Supplementary Appendix 2

Supplementary table 1. Study schema for discovery, internal and external validation analyses.

	Discovery	Internal validation	External validation 1	External validation 2	Pooled validation
Setting	Pune, India	Pune, India	Chennai, India	Khayelitsha, South Africa	India and South Africa
Design	Prospective cohort study	Case-control analysis	Case-control analysis	Case-control analysis	Case-control analysis
Sample size	30 adults with drug-sensitive pulmonary tuberculosis	40 adults with drug-sensitive pulmonary tuberculosis	194 adults with drug-sensitive pulmonary tuberculosis	129 adults with rifampicin sensitive pulmonary tuberculosis	363 adults with drug-sensitive pulmonary tuberculosis
Treatment outcomes	4 with failure	20 with failure	18 with failure, 35 with recurrence and 19 deaths	9 with failure, 4 with recurrence and 5 deaths	47 with failure, 39 with recurrence and 24 deaths
HIV coinfection, n (%)	2 (7%)	3 (8%)	0	76 (59%)	79 (22%)
Diabetes comorbidity, n (%)	7 (23%)	3 (8%)	115 (59%)	10 (8%)	128 (35%)
Laboratory	NIH-NIRT-ICER, Chennai	BJGMC, Pune	NIH-NIRT-ICER, Chennai	Wellcome Center, Cape Town	BJGMC, NIH-NIRT-ICER and Wellcome Center

Supplementary table 2. Baseline characteristics and treatment outcomes of participants in the full cohort and those selected in the random sub-cohort for discovery analysis.

Characteristics	Full cohort (n=445)	Sub-cohort (n=30)	p-value
Age in years, median (IQR)	38 (27-49)	35 (28-51)	0.95
Male sex, n (%)	286 (64)	21 (70)	0.69
BMI in kg/m^2, median (IQR)	17.7 (15.8-20.4)	18.0 (15.8-19.9)	0.97
Ever-smokers, n (%)	144 (32)	8 (27)	0.68
HIV coinfection, n (%)	33 (8)	2 (7)	0.99
Diabetes, n (%)	99 (22)	7 (23)	0.82
Pre-treatment illness duration in days, median (IQR)	45 (30-90)	60 (20-90)	0.59
Percent of lung fields affected on CXR, median (IQR)	60 (25-80)	50 (24-68)	0.30
Cavitation on CXR, n (%)	167 (45)	10 (40)	0.68
Culture confirmed TB, n (%)	368 (84)	27 (90)	0.45
Smear positive TB, n (%)	305 (69)	20 (67)	0.84
Treatment outcomes, n (%)			
Failure	45 (10)	4 (13)	0.99
Recurrence	22 (5)	0	-
Death	20 (4)	0	-

TB – tuberculosis, IQR – interquartile range, BMI – body mass index, CXR – chest radiograph, n – sample size.

Supplementary table 3. Baseline characteristics of culture confirmed tuberculosis patients who failed treatment (cases) and those who were cured (controls) in the internal validation cohort.

Characteristics	Cases (n=20)	Controls (n=20)	p-value
Age in years, median (IQR)	27 (20-32)	26 (20-32)	0.92
Male sex, n (%)	15 (75)	15 (75)	0.99
BMI in kg/m^2, median (IQR)	16.0 (14.2-17.7)	17.4 (15.8-19.1)	0.02
Ever-smokers, n (%)	6 (30)	5 (25)	0.99
Alcohol dependence, n (%)	9 (45)	7 (35)	0.74
HIV coinfection, n (%)	2 (10)	1 (5)	0.99
Diabetes, n (%)	1 (5)	2 (10)	0.99
Pre-treatment illness duration in days, median (IQR)	35 (28-68)	30 (15-45)	0.03
Percent of lung fields affected on CXR, median (IQR)	58 (38-78)	60 (23-73)	0.43
Cavitation on CXR, n (%)	8 (40)	8 (40)	0.99
Smear positive TB, n (%)	14 (70)	11 (55)	0.51

TB – tuberculosis, IQR – interquartile range, BMI – body mass index, CXR – chest radiograph, n – sample size.

Supplementary table 4. Baseline characteristics of tuberculosis patients who experienced an unfavorable treatment outcome (cases) and those who were cured (controls) in the Indian external validation cohort.

Characteristics	Cases (n=72)	Controls (n=122)	p-value
Age in years, median (IQR)	45 (39-52)	45 (36-50)	0.40
Male sex, n (%)	64 (89)	104 (85)	0.52
BMI in kg/m^2, median (IQR)	16.8 (15.2-18.9)	17.2 (15.4-19.2)	0.58
Ever-smokers, n (%)	41 (57)	50 (41)	0.03
Diabetes, n (%)	42 (58)	73 (59)	0.88
Pre-treatment illness duration in days, median (IQR)	4 (4-8)	5 (4-8)	0.56
Percent of lung fields affected on CXR, median (IQR)	26 (15-40)	24 (14-40)	0.36
Cavitation on CXR, n (%)	18 (31)	30 (32)	0.99
Smear positive TB, n (%)	61 (91)	94 (90)	0.80
Culture confirmed TB, n (%)	64 (96)	104 (98)	0.40

TB – tuberculosis, IQR – interquartile range, BMI – body mass index, CXR – chest radiograph, n – sample size.

Supplementary table 5. Baseline characteristics of TB patients who experienced an unfavorable treatment outcome and those who were cured in the South African external validation cohort.

Characteristics	Unfavorable outcome (n=18)	Cure (n=111)	p-value
Age in years, median (IQR)	36 (30-48)	35 (30-43)	0.78
Male sex, n (%)	11 (61)	63 (57)	0.80
BMI in kg/m^2, median (IQR)	19.9 (19.0-23.0)	21.0 (19.1-23.3)	0.15
Ever-smokers, n (%)	8 (44)	52 (47)	0.99
Cavitation on CXR, n (%)	7 (39)	60 (54)	0.31
HIV coinfection, n (%)	13 (72)	63 (57)	0.30
ART receipt, n (%)	7 (39)	22 (20)	0.12
CD4 count, median (IQR)	178 (61-594)	194 (69-364)	0.98
Smear positive TB, n (%)	9 (50)	82 (74)	0.05

TB – tuberculosis, IQR – interquartile range, BMI – body mass index, CXR – chest radiograph, n – sample size, ART – antiretroviral therapy.

Supplementary table 6. Discriminatory ability of baseline IL-6 added to a risk-prediction model for unfavorable tuberculosis treatment outcomes.

Baseline variables in the prediction model	AUC (95%CI) excluding baseline IL-6	AUC (95%CI) including baseline IL-6	p-value for gain in AUC by baseline IL-6
Cavitation on CXR	0.52 (0.46-0.57)	0.68 (0.62-0.74)	<0.001
Smear grade $\geq$ 2	0.50 (0.45-0.55)	0.65 (0.59-0.71)	<0.001
BMI $\leq$ 18.5 kg/m^2	0.60 (0.51-0.70)	0.72 (0.62-0.82)	0.002
Cavitation and smear grade $\geq$ 2 and BMI $\leq$ 18.5 kg/m^2	0.66 (0.56-0.77)	0.76 (0.67-0.85)	0.02

AUC – area under the curve calculated by the C-statistic, CI – confidence interval, BMI – body mass index.