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Can hepatitis B virus infection predict tuberculosis treatment liver toxicity? Development of a preliminary prediction rule

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SUMMARY

BACKGROUND: Liver toxicity due to tuberculosis (TB) treatment is a frequent cause of treatment interruption, and may sometimes lead to a change in therapy to a less potent regimen.

OBJECTIVE: To estimate the risk of hepatotoxicity in patients with or without hepatitis B virus (HBV) infection receiving TB treatment and to develop a clinical prediction rule.

DESIGN: A prospective observational follow-up was conducted. Data from 154 patients who underwent TB treatment were analysed. Crude risk ratios were estimated and a Cox proportional hazards model was fit.

RESULTS: The mean follow-up time was 187 days. Crude risk ratios showed that ethnicity, human immunodeficiency virus infection, multiple sexual partners, highly active antiretroviral treatment, and clinical forms of TB were possible predictors of liver toxicity. HBV infection and other sexually transmitted diseases showed considerable relative risk, although not statistically significant. The Cox proportional hazards model identified the following predictors of hepatotoxicity: White ethnicity, multiple sexual partners, high baseline alanine transferase and clinical forms of TB. Active HBV, indicated by the detection of surface antigen HBV, could predict hepatotoxicity, although with low precision.

CONCLUSION: Using this information, we were able to apply a score and draw a nomogram to estimate survival probabilities and median times to event for each patient.

KEY WORDS: tuberculosis; hepatitis B; anti-tuberculosis agents; drug toxicity; nomograms; HIV

HEPATITIS B VIRUS (HBV) infection is a major global health problem, with an estimated 2 billion people infected worldwide. Currently, over 350 million people are chronically infected, causing 1–2 million deaths per year.[1] Individuals infected by the human immunodeficiency virus (HIV) may frequently be co-infected with HBV, as these diseases share similar transmission routes. Tuberculosis (TB) is the leading clinical manifestation of the acquired immunedeficiency syndrome (AIDS), and the number of cases continues to rise in settings with a high prevalence of HIV.[2] A high prevalence of HBV infection among TB patients, as well as among the HIV co-infected, was estimated previously.[3]

After the introduction of highly active antiretroviral treatment (HAART), the survival and quality of life of HIV patients improved. Although the incidence of most opportunistic diseases decreased dramatically after the HAART era,[4] the impact on TB incidence seems to be evident only over longer periods of observation.[5–7] The simultaneous use of HAART and anti-tuberculosis drugs results in a decline in TB morbidity and mortality;[8] however, the therapeutic benefits may be limited by the incidence of adverse effects due to combination treatment for TB and HIV,[9] including liver toxicity.[10]

Several studies have suggested that HBV infection is a risk factor for the development of hepatotoxicity during TB treatment. Elevated liver enzymes following the initiation of anti-tuberculosis and/or antiretroviral treatment (ART) often lead to treatment interruption.[10–14]

The aim of the present study was to estimate the incidence of liver toxicity in a group of patients with and those without HBV infection during TB treatment. We also developed a preliminary prognosis score (clinical prediction rule) based on a Cox proportional hazard model.

STUDY POPULATION AND METHODS

Design and settings

This prospective observational follow-up study was conducted at the Instituto de Pesquisa Clinica Evandro Chagas–Fundação Oswaldo Cruz, Rio de Janeiro, Brazil, a reference centre for infectious diseases, including TB and HIV, providing both in- and out-patient treatment. This investigation was approved by the

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institutional ethics committee and review board on 22 September 2003, registered at Sistema Nacional de Informação sobre Ética em Pesquisa* (no. 0013.0.009.000-03).

Patient population

Patient recruitment was performed from 2003 to 2005. Eligibility criteria were 1) sputum smear with acid-fast bacilli or culture positive for *Mycobacterium tuberculosis* at the Institute or documented diagnosis elsewhere, but with no previous treatment in at least the previous 30 days; 2) hepatitis serology recorded in the medical chart; 3) undergoing treatment or starting treatment in the recruitment period; and 4) signed written consent. Exclusion criteria were 1) patients who were later identified as misdiagnosed and TB treatment interrupted; 2) patients who did not have at least two visits registered in the medical record; 3) pregnancy; 4) absence of HIV serology in medical chart; 5) age <18 years.

Data collection

The TB team was composed of three to five physicians (depending on the time period), a nurse and laboratory personnel. All patients were submitted to a standardised clinical evaluation protocol, divided into two parts: 1) baseline evaluation and 2) follow-up evaluation. The Brazilian Ministry of Health recommendation for TB treatment at the time was rifampicin (RMP; 600 mg/day), isoniazid (INH; 400 mg/day) and pyrazinamide (PZA; 2 g/day) for every patient with weight >45 kg or adjusted for weight if <45 kg. After at least 2 months of treatment, PZA was discontinued. For those with HIV and current use of HAART, ART was preferentially switched to a combination with efavirenz (EFZ); for treatment-naïve patients, TB treatment usually lasted 30 to 60 days before the introduction of HAART.

The clinical protocol was an initial visit with clinical and laboratory evaluation, follow-up at days 15 and 30 and then once each month until therapy was completed, and two final visits 6 months apart after completion of therapy.

Alanine transferase (ALT) values were obtained at baseline, at days 15 and 30, and once monthly throughout the course of TB treatment. If judged necessary by the assistant physician, ALT values were obtained more frequently. All clinical and laboratory data of interest were recorded in the medical charts. These data were later extracted from the medical records and clinical research forms were completed.

Outcome

The outcome of interest was liver toxicity due to TB treatment. This was defined as an increase in serum ALT levels beyond twice the normal upper limit (ALT ⩾45 international units [IU]/l), as adopted by the Council of International Organisations of Medical Sciences (CIOMS), or at least a two-fold increase in ALT initial levels for those patients with a baseline ALT of >90 IU/l.

Exposures

Clinical data were used to explore possible predictors of liver toxicity as categorical (Table 1) or continuous (Table 2): alcoholism, as defined by a positive CAGE questionnaire;[15] tobacco use (binary), defined as current use reported by the patient; income, defined as up to 3 times the minimum wage or >3 times the minimum wage as reported by the patient; multiple sexual partners, 'yes' if two or more sexual partners in one year and 'no' otherwise; sexually transmitted diseases (STDs; binary), 'yes' for the diagnosis of STDs, other than HIV and hepatitis, such as syphilis, human T-cell leukaemia virus, herpes or genital ulcers, and 'no' otherwise; TB clinical form, pulmonary or extra-pulmonary/disseminated (two or more sites with evidence of infection); HBV, defined as serological detection of hepatitis B virus surface antigen (HBsAg).

Analysis

Risks within a 95% confidence interval (95%CI) were estimated by the Wilson (binomial) method.[16] Crude risk ratios (relative risk [RR]) and their 95%CIs were estimated by the Wald method, and a hypothesis test of independence (null hypothesis RR = 1) was performed for each RR.[16] Hypothesis test (*t*-test) was performed to compare continuous variables. An overall Kaplan-Meier and cumulative hazard curves[17] were plotted with their respective 95%CIs. A survival Cox proportional hazards model was then fitted. A time-dependent Cox analysis was performed with the ART as the time-dependent variable. However, using this strategy, none of the fitted models obeyed the proportionality assumption. Different nested Cox models were tested by the deviance statistics, with a significance threshold of 0.05. All variables introduced in the model were tested for proportionality (Schoenfeld residuals) and functional form (Martingale residuals) when appropriate. To help the readers to predict the event or estimate the median time to a possible event, a nomogram[18] was constructed from the fitted Cox model. This graphically represents a risk score for liver toxicity. All analyses were carried out using *R* (packages Epitools, Survival and Design).[19]

RESULTS

Of 395 patients initially screened, 241 met one or more exclusion criteria, primarily the absence of HBV serology in the medical chart; 154 patients were finally analysed.

* http://portal.saude.gov.br/sisnep/pesquisador/menuusuario.cfm

Table 1 Baseline characteristics and crude comparisons of dichotomous variables

Variable	*n*	%	Toxicity risk	95% confidence limits	RR	95% confidence limits	*P* value*
Sex							
Male	99	64.3	0.22	0.15–0.31	1.53	0.73–3.20	0.2491
Female	55	35.7	0.15	0.08–0.26	1.00		
Ethnicity							
White	72	46.8	0.26	0.18–0.38	1.97	1.00–3.85	0.0425
Non-White	82	53.3	0.13	0.08–0.23	1.00		
HIV							
Positive	60	39.0	0.32	0.21–0.44	2.71	1.39–5.28	0.0023
Negative	94	61.0	0.12	0.07–0.20	1.00		
HBsAg							
Positive	6	3.9	0.50	0.19–0.81	2.74	1.15–6.54	0.0542
Negative	148	96.1	0.18	0.13–0.25	1.00		
Anti-HBc							
Positive	50	32.5	0.22	0.13–0.35	1.20	0.62–2.33	0.5841
Negative	104	67.5	0.18	0.12–0.27	1.00		
Anti-HBs							
Positive	42	27.3	0.10	0.04–0.22	0.41	0.15–1.11	0.0561
Negative	112	72.7	0.23	0.16–0.32	1.00		
Anti-HCV							
Positive	9	5.8	0.11	0.02–0.44	0.56	0.09–3.64	0.5135
Negative	145	94.2	0.20	0.14–0.27	1.00		
Neighbourhood							
Downtown	107	69.5	0.19	0.12–0.27	0.88	0.45–1.73	0.7092
Suburb	47	30.5	0.21	0.12–0.35	1.00		
Alcohol							
Yes	25	16.2	0.24	0.12–0.43	1.29	0.59–2.83	0.5330
No	129	83.8	0.19	0.13–0.26	1.00		
Tobacco							
Yes	46	29.9	0.17	0.09–0.31	0.85	0.41–1.78	0.6692
No	108	70.1	0.20	0.13–0.29	1.00		
Family income							
0–3 min. wages	24	15.6	0.13	0.04–0.31	0.60	0.20–1.83	0.3473
>3 min. wages	130	84.4	0.21	0.15–0.29	1.00		
Education							
High school or higher	45	29.2	0.18	0.09–0.31	0.88	0.42–1.83	0.7317
Middle school or less	109	70.8	0.20	0.14–0.29	1.00		
Number of inhabitants							
>4	21	13.6	0.24	0.11–0.45	1.27	0.55–2.94	0.5899
1–4	133	86.4	0.19	0.13–0.26	1.00		
Number of rooms							
>3	20	13.0	0.20	0.08–0.42	1.03	0.40–2.64	0.9499
<3	134	87.0	0.19	0.14–0.27	1.00		
Marital status							
Married	66	42.9	0.17	0.10–0.27	0.77	0.40–1.51	0.4451
Single	88	57.1	0.22	0.14–0.31	1.00		
Sexual preference							
Homo or bisexual	29	18.8	0.31	0.17–0.49	1.85	0.95–3.60	0.0812
Heterosexual	125	81.2	0.17	0.11–0.24	1.00		
Multiple partners							
Yes	52	33.8	0.37	0.25–0.50	3.39	1.75–6.58	0.0001
No	102	66.2	0.11	0.06–0.18	1.00		
Injecting drug use							
Yes	4	2.6	0.00	0.00–0.49	NA	NA	0.3189
No	150	97.4	0.20	0.14–0.27	1.00		
Blood transfusion							
Yes	11	7.1	0.27	0.10–0.57	1.44	0.52–4.02	0.4983
No	143	92.9	0.19	0.13–0.26	1.00		
HAART							
Yes	49	31.8	0.31	0.20–0.45	2.14	1.14–4.02	0.0172
No	105	68.2	0.14	0.09–0.22	1.00		
STD							
Yes	28	18.2	0.32	0.18–0.51	1.93	0.99–3.75	0.0614
No	126	81.8	0.17	0.11–0.24	1.00		
TB clinical form							
Extra-pulmonary/disseminated	55	35.7	0.31	0.20–0.44	2.35	1.24–4.48	0.0076
Pulmonary	99	64.3	0.13	0.08–0.21	1.00		

*Null hypothesis is RR = 1.
RR = risk ratio; HIV = human immunodeficiency virus; HBsAg = hepatitis B surface antigen; HBc = hepatitis B core antigen; HBs = hepatitis B surface; HCV = hepatitis C virus; NA = not assigned; HAART = highly active antiretroviral treatment; STD = sexually transmitted diseases; TB = tuberculosis.

Table 2 Baseline characteristics and crude comparison of continuous variables

Variable, outcome	*n*	Mean	SD	*t*-test *P* value	Median	Quantile 10	Quantile 90
Age							
Overall	154	39.08	12.63		38	24	56
With	30	37.90	10.47	0.5174	36	28	50
Without	124	39.36	13.12		38	24	56
CD4+							
Overall	45	201	175		160	38	420
With	18	202	209	0.9780	134	45	442
Without	27	201	153		171	39	387
HIV viral load							
Overall	42	217407	646899		12250	0	349000
With	17	272284	889633	0.5174	1400	0	316000
Without	25	180090	428586		27000	0	422000
ALT							
Overall	154	42	20		37	26	63
With	30	51	28	0.0669	42	31	105
Without	124	40	17		37	26	62
AST							
Overall	154	29	21		22	13	51
With	30	35	20	0.0764	29	17	63
Without	124	28	21		22	13	47
AP							
Overall	154	133	87		105	76	197
With	30	137	110	0.7860	102	80	210
Without	124	132	81		106	76	193
GGT							
Overall	154	99	103		64	27	212
With	30	113	112	0.4259	72	41	177
Without	124	95	101		64	25	212
Bilirubin							
Overall	154	0.49	0.34		0.40	0.20	0.90
With	30	0.52	0.45	0.6759	0.40	0.20	0.90
Without	124	0.48	0.31		0.40	0.20	0.90

SD = standard deviation; with = with liver toxicity; without = without liver toxicity; HIV = human immunodeficiency virus; ALT = alanine transferase; AST = aspartate aminotransferase; AP = alkaline phosphatase; GGT = gamma glutamyl transpeptidase.

Baseline characteristics

All patients included in the analysis started TB treatment with RMP, INH and PZA. There were about twice as many men as women, and the same number of White and non-White subjects (Table 1). The HIV prevalence was almost 40%. The age of the patients ranged from 18 to 79 years, with a mean age of 39.1 years (standard deviation [SD] 12.6; Table 2).

Prevalence of active HBV infection (HBsAg) was 4%, 1% among TB patients and 8.3% among TB-HIV patients. Fifty patients (32%) had HBV core antigen (HBcAg) antibodies. Similar to HBsAg, HBcAg antibodies were more prevalent among HIV patients (50.6%) than TB-HIV patients (20.2%). Hepatitis C virus (HCV) prevalence in the sample was 6% (10% among HIV-positives and 3% among HIV-negatives). Other baseline characteristics are shown in Table 1.

Approximately half ($n = 29$) of the patients with HIV were already on HAART when they started TB treatment. Twenty-six patients had changes in ART after the introduction of TB treatment, either because they were using no ARVs or because they were using non-recommended ARVs in combination with RMP. Table 3A shows that the most common combinations

Table 3 Antiretroviral therapy for HIV patients

	n	%
A At TB diagnosis		
AZT 3TC EFZ	13	21.7
AZT 3TC LOP	1	1.7
AZT 3TC NFV	2	3.3
AZT 3TC RTV IDV	1	1.7
AZT 3TC RTV SQV	2	3.3
d4T 3TC EFZ	5	8.3
d4T 3TC IDV	1	1.7
d4T 3TC RTV SQV	1	1.7
d4T DDI LOP	1	1.7
d4T DDI NFV	1	1.7
ddI 3TC NFV	1	1.7
No ARV	31	51.7
Total	60	100
B Switched to after start of TB treatment		
AZT 3TC EFZ	18	69.2
AZT 3TC RTV SQV	4	15.4
AZT 3TC TNF RTV SQV	1	3.9
D4T 3TC EFZ	1	3.9
ddI TNF RTV SQV	1	3.9
No ARV	1	3.9
Total	26	100

HIV = human immunodeficiency virus; TB = tuberculosis; AZT = zidovudine; 3TC = lamivudine; EFZ = efavirenz; LOP = lopinavir; NFV = nelfinavir; RTV = ritonavir; IDV = indinavir; SQV = saquinavir; d4T = estavudine; ARV = antiretroviral; TNF = tenofovir; ddI = didanosine.

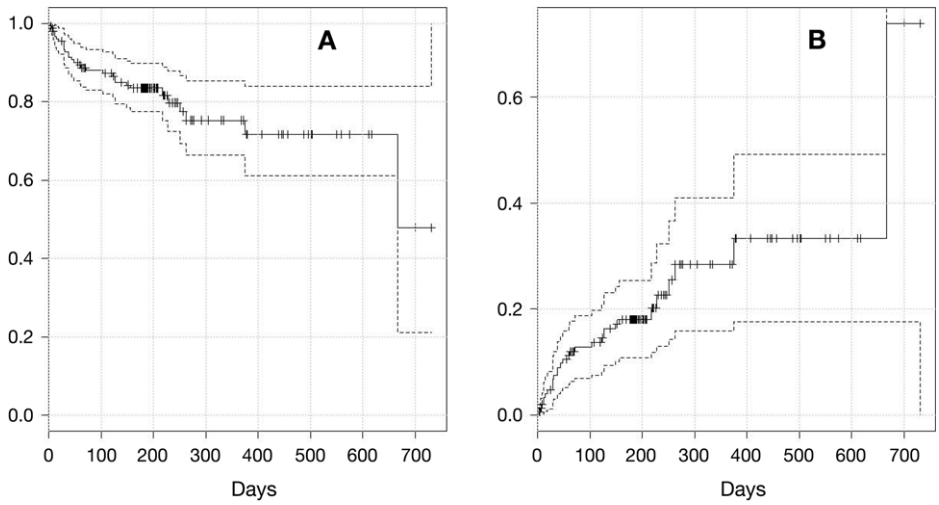


Figure 1 Kaplan-Meier (**A**) and cumulative (**B**) hazard curves for overall liver toxicity and its 95% confidence intervals.

were those including EFZ. In clinical routine, therapy-naïve HIV patients were expected to start ART after 30 days of TB treatment. Table 3B shows the changes in ART made after TB treatment was initiated. Again, combinations with EFZ were the most common. Not all patients initiated ART during TB treatment, and there was one patient for whom it was interrupted due to non-liver-related intolerance.

Incidence of liver toxicity

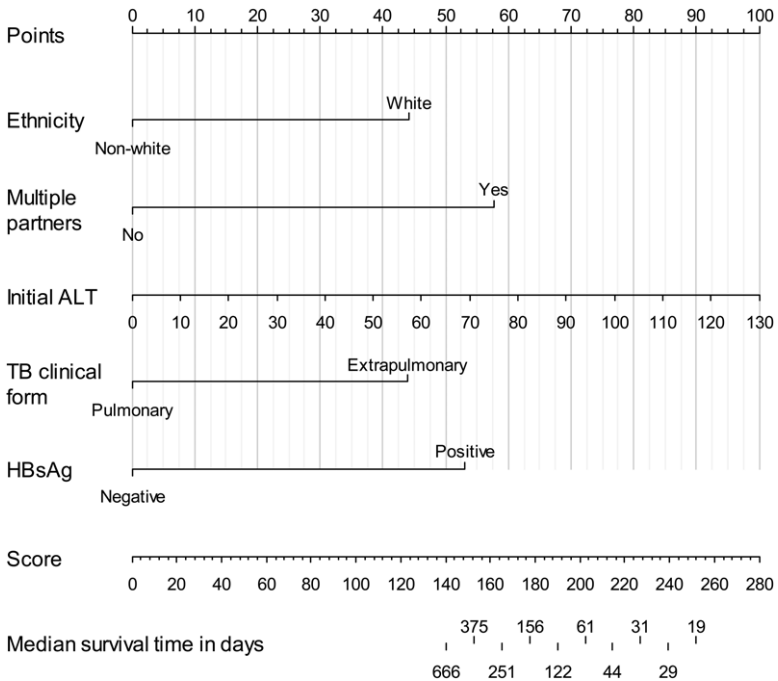
The overall crude incidence of liver toxicity was 19.5%. The overall Kaplan-Meier curve and cumulative hazard are shown in Figure 1. The figure demonstrates that the risk increases significantly through the second and third months of treatment and becomes more stable from this time on. Many observations were censored at about 180 days of follow-up, when most of the non-HIV-infected patients ended TB treatment. The mean follow-up time was 187 days (median 209, range 3–731).

The primary hypothesis, an increase in the risk of TB treatment-related liver toxicity in the presence of concurrent HBV infection, was supported by the crude relative risks (RR 2.74) shown in Table 1, although the risks were not significant at 95%. The factors that showed some increase in risk of liver toxicity were HIV infection (RR 2.53), White ethnicity (RR 2.16), multiple sexual partners (RR 3.20), use of HAART (RR 2.00), STDs (RR 2.02) and extra-pulmonary (or disseminated) TB (RR 2.55). Initial ALT showed a *P* value close to the decision threshold of 0.05, although this was not significant.

Table 4 Output of the final Cox regression model for liver toxicity for patients under tuberculosis treatment (n = 154)

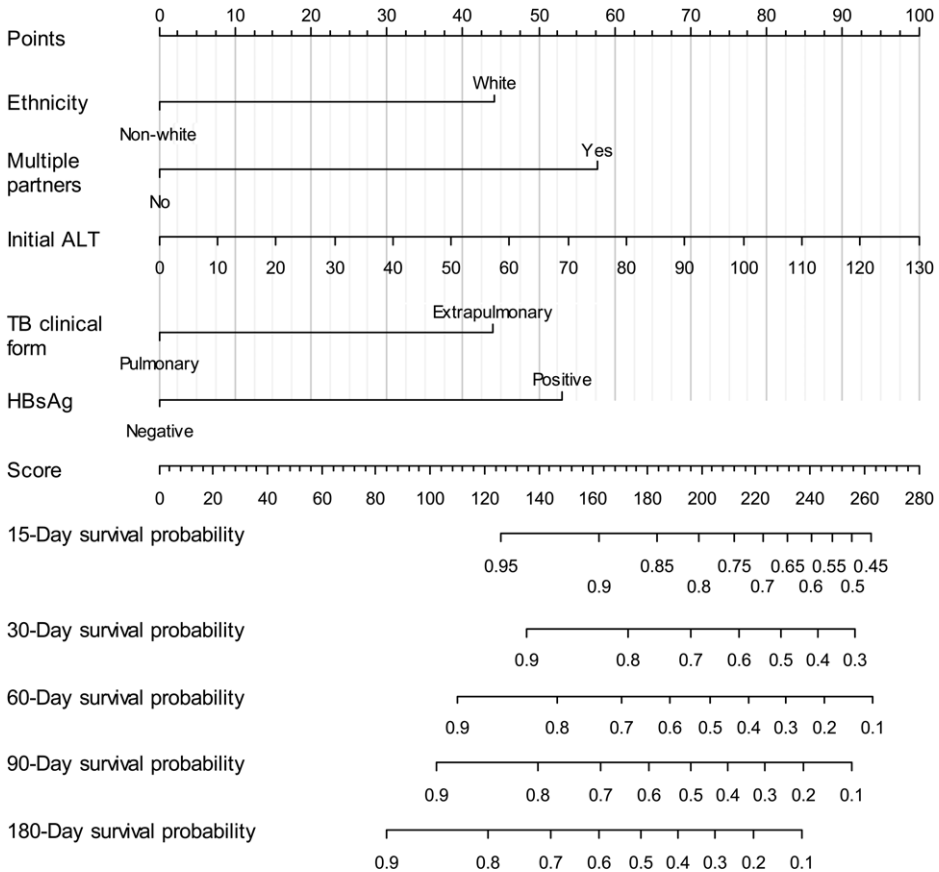
	Regression coefficient	Adjusted risk ratio	SE (coef)	z	P value
Ethnicity: White	0.89	2.44	0.40	2.24	0.02502
Multiple partners: yes	1.16	3.20	0.39	2.97	0.00298
ALT	0.02	1.02	0.01	2.06	0.03937
Extra-pulmonary TB	0.88	2.42	0.42	2.13	0.03330
HBsAg: positive	1.07	2.91	0.73	1.46	0.14490
			Exp (−coef)	95%CL	
Ethnicity: White		2.44	0.41	1.12–5.31	
Multiple partners: yes		3.20	0.31	1.49–6.90	
ALT		1.02	0.99	1.00–1.03	
Extra-pulmonary TB		2.42	0.41	1.07–5.46	
HBsAg: positive		2.91	0.34	0.69–12.27	
R^2	0.17 (maximum possible = 0.83)				
LR	28.37 on 5 df, P = 3.082e-05*				
Wald test	28.37 on 5 df, P = 3.085e-05*				
Score (log-rank) test	31.27 on 5 df, P = 8.266e-06*				

* P value of the hypothesis test whether coefficient is different from 1.
SE = standard error; z = value for normal distribution; ALT = alanine transferase; TB = tuberculosis; HBsAg = hepatitis B surface antigen; exp(−coef) = adjusted risk ratio for vice-versa reference category; 95%CL = 95% confidence limits for the adjusted risk ratio; LR = likelihood ratio; df = degrees of freedom.



Draw a vertical line from your patient characteristics toward the upper line and sum the points. After doing this for all characteristics, sum all points from all five characteristics and draw a vertical line from the 'Score' line toward the 'Median survival' line.

Figure 2 Nomogram to estimate median time to liver toxicity in patient under TB therapy. ALT = alanine transferase; TB = tuberculosis; HBsAg = hepatitis B surface antigen.



Draw a vertical line from your patient characteristics toward the upper line and sum the points. After doing this for all characteristics, sum all points from all the five characteristics and draw a vertical line from the 'Score' line toward any 'Survival probability' line. This is the patient's probability of not having the event up to a certain day of therapy.

Figure 3 Nomogram to estimate survival probabilities to liver toxicity in patients under TB therapy. ALT = alanine transferase; TB = tuberculosis; HBsAg = hepatitis B surface antigen.

Prediction score

After comparing several possible combinations of predictors, a final model including five variables was fit (Table 4). HBV infection did not increase the prediction of the model, but, as observed for the crude risk ratio, HBsAg presented with a high risk ratio and was forced into the model. HIV, HAART and STDs, which were initially predictors, were discarded when 'multiple sexual partners' was introduced into the model. Initial ALT, which was not at first a predictor of liver toxicity, was in fact found to increase the predictive power of the model. Ethnicity (White, RR 2.43), multiple sexual partners (yes, RR 3.20), TB clinical form (extra-pulmonary/disseminated, RR 2.42), HBsAg (RR 2.91) and initial ALT (each unit increase in ALT = an increase in risk of 1.6%, RR 1.01) composed the final model (Table 4).

The prognostic score was developed based on the nomogram (Figures 2 and 3). The graph shows the behaviour of individual patient prediction. As an example on how to use the nomogram, suppose that a patient is White. Draw a vertical line from 'White' toward the upper line of the graph and register the points (44 points). The same patient has multiple sexual partners; draw another vertical line from 'Yes' toward the upper line (58 points); he/she has pulmonary TB (0 point) and an initial ALT of 45 (35 points). The same patient has HBsAg (52 points). Total points summed 189. To ascertain the median time to event represented by this score, draw a vertical line from the 'Score' line toward 'Median survival time in days'. In Figure 3, the same nomogram is represented, but instead of median time to event the survival probabilities in certain periods are represented.

DISCUSSION AND CONCLUSIONS

HIV prevalence in this sample is very high compared to the general population, and even in the population of TB patients (about 15%).[2] However, this 40% HIV prevalence was previously estimated at our institute, and appears to have been stable over the past 10 years. We believe that the prevalence is high because the institute is a referral centre, treating a population with specific characteristics.

The effect of the factor of multiple sexual partners was an unexpected finding, overriding the effect of HAART and HIV. This may represent systemic clinical manifestations related to the combination of the effect of HIV and other STDs, or the finding may be a proxy for intravenous drug use, which would be difficult to measure accurately.

The high prevalence of HBV infection among TB patients and other clinical characteristics were estimated previously at our centre,[3] and seem to be similar to those presented here. These later justified the introduction of hepatitis serology into the routine care protocol for TB. Data available from different Brazilian regions show that HBsAg prevalence in the HIV population ranged from 3.8% to 8.5%, and prevalence of anti-hepatitis B core antigen (anti-HBc) ranged from 39% to 45%.[20–26] These results are very similar to findings in this study. However, no data were available regarding HBV infection in TB or TB-HIV patients for comparison with these findings.

Liver toxicity may cause morbidity and mortality, and diminishes treatment effectiveness by interrupting and prolonging treatment or even resulting in hospitalisation. The incidence of hepatotoxicity was estimated at between 2% and 28% in TB patients,[27] and between 2% and 18% among patients on HAART (without TB). This investigation shows the risk of hepatotoxicity with the combined use of TB treatment and HAART, which does not appear to be different from the published risk of toxicity from TB treatment alone. These findings may be relevant, as physicians may use the evidence to make decisions regarding whether to start treatment with more potent and hepatotoxic drug combinations, such as RMP, INH and PZA, or to start with a less hepatotoxic, but also less potent combination, such as ofloxacin, streptomycin and ethambutol. There were also concerns about the higher doses of anti-tuberculosis drugs recommended in Brazil at the time and used in other countries as compared with the World Health Organization recommendations,[2] but the doses of anti-tuberculosis drugs used in this study did not appear to increase liver toxicity.

Although this investigation had a pragmatic approach, some limitations must be considered. These results may not be directly applicable to other situations. The absence of data exploring other factors previously associated with hepatotoxicity[27–30] may result in confounding. The small sample size may affect the study results: 1) the sample size reduces the power to detect the prediction ability of HCV, HBV and HIV; and 2) validation of the fitted model with re-sampling techniques or splitting the sample into two is not possible. Furthermore, testing of prediction rules in different clinical scenarios is necessary to verify that results are valid and generally applicable.[31]

The main findings of this investigation were the following: 1) it is possible to predict the likelihood of liver toxicity before initiating TB treatment; 2) White ethnicity, extra-pulmonary (or disseminated) TB, multiple sexual partners, presence of HBsAg and high initial ALT were predictors of liver toxicity; 3) in contrast with widely accepted beliefs,[28,27] HCV and HIV (or HAART) were not predictors of liver toxicity.

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RÉSUMÉ

CONTEXTE : La toxicité hépatique due au traitement de la tuberculose (TB) est une cause fréquente d'interruption du traitement qui conduit parfois au passage du traitement vers un régime moins puissant.

OBJECTIF : Estimer le risque d'hépatotoxicité chez les patients avec ou sans infection due au virus de l'hépatite B (HBV) bénéficiant d'un traitement TB et d'élaborer une règle clinique de prédiction.

SCHÉMA : On a mené un suivi prospectif de caractère observationnel. Les données provenant de 154 patients soumis à un traitement TB ont été analysées. Les ratios bruts de risque ont été estimés et l'on a adapté le modèle de risque proportionnel de Cox.

RÉSULTATS : La période moyenne de suivi a été de 187 jours. Les ratios bruts de risque ont montré que les facteurs prédictifs potentiels de toxicité hépatique étaient

l'ethnie, l'infection par le virus de l'immunodéficience humaine, le fait d'avoir des partenaires sexuels multiples, le traitement antirétroviral hautement actif (HAART) et les formes cliniques de TB. L'infection HBV et d'autres maladies sexuellement transmissibles se sont avérées représenter un risque relatif considérable bien que non significatif sur le plan statistique. Le modèle de risque proportionnel de Cox a identifié les facteurs prédictifs d'hépatotoxicité suivants : la race blanche, les partenaires sexuels multiples, un taux initial élevé d'alanine transférase et les formes cliniques de la TB. Une hépatite B active, signalée par la détection de HBsAg (l'antigène de surface) pourrait prédire l'hépatotoxicité, bien qu'avec une précision limitée.

CONCLUSION : En utilisant cette information, nous avons pu appliquer un score et dessiner un nomogramme pour estimer pour chacun des patients les probabilités de survie et les durées médianes avant l'événement.

RESUMEN

MARCA DE REFERENCIA: La toxicidad hepática causada por el tratamiento antituberculoso constituye una causa frecuente de interrupción del tratamiento y algunas veces lleva al cambio por una pauta terapéutica menos eficaz.

OBJETIVOS: Calcular el riesgo de hepatotoxicidad en pacientes con infección por el virus de la hepatitis B (HBV) o sin ella que reciben tratamiento antituberculoso y formular una regla de pronóstico clínico.

MÉTODOS: Se llevó a cabo un estudio prospectivo de observación del seguimiento. Se analizaron los datos de 154 pacientes que recibieron tratamiento antituberculoso, se calcularon los riesgos relativos brutos y se aplicó un modelo de riesgos instantáneos proporcionales de Cox.

RESULTADOS: El seguimiento promedio fue de 187 días. Los riesgos relativos pusieron en evidencia que la etnia, la infección por el virus de la inmunodeficiencia humana, la multiplicidad de compañeros sexuales, el tratamiento antirretrovírico de gran actividad y las formas clínicas de tuberculosis constituían posibles factores pronósticos de hepatotoxicidad. La infección por el HBV y otras enfermedades de transmisión sexual demostraron un riesgo relativo considerable, pero sin significación estadística. Según el modelo de riesgos instantáneos proporcionales de Cox, son factores pronósticos de hepatotoxicidad: la etnia blanca, la multiplicidad de compañeros sexuales, una alta concentración sérica inicial de alanina aminotransferasa y las formas clínicas de la TB. Una infección activa por el HBV, indicada por la detección del antígeno de superficie, podría predecir la aparición de hepatotoxicidad, pero con baja precisión.

CONCLUSIÓN: En virtud de esta información se pudo aplicar una calificación y trazar un nomograma que permite calcular las probabilidades de supervivencia y el tiempo medio hasta la aparición de un acontecimiento adverso en cada paciente.