associated mortality. Unsuccessful  
166 treatment was defined as a combination of defaulted and failed treatment. Treatment default  
167 cases met one of the following four conditions: interruption of TB treatment for  $\geq 2$   
168 consecutive months, incomplete treatment for 6 months within a 9-month treatment period,  
169 incomplete treatment for 9 months within a 12-month treatment period and completion of  
170  $< 80\%$  of the treatment. Failed treatment was defined as a positive sputum smear or culture  
171 at 5 months or more after treatment initiation. For extra-pulmonary TB, treatment failure was  
172 defined by a physician according to a national guideline [8]. All treatment outcomes were  
173 determined by a physician in daily clinical practice. The operational definitions of these



174 variables followed those in the manual OSIRIS guideline published by RIVM [9]  
175 **(Supplementary Table S1).**

176

### 177 *Statistical analysis*

178 Distributions of subjects' characteristics and the cumulative incidences were examined using  
179 descriptive statistics. The cumulative incidence of the study outcomes were calculated by  
180 dividing incidence of the outcome with the number of DSTB cases during the observation  
181 period. We eliminated potential predictors if >10% of the data were missing. We used the chi-  
182 square test or Fisher's exact test (when expected cell size was <5) for univariate analyses of  
183 categorical covariates. Variables with a p-value of <0.25 in the univariate analysis were  
184 considered for inclusion in the multivariate analysis. If the number of variables exceeded the  
185 assumption of 10 events per variable examined, we considered a stricter univariate p-value  
186 (<0.15) for inclusion in the multivariate analysis [10]. To increase the statistical power and  
187 validity, we minimised the degree of freedom in the predictor model by combining predictors  
188 that measured a similar concept and had similar estimated risks in the univariate analysis  
189 [10]. Variables for which there were no incidences of the study outcome in the indicator  
190 group were not included in the multivariate analysis. A backward step elimination based on a  
191 p-value of >0.05 was used for the multivariate analysis. We used complete case analysis that  
192 excluded patients with missing values [10]. Odds ratios (ORs) with 95% confidence intervals  
193 (CIs) were calculated to quantify the level of association between variables and outcomes.  
194 The calibration of the multivariate analysis model was assessed using the Hosmer–  
195 Lemeshow test, while discrimination was estimated using a receiver operating characteristic  
196 curve with a 95% CI. We used Statistical Package for the Social Science, version 23 (SPSS;  
197 IBM Corp., NY, USA) for Windows™ in all statistical analyses; a final p-value of <0.05 was  
198 considered significant in the multivariate analysis. We followed the STROBE guidelines for  
199 reporting this study [11].

200

201 **Result**202 *Baseline characteristics of study subjects*

203 Of the 10,303 adult cases with TB registered during the study period, we identified 5,674  
204 cases with DSTB who fulfilled the study criteria (**Figure 1**). Most patients with DSTB were  
205 foreign-born (71%, n/N = 4,042/5,674; **Table 1**). As described in **Figure 1**, 192 patients with  
206 DSTB were lost to observation and had missing information about treatment outcomes.  
207 Missing information about TB treatment outcomes was significantly more frequent ( $p < 0.05$ )  
208 among males, foreign-born patients, prisoners, those with pulmonary TB, those with TB  
209 diagnosis from outside the Netherlands, immigrants, illegal immigrants and those with a  
210 history of travel from/to an endemic area >3 months earlier (**Supplementary Table S2**).

211

212 *Incidence of DSTB*

213 We observed a significant declining trend in the number of DSTB cases within the study  
214 period ( $p < 0.05$ ), with cumulative incidences of unsuccessful TB treatment and TB-  
215 associated mortality as 2.6% (146/5,674) and 2.0% (112/5,674), respectively. The highest  
216 annual cumulative incidence for both these outcomes was identified in 2011 (**Fig. 2**).

217

218 *Predictors for outcomes*

219 We combined asylum seekers and immigrants as one covariate in the analysis because  
220 similar residential status outside the Netherlands was thought to yield relatively similar  
221 statistical associations in the univariate analysis. In the univariate analysis, immigrants and  
222 asylum seekers had ORs (95% CI) of 0.90 (0.48–1.67) and 1.57 (0.97–2.54) for unsuccessful  
223 treatment outcome, while for mortality outcome had ORs (95% CI) of 0.19 (0.05–0.80) and  
224 0.09 (0.12–0.62), respectively.

225 In the univariate analysis, sex, age, homelessness and prisoner status were  
226 significantly associated ( $p < 0.05$ ) with unsuccessful treatment. Furthermore, multivariate  
227 analyses revealed a final prediction model comprising age of 18–24 years (OR, 2.04; 95%  
228 CI: 1.34–3.10), homelessness (OR, 2.56; 95% CI: 1.16–5.63), prisoner status (OR, 5.39;

229 95% CI: 2.90–10.05) and diabetes (OR, 2.02; 95% CI: 1.03–3.97) as significant predictors for  
230 unsuccessful treatment (**Table 2**).

231         Regarding mortality, age; pulmonary diagnostic type; initial TB location, such as lung,  
232 CNS and miliary TB; previous TB diagnosis; non-immigrant status; non-asylum seeker;  
233 native-born status and comorbidities, such as diabetes, malignancy, renal  
234 insufficiency/dialysis and organ transplantation, were significantly associated with death in  
235 the univariate analysis ( $p < 0.05$ ). Finally, we identified age of 75–84 (OR, 5.58; 95% CI:  
236 3.10–10.03) or  $\geq 85$  years (OR, 9.35; 95% CI: 4.31–20.30), combined pulmonary and extra-  
237 pulmonary TB (OR, 4.97; 95% CI: 1.42–17.41), central nervous system (OR, 120; 95% CI:  
238 34.43–418.54) or miliary TB (OR, 10.73; 95% CI: 2.50–46.02), drug addiction (OR, 3.56;  
239 95% CI: 1.34–9.47), renal insufficiency/dialysis (OR, 3.23; 95% CI: 1.17–8.96) and immigrant  
240 or asylum seeker status (OR, 0.11; 95% CI :0.01–0.84) as significant predictors for mortality  
241 (**Table 3**).

**242 Discussion**

243 Although most cases in our study involved foreign-born patients, no significant differences in  
244 treatment outcomes were observed between native- and foreign-born patients. Immigrants  
245 and asylum seekers had a lower risk of death than other patients and no significant  
246 difference in the risk for unsuccessful TB treatment. Overall, approximately 5 in 100 treated  
247 DSTB cases had a poor TB treatment outcome, of which 2.6% (146/5,674) were attributed to  
248 unsuccessful treatment and 2.0% (112/5,674) to TB-associated mortality. Predictors for  
249 unsuccessful treatment included age of 18–24 years, homelessness, prisoner status and  
250 diabetes. Furthermore, age of  $\geq 75$  years, drug addiction, combined pulmonary and extra-  
251 pulmonary TB and several comorbidities [renal insufficiency, central nervous system (CNS)  
252 and miliary TB] were predictors for TB-associated mortality. Moreover, male sex, foreign-  
253 born patients, immigrants, illegal immigrants, travellers from/in endemic areas for  $>3$  months,  
254 those diagnosed with TB from outside of the Netherlands, those with pulmonary TB and  
255 prisoners were more likely to be lost to treatment follow-up which indicates potential high risk  
256 of poor outcomes.

257 Diabetes was identified as a risk factor for unsuccessful TB treatment in this study.  
258 Previous studies have demonstrated that the correlation of diabetes with TB treatment failure  
259 [12] could be attributed to altered drug absorption [13] and immune system as well as drug  
260 interaction [14]. We further identified renal insufficiency/dialysis as a risk factor for TB-  
261 associated mortality. In patients undergoing dialysis, altered immune response associated  
262 with uraemia and dialysis exacerbation have been identified as predisposing factors for  
263 active TB development [15]. Patients with end-stage renal disease are more susceptible to  
264 TB [16]. Furthermore, drug-induced hepatitis has been identified more frequently in patients  
265 with TB and chronic renal failure than in those with TB but without chronic renal failure that  
266 increase the risk of TB-associated mortality [17].

267 Our finding of age being a relevant predictor was supported by a retrospective  
268 population-based pulmonary TB study in a South African province, in which younger patients

269 (age <25 years) more likely defaulted treatment [18]. Moreover, a multi-centre prospective  
270 cohort study in Spain reported that elderly people were more likely to die from TB [19].

271 A previous Dutch study (1993–1997) showed an association between the risk of  
272 treatment default and being in the high-risk group (asylum seekers, immigrants, illegal  
273 immigrants, homeless individuals, prisoners and eastern European nationals) [6]. However,  
274 the present study did not show that immigrants and asylum seekers as a high-risk group in  
275 terms of outcomes (unsuccessful treatment and TB-associated mortality). It seems that  
276 asylum seekers and immigrants received a successful treatment during the study period.

277 According to the national guideline, immigrants and asylum seekers comprise a high-  
278 risk priority group for TB screening and monitoring [20]. People from TB-endemic countries  
279 who plan to reside in the Netherlands for >3 months are required to undergo regular chest X-  
280 ray for 2 years. TB diagnosis leads to the administration of regular treatment and monitoring,  
281 together with treatment support from a nurse at Municipal Public Health Services. To ensure  
282 TB treatment compliance, municipal health centres work closely with medical service  
283 providers to asylum seekers and prisoners as well as with social workers from institutions for  
284 homeless care. Total TB control expenditures are covered by health insurance and funding  
285 from municipal authorities and the government [21]. For uninsured patients, the treatment  
286 cost is covered by municipalities via the public health act or budgeted financial support for  
287 illegal immigrants [22]. Two modern TB hospitals have been established for the long-term  
288 admission and specialised treatment of clinically complex or socially problematic TB cases to  
289 support successful treatment [23]. TB management is standardised according to a national  
290 TB guideline [8] and framework of the National Tuberculosis Control and Plan [21].

291 We identified homeless individuals and prisoners as being at a risk of unsuccessful  
292 TB treatment and drug addicts as a dominant risk group for TB-associated mortality. These  
293 vulnerable and hard-to-reach patients have both individual problems and challenges related  
294 to healthcare facility access. Specifically, individuals in these groups lack awareness and  
295 knowledge of TB and experience stigma, unstable accommodation and challenges in terms  
296 of transportation, costs and treatment duration [24]. Furthermore, drug users are frequently

297 homeless individuals, prisoners or HIV-positive [25], all of which further increase the risk of  
298 poor TB treatment outcome. Therefore, hard-to-reach patients should be admitted into a  
299 modern TB hospital to intensify treatment and monitoring and enable successful outcomes.

300 Our results were inconsistent with those of several other local studies regarding the  
301 determinants for poor TB treatment outcomes in Pakistan [26], China [27], South Korea [28],  
302 and Germany [29]. For instance, a study in Hamburg identified alcohol dependence as a  
303 determinant for disease persistence and treatment interruption. These inter-study differences  
304 can be explained by differences in risk factors across settings due to differences in  
305 healthcare systems, government support and patients' social, clinical and behavioural  
306 characteristics. Previous analyses also included subjects with drug-resistant TB, a specific  
307 high-risk group that requires longer and other treatment, and more study on their prognosis is  
308 needed.

309 Several potential limitations need to be acknowledged. First, because we used data  
310 from an administrative database, our dataset relied on reports from clinicians without any  
311 direct observations by current investigators, which may have led to inaccuracies. Second,  
312 several prominent predictors which may have further increased the discriminative value of  
313 multivariate models, such as HIV, treatment delay duration, BCG vaccination history,  
314 insurance coverage, education level, income and patient beliefs, could not be analysed due  
315 to unavailability of data for a large number of patients. Third, a low mortality rate in this study  
316 led to low precision of the associations between mortality outcome and some predictors,  
317 such as age and initial TB location (CNS and miliary TB). However, we believe that the  
318 systematic approach for data collection supported by information technology, national  
319 guideline, control system for data collection and an integrated referral system for patients  
320 with TB in the Netherlands led to a minimal bias in this study. Importantly, expanding the  
321 national database coverage to include patients throughout the Netherlands will improve the  
322 applicability of our results to the Dutch DSTB population.

323 In conclusion, although most DSTB cases included foreign-born patients, these  
324 patients achieved similar TB treatment success compared with native-born patients. We

325 observed a relatively low incidence of unsuccessful TB treatment and TB-associated  
326 mortality among DSTB cases in the Netherlands. However, to reduce further disease  
327 transmission and inhibit drug resistance, the potential for unsuccessful treatment should be  
328 considered among patients with DSTB aged 18–24 years and those who are homeless,  
329 prisoners or diabetic. Furthermore, patients aged  $\geq 75$  years, drug addicts, those diagnosed  
330 with CNS TB, miliary TB, renal insufficiency comorbidity, combined pulmonary and extra-  
331 pulmonary TB should be carefully monitored to prevent premature mortality. Further study is  
332 needed to investigate the quality of TB management, barriers and effective interventions for  
333 improved treatment in high-risk groups.

334

### 335 **Transparency declaration**

### 336 **Conflict of Interest**

337 All authors report no conflicts of interest relevant to this article.

338

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347

### 348 **Contributions**

349 All the authors designed the study. ISP, EH and JWA analysed the data. ISP wrote the first  
350 draft of the article. All the authors revised the article and approved the final version.

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465 **FIGURES AND TABLES**

466

467 **Figure 1.** Flow diagram of the included subjects. *M. tb*, *Mycobacterium tuberculosis*; H,  
468 isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; MDR, multi-drug-resistant; XDR,  
469 extensively drug-resistant; DSTB, drug-susceptible tuberculosis; DRTB, drug-resistant  
470 tuberculosis.

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473 **Figure 2.** Annual cumulative incidence for TB treatment outcomes during 2005–2015. DSTB,  
474 drug-susceptible tuberculosis; TB, tuberculosis

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489 **Table 1.** Characteristics of subjects (N = 5,674)

No	Characteristics	Frequency (%)
<b>1</b>	<b>Socio-demographic</b>	
	Male	3,426 (60.4)
	Age (years):	
	18–24	867 (15.3)
	25–74	4,246 (74.8)
	75–84	422 (7.2)
	≥85	139 (2.4)
	Country of birth*:	
	The Netherlands	1,617 (28.5)
	Somalia	741 (13.1)
	Maroco	539 (9.5)
	Indonesia	275 (4.8)
	Suriname	274 (4.8)
	Turkey	187 (3.3)
	Others	2,041 (36)
	Urban domicile <sup>†</sup>	1,997 (35.2)
	Insurance coverage for TB* <sup>§</sup>	57 (10.3)
<b>2</b>	<b>Current TB diagnosis</b>	
	Pulmonary diagnosis	
	ETB	1,890 (33.3)
	PTB	3,012 (53.1)
	ETB + PTB	772 (13.6)
	Initial TB location	
	Lungs	3,505 (61.8)
	Central nervous system	70 (1.2)
	Miliary	125 (2.2)
	Others	1,974 (34.8)
	TB diagnosis outside of the Netherlands	50 (0.9)
	Treatment delay >4 weeks*	1,053 (18.5)
<b>3</b>	<b>History of TB disease &amp; treatment</b>	
	Previously diagnosed TB*	358 (6.3)
	Previously treated LTBI*	184 (3.2)
	BCG vaccination*	1,555 (27.4)
<b>4</b>	<b>TB risk group</b>	
	TB contact	375 (6.6)
	Immigrant	471 (8.3)
	Asylum seeker	527 (9.3)

	Illegal immigrant	201 (3.5)
	Homeless individuals	132 (2.3)
	Health care workers	46 (0.8)
	Travelers from/in endemic area >3 month	130 (2.3)
	Prisoners	143 (2.5)
	Alcohol addicts	111 (2.0)
	Drug addicts	152 (2.7)
<b>5</b>	<b>Comorbidities</b>	
	Diabetes	268 (4.7)
	HIV positive	229 (4.0)
	Malignancy	135 (2.4)
	Renal insufficiency/ dialysis	91 (1.6)
	Organ transplantation	22 (0.4)
<b>6</b>	<b>Outcomes</b>	
	Cure or completed treatment	5,190 (91.5)
	Defaulted treatment	144 (2.5)
	Failed treatment	2 (0.0)
	Death due to TB	112 (2.0)
	Death due to non-TB	226 (4.0)

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491 *Notes:* \*missing data : Country of birth 15 (0.3%), Previously diagnosed TB 437 (7.7%), Previously  
 492 treated LTBI 466 (8.2%), BCG vaccination 2,812 (49.6%), HIV positive 3,329 (58.7%), treatment delay  
 493 4,056 (71.5), insurance coverage for TB 5,062 (89.2%); <sup>§</sup>the information was documented from 2014;  
 494 <sup>†</sup>Urban domicile : Amsterdam, Rotterdam, the Hague and Utrecht; TB, tuberculosis; ETB, extra-  
 495 pulmonary tuberculosis; PTB, pulmonary tuberculosis; LTBI, latent tuberculosis infection; BCG,  
 496 Bacillus Calmette–Guérin; HIV, human immunodeficiency virus.

**Table 2.** Predictors for unsuccessful tuberculosis treatment outcome (N = 5,674)

No	Predictors	Unsuccessful treatment		Univariate analysis		Multivariate analysis*	
		No (n = 5,528; %)	Yes (n= 146; %)	OR (95%CI)	p-value	aOR (95%CI)	p-value
<b>1</b>	<b>Socio-demographic characteristics</b>						
	Male	3325 (60.1)	101 (69.2)	1.35 (1.04-1.76)	0.025	1.35 (0.91-2.01)	0.13
	Age (years)				0.000		0.004
	18–24	834 (15.1)	33 (22.6)	1.66 (1.11-2.48)		2.04 (1.34-3.10)	
	25–74	4147 (75)	99 (67.8)	Ref.		Ref.	
	75–84	415 (7.5)	7 (4.8)	0.71 (0.33-1.53)		0.83 (0.36-1.93)	
	≥85	132 (2.4)	7 (4.8)	2.22 (1.01-4.87)		2.24 (0.89-5.67)	
	Born in the Netherlands**	1579 (28.6)	38 (26.2)	0.89 (0.61-1.29)	0.52	Not included	-
	Urban domicile	1946 (35.2)	51 (34.9)	0.99 (0.70-1.40)	0.95	Not included	-
<b>2</b>	<b>Current TB diagnosis</b>						
	Pulmonary diagnosis				0.76	Not included	-
	ETB	1839 (33.3)	51 (34.9)	Ref.			
	PTB	2934 (53.1)	78 (53.4)	0.96 (0.67-1.37)			
	ETB + PTB	755 (13.7)	17 (11.6)	0.81 (0.47-1.42)			
	Initial TB location				0.11		0.52
	Lungs	3416 (61.8)	89 (61)	0.89 (0.64-1.25)		0.75 (0.52-1.10)	
	Central nervous system	70 (1.3)	0 (0)	n/a		n/a	
	Miliary	124 (2.2)	1 (0.7)	0.28 (0.04-2.01)		n/a	
	Others	1918 (34.7)	56 (38.4)	Ref.		Ref.	
	TB diagnosis outside of the Netherlands	48 (0.9)	2 (1.4)	1.59 (0.38-6.58)	0.37	Not included	-
<b>3</b>	<b>History of TB disease &amp; treatment</b>						
	Previously diagnosed TB**	345 (6.8)	13 (9.8)	1.50 (0.84-2.68)	0.17	1.46 (0.75-2.81)	0.26
	Previously treated LTBI**	177 (3.5)	7 (5.3)	1.56 (0.72-3.39)	0.23	1.82 (0.83-4.00)	0.14
<b>4</b>	<b>TB risk group</b>						
	TB contacts	366 (6.6)	9 (6.2)	0.93 (0.47-1.83)	0.83	Not included	-
	Immigrants & asylum seekers	966 (17.5)	31 (21.2)	1.27 (0.85-1.90)	0.24	1.34 (0.84-2.14)	0.22
	Illegal immigrants	198 (3.6)	3 (2.1)	0.57 (0.18-1.79)	0.32	Not included	-
	Homeless individuals	123 (2.2)	9 (6.2)	2.89 (1.44-5.80)	0.007	2.56 (1.16-5.63)	0.02
	Health care workers	46 (0.8)	0 (0)	0.40 (0.02-6.56)	0.52	Not included	
	Travelers from/in endemic area >3 month	128 (2.3)	2 (1.4)	0.59 (0.14-2.39)	0.78	Not included	

	Prisoners	127 (2.3)	16 (11)	5.23 (3.03-9.06)	0.000	5.39 (2.90-10.05)	0.000
	Alcohol addicts	107 (1.9)	4 (2.7)	1.43 (0.52-3.93)	0.54	Not included	-
	Drug addicts	146 (2.6)	6 (4.1)	1.58 (0.69-3.64)	0.28	Not included	-
<b>5</b>	<b>Comorbidities</b>						
	Diabetes	257 (4.6)	11 (7.5)	1.67 (0.89-3.13)	0.11	2.02 (1.03-3.97)	0.04
	Malignancy	129 (2.3)	6 (4.1)	1.79 (0.78-4.14)	0.16	2.09 (0.81-5.35)	0.13
	Renal insufficiency/dialysis	91 (1.6)	0(0)	0.20 (0.01-3.28)	0.26	Not included	-
	Organ transplantation	21 (0.4)	1 (0.7)	1.81 (0.24-13.54)	0.44	Not included	-

Notes: \*Number of analysed cases, 5,674; Hosmer & Lemeshow test, 0.99; area under the curve, 0.64 (0.59–0.69); n/a, not applicable due to a small number of events; Ref., reference; OR, odds ratio; aOR, adjusted odds ratio; \*\*missing values: country of birth, 15 (0.3%); previous TB diagnosis, 437 (7.7%); previous LTBI treatment, 466 (8.21%); ETB, extra-pulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis; LTBI, latent tuberculosis infection.



**Table 3.** Predictors for mortality outcome due to tuberculosis (N = 5,674)

No	Predictors	Mortality due to TB		Univariate analysis		Multivariate analysis*	
		No (n=5,562; %)	Yes (n=112; %)	OR (95%CI)	p-value	aOR (95% CI)	p-value
<b>1</b>	<b>Socio-demographic characteristics</b>						
	Male	3354 (60.3)	72 (64.3)	1.19 (0.80-1.75)	0.39	Not included	-
	Age (years)				0.000		0.000
	18–24	863 (15.5)	4 (3.6)	0.31 (0.11-0.86)		0.45 (0.13-1.52)	
	25–74	4184 (75.2)	62 (55.4)	Ref.		Ref.	
	75–84	389 (7)	33 (29.5)	5.73 (3.71-8.84)		5.58 (3.10-10.03)	
	≥85	126 (2.3)	13 (11.6)	6.96 (3.73-12.99)		9.35 (4.31-20.30)	
	Born in the Netherlands**	1560 (28.1)	57 (51.8)	2.75 (1.88-4.02)	0.000	1.26 (0.75-2.12)	0.38
	Urban domicile	1954 (35.1)	43 (38.4)	1.15 (0.78-1.69)	0.47	Not included	-
<b>2</b>	<b>Current TB diagnosis</b>						
	Pulmonary diagnosis				0.000		0.038
	ETB	1876 (33.7)	14 (12.5)	Ref.		Ref.	
	PTB	2951 (53.1)	61 (54.5)	2.77 (1.55-4.97)		4.04 (0.92-17.75)	
	ETB + PTB	735 (13.2)	37 (33)	6.75 (3.63-12.55)		4.97 (1.42-17.41)	
	Initial TB location				0.000		0.000
	Lungs	3432 (61.7)	73 (65.2)	5.98 (2.75-13.01)		2.03 (0.45-9.04)	
	Central nervous system	57 (1)	13 (11.6)	64.09 (24.64-166.68)		120 (34.43-418.54)	
	Miliary	106 (1.9)	19 (17)	50.37 (20.72-122.45)		10.73 (2.50-46.02)	
	Others	1967 (35.4)	7 (6.3)	Ref.		Ref.	
	TB diagnosis outside of the Netherlands	49 (0.9)	1 (0.9)	1.01 (0.14-7.41)	0.98	Not included	-
<b>3</b>	<b>History of TB disease &amp; treatment</b>						
	Previously diagnosed TB**	347 (6.7)	11 (14.5)	2.35 (1.23-4.49)	0.008	1.23 (0.61-2.48)	0.57
	Previously treated LTBI**	182 (3.5)	2 (2.7)	0.76 (0.18-3.10)	0.69	Not included	-
<b>4</b>	<b>Risk group of TB</b>						
	TB contact	371 (6.7)	4 (3.6)	0.52 (0.19-1.4)	0.19	Not included	-
	Immigrants and asylum seekers	994 (17.9)	3 (2.7)	0.13 (0.04-0.40)	0.000	0.11 (0.01-0.84)	0.03
	Illegal immigrants	200 (3.6)	1 (0.9)	0.24 (0.034-1.74)	0.19	Not included	-
	Homeless individuals	127 (2.3)	5 (4.5)	2.00 (0.80-4.99)	0.19	Not included	-
	Health care workers	45 (0.8)	1 (0.9)	1.10 (0.15-8.08)	0.60	Not included	-
	Travelers from/in endemic	128 (2.3)	2 (1.8)	0.77 (0.18-3.16)	0.72	Not included	-

	area >3 month						
	Prisoners	143 (2.6)	0 (0)	0.17 (0.01-2.71)	0.21	Not included	-
	Alcohol addicts	109 (2)	2 (1.8)	0.91 (0.22-3.73)	0.89	Not included	-
	Drug addicts	146 (2.6)	6 (5.4)	2.10 (0.91-4.86)	0.12	3.56 (1.34-9.47)	0.01
<b>5</b>	<b>Comorbidities</b>						
	Diabetes	256 (4.6)	12 (10.7)	2.49 (1.35-4.59)	0.003	1.10 (0.46-2.65)	0.84
	Malignancy	128 (2.3)	7 (6.3)	2.83 (1.29-6.20)	0.017	2.13 (0.89-5.11)	0.89
	Renal insufficiency/dialysis	82 (1.5)	9 (8)	5.84 (2.86-11.94)	0.000	3.23 (1.17-8.96)	0.024
	Organ transplantation	19 (0.3)	3 (2.7)	8.03 (2.34-27.53)	0.009	1.88 (0.18-19.54)	0.60

*Notes:* \* Number of analysed cases 5,674, Hosmer & Lemeshow test 0.59, area under curve 0.85 (0.82-0.88); n/a, not applicable due to a small number of event; Ref., reference; OR, odds ratio; aOR, adjusted odds ratio; \*\*missing value: Country of birth 15 (0.3%), previously diagnosed TB 437 (7.7%), previously treated LTBI 466 (8.21%); ETB, extra-pulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis; LTBI, latent tuberculosis infection.

